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Volume 57 Issue 4 July-August 2012

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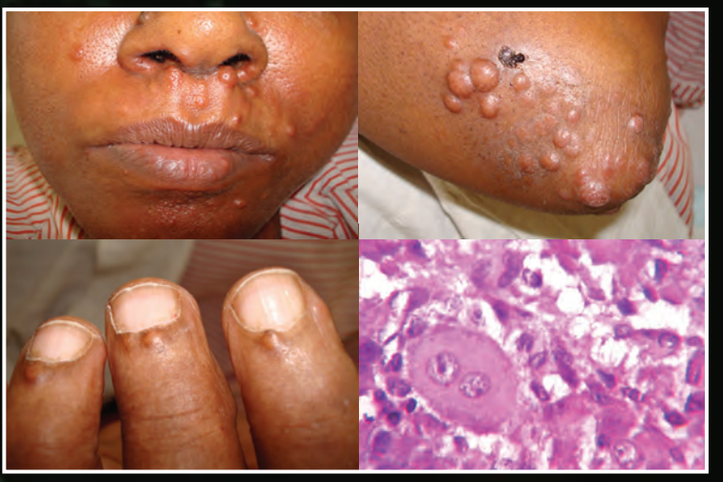
Asian Academy of Dermatology and Venereology



Multicentric Reticulohistiocytosis

Highlights of the issue

- Rational and ethical use of topical corticosteroids
- Cutaneous manifestations of internal malignancy
- Netherton syndrome and SPINK5 gene
- Pediatric dermatoses of south west Rajasthan
- High risk factors for severe hand foot and mouth disease
- In-transit metastases from squamous cell carcinoma

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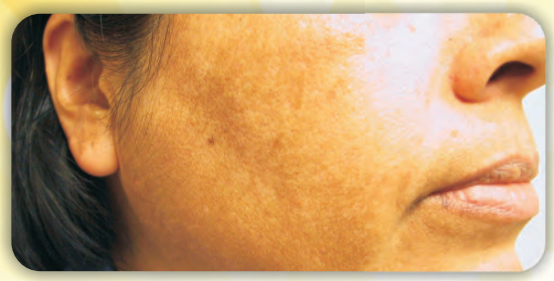

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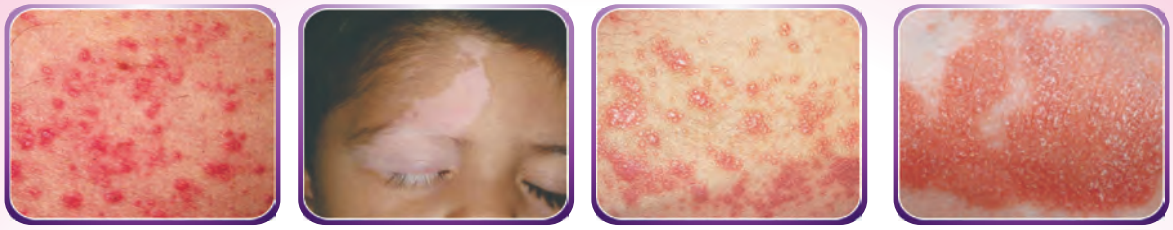

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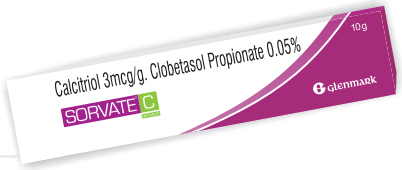

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1. Cutis 2009; 83:205-212 2. Skin Therapy Letter; 2005;10(9):1-4 3. J Drugs Dermatol, 2009 Aug; 8(8 Suppl): 9-16

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Review Article

Rational and Ethical Use of Topical Corticosteroids Based on Safety and Efficacy

Sanjay K Rathi, Paschal D'Souza[1]

Consultant Dermatologist, Siliguri, West Bengal, [1]Professor and Head, Department of Dermatology, ESIC-PGIMSR, New Delhi, India

Abstract

Topical corticosteroids (TC) have greatly contributed to the dermatologist's ability to effectively treat several difficult dermatoses. The available range of formulations and potency gives flexibility to treat all groups of patients, different phases of disease, and different anatomic sites. However, the rapid rise in incidence of improper use of these drugs by dermatologists, general physicians, and patients threatens to bring disrepute to the entire group of these amazing drugs. Responsibility to disseminate proper knowledge regarding when, where, and how to use TC both to internists and patients rests primarily with the dermatologist. Benefits of rational and ethical use and the harm of overuse and misuse for nonmedical, specially for cosmetic purposes, should be clearly conveyed before penning a prescription involving TC. Simultaneous efforts to use political, legal, and other institutions to prevent misuse of these drugs by rationing their availability only through proper prescriptions will greatly help the cause. This will hopefully bring down both the extremes of ever increasing cases of steroid-induced dermatoses on one hand and the irrational fears of using TC in well justified indications on the other.

Key Words: *Abuse, adverse effects, ethical use, indications, misuse, rational use, steroid responsive dermatoses, topical corticosteroids*

What was known?
1. TC are used extensively by dermatologists for various dermatoses.
2. Clinical efficacy and adverse effects of TC vary according to potency of the molecule, vehicle used, site and duration of application, and the age of a patient.
3. Various modifications in the structure of TC molecule have been done to increase the potency which usually also increases the adverse effect profile.
4. They have well-known adverse effects, mostly local.

Introduction

The topical corticosteroids (TC) are among the most commonly prescribed medication in an out-patient dermatology setting since they were first introduced in early 1950s.[1-3] Probably no other group of drugs has had such a profound impact on the speciality as TC. Using them, it has become so much easier to treat several dermatoses which otherwise were the cause of significant morbidity among people.

However, over the years it has become increasingly apparent that TC are being abused by doctors and patients alike. Apart from the well-known indications such as psoriasis, atopic dermatitis, vitiligo, lichen planus, lichen simplex chronicus, discoid lupus erythematosus, etc., they are being used for conditions such as melasma, urticaria, and even undiagnosed skin rash by dermatologists and general physicians.[4] This is because of the quick amelioration of signs and symptoms of many skin disorders by the application of TC in the first instance. This can buy time and hold patient a while longer more so with a nonspecialist. Studies in patients presenting with steroid-related eruptions have shown that there are several nonmedical advisers like friends, neighbors, beauticians, barbers, etc. telling them to use it as fairness/cosmetic creams,[5] anti-acne, anti-fungal therapy and for that matter any skin eruptions.[6] There is a tendency to reuse old prescription for a recurrent or new rash. Prescription sharing with relatives and friends on the presumption that similar looking skin problems can be self-treated by simple prescription copying is rampant. To compound this problem, there is easy availability of these drugs almost for the asking without a valid prescription at every chemist shop. Moreover, store pharmacists also double up as doctors doling out advice about which TC to use. These instances, although reported from many places worldwide,[7-9] have significant impact in our country of a billion plus people with an adverse specialist-to-patient ratio.

The awareness of this significant problem has led to a flurry of activity as evidenced by discussions about TC misuse by dermatologists at various forums in the country and abroad.[5,10-12] Presently, the hope is to contain, if not entirely, reverse TC misuse due to the prevailing situation in our country. As a dermatologist, the onus of responsibility lies on us, for whom these drugs are a strong weapon to fight many skin diseases, to correctly educate the society including our non-dermatologist medical fraternity about ethical and rational use of TC. It is good to recall the Biologist Van Rensselaer Potter who proposed the term "bioethics" in 1970,[13] to encompass a field that lay at the intersection of ethics and the biological sciences in general. The primary goal underlying all ethical issues in health care, in our case the use of TC, is to see that the

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knowledge gained through research should benefit and not cause harm to the society and that knowledge should be disseminated correctly.

Choosing Topical Corticosteroid

A bunch of TC is available for the management of dermatoses. A basic understanding of them certainly helps clinicians to select appropriate preparations that maximize therapeutic efficacy and minimize the potential for adverse effects. For successful treatment with TC, key factors to be considered are accurate diagnosis, selecting the correct drug, keeping in mind the potency, delivery vehicle, frequency of application, duration of treatment and adverse effects, and proper patient profiling.[4]

Know the Disease

The TC are effective for skin conditions that are characterized by hyper-proliferation, inflammation, and immunologic involvement.[14] They are also widely used in the treatment of vesiculo-erosive diseases of the oral mucosa to reduce pain and inflammation.[15] They can provide symptomatic relief for burning and pruritic lesions.[16] Many dermatoses are treated with TC [Table 1], but evidence of effectiveness has been established only for a small number of conditions. It is important to prescribe TC only after having a correct diagnosis in a patient and for those dermatoses where there is reasonable evidence of efficacy. We should strongly resist the temptation to use TC for everything that we do not understand or where nothing else is working. This may provide temporary benefits, but makes diagnosis even more difficult for the next time apart from exposing the patient to the risk of adverse effects. Knowing the correct indication, different strengths of topical steroids may be used to treat different phases of the disease.

Know the Drug

Potency

Potency is the amount of drug required to produce a desired therapeutic effect. The potency of TC is usually assessed by measurement of vaso-constrictive properties.[17] This helps to classify TC based on the extent to which the agent causes cutaneous vasoconstriction ('blanching effect') in a normal, healthy person. This is a useful but not perfect method for predicting the clinical effectiveness of steroids.[18] In fact, the anti-inflammatory potency of some TC may vary among patients, depending not only on the strength of the formulation but also on the frequency of administration, the duration of treatment, and sites of application.[19,20] Sometimes potency may also differ between generic formulations and their brand name equivalent.[16]

Table 1: Steroid responsive dermatoses

Group	Steroid responsive dermatoses
Dermatitis	Atopic dermatitis, lichen simplex chronicus, prurigo, seborrhoeic dermatitis, nummular eczema, cumulative insult dermatitis, allergic contact dermatitis, pompholyx
Papulosquamous	Psoriasis, lichen planus
Pigmentary	Vitiligo
Vesiculo-bullous	Bullous pemphigoid, pemphigus foliaceus, cicatricial pemphigoid
Auto-immune	Lupus erythematosus, dermatomyositis, morphoea
Others	Lichen sclerosis et atrophicus, alopecia areata, keloid, pyoderma gangrenosum, insect bite reactions, early stage of cutaneous T-cell lymphoma, polymorphic eruption of pregnancy

Since the time hydrocortisone was first shown to be clinically effective as a topical preparation in 1952, the molecule has been structurally modified by halogenation, methylation, acetylation, esterification, etc. with the aim to increase potency and reduce adverse effects.[16] The ideal TC is yet to be developed. Modifications such as halogenation increase the potency but also the adverse effects.[21] Esterification has been reported to improve the safety profile while increasing the efficacy of TC.[22]

TC are divided into four groups according to their potency in keeping with the British National Formulary (BNF), while American system classifies them into seven classes,[23] with class I being the super potent or ultra potent and class VII represent the least potent [Table 2]. Although a thorough knowledge of drugs in each class may be ideal, practically a physician should become familiar with one or two agents in each category of potency to safely and effectively treat steroid-responsive skin conditions.

As a general rule, low potency steroids are the safest agents for long-term use, on large surface areas, on the face, or on areas with thinner skin and for children. More potent TC are helpful for severe disease and for thicker skin of palms and soles. High and ultra-high potency steroids should not be used on the face, groin, axillae, and under occlusion; except in rare situations and for short duration.[24]

Vehicle

TC are available in several formulations and with varying strength, which may differ in potency based on their vehicle in which they are formulated. The selection of vehicle depends on the type of lesions and the anatomical region. They are available in ointments, creams, gels, lotions, solutions, etc.[25]

Ointments provide more lubrication and occlusion than other preparations and are the most useful for treating dry and thick, hyper-keratotic lesion. Their occlusive nature adds on to improve steroid absorption. However, they should not be used on hairy area and may cause maceration and folliculitis, if used in intertriginous areas and their greasy nature may result in poor patient satisfaction and compliance.[4]

Table 2: Relative potency of topical corticosteroids*

Topical steroid class American classification	Topical steroid class British classification	Common representative topical steroids	Indications
I	I	Clobetasol propionate 0.05% cream or ointment	Alopecia areata
Superpotent corticosteroids	Very potent	Halobetasol propionate 0.05% cream or ointment	Atopic dermatitis (resistant)
		Betamethasone dipropionate 0.05% ointment	Discoid lupus
II	II	Betamethasone dipropionate 0.05% cream	Hyperkeratotic eczema
Potent corticosteroids	Potent	Fluocinonide 0.05% ointment	Lichen planus
		Halcinonide 0.1% cream	Lichen sclerosus (skin)
		Mometasone furoate 0.1% ointment	Lichen simplex chronicus
III		Betamethasone dipropionate 0.05% lotion	Nummular eczema
Upper mid-strength corticosteroids		Fluticasone propionate 0.005% ointment	Psoriasis
		Triamcinolone acetonide 0.1% ointment	Severe hand eczema
		Halometasone 0.05% cream	
IV		Fluocinolone acetonide 0.025% ointment	Asteatotic eczema
Mid-strength corticosteroids		Mometasone furoate 0.1% cream or lotion	Atopic dermatitis
V	III	Betamethasone valerate 0.1% cream	Lichen sclerosus (vulva)
Lower mid-strength corticosteroids	Moderate	Fluocinolone acetonide 0.025% cream	Nummular eczema
		Fluticasone propionate 0.05% cream	Scabies (after scabicide)
		Hydrocortisone butyrate 0.1% cream	Seborrheic dermatitis
			Severe dermatitis
			Severe intertrigo (short-term)
			Stasis dermatitis
VI		Alclometasone dipropionate 0.05% cream or ointment	Dermatitis (diaper)
Mild corticosteroids		Desonide 0.05% cream	Dermatitis (eyelids)
		Fluocinolone acetonide 0.01% cream	Dermatitis (face)
		Triamcinolone acetonide 0.025% cream	Intertrigo
			Perianal inflammation
VII	IV	Hydrocortisone 1% or 2.5% cream, 1% or 2.5% lotion, or 1%	
Least potent corticosteroids	Mild	2.5% ointment	
		Hydrocortisone acetate (1% or 2.5% cream, 1% or 2.5% lotion, or	

Courtesy *Adapted from Ference JD, Last AR. Choosing topical corticosteroids. Am Fam Physician 2009;79:135–140

Creams have good lubricating qualities and their ability to vanish into the skin make them cosmetically appealing. For acute exudative inflammation and in intertriginous areas, creams are better for their nonocclusive and drying effect. Creams are generally less potent than ointment of the same medication, but they often contain preservatives which can cause irritation, stinging, and allergic reaction.[4]

Lotion and gels are the least greasy and occlusive of all topical steroid vehicles. Lotions are useful for hairy areas because they penetrate easily and leave little residue. Gel dry quickly and can be applied on the scalp or other hairy areas as they do not cause matting.[26,27] Foams and mousses and shampoo are effective vehicle for delivering steroid to the scalp but are costly.

Occlusion increases steroid penetration and can be used in combination with all vehicle. Simple plastic dressing results in a seven-fold increase in steroid penetration compared with dry skin.[16] However irritation, folliculitis and infection can develop rapidly from occlusive dressings and patients should be counseled to monitor the treatment site closely. Applying a topical steroid after a shower or bath improves its effectiveness due to hydration.[28] Flexural areas such as groin, axillae, infra-mammary are self-occlusive where vehicles such as ointments should be avoided.

Dose, frequency of application, and duration

Sometime the most well-meaning dermatologist and other medical care givers fail to spend enough time with the patient. All of us come across instances when vastly different clinical efficacy and/or adverse effect profile is

seen for the same TC given for similar indication in two different patients. This is because without proper guidance, patients differ greatly in the way they would use TC in terms of the amount, the frequency, and duration of use thus causing differences in the efficacy and the harm profile they experience. Rational use involves putting across proper guidelines in this area.

With regards to the quantity of TC, the standardized technique devised by Long and Finley,[29] which uses the "finger tip unit" (FTU), has been recommended to measure the amount of ointment necessary for a specific anatomic area. A FTU is defined as the amount that can be squeezed from the finger tip to the first crease of the finger with a 5 mm diameter nozzle. Using a standard nozzle tube, one FTU equals 0.5 g cream/ointment.[30]

The use of FTU is greatly promoted worldwide to reduce the variation in uses of TC and to encourage adherence to therapy. The recommended doses in terms of FTU will depend on which part of the body is being treated. This is because the skin is thinner in certain parts of the body and more sensitive to the effects of TC. Tables 3 and 4 show guidelines as to the amount of ointment needed in adult and children, respectively, based on specific anatomic areas.

Table 3: FTU guidelines for adults*

Guidelines for adults		
Anatomic area	**FTU required**	**Amount needed for twice daily regimen in g**
Face and neck	2.5	2.5
Anterior and posterior trunk	7	7
Arm	3	3
Hand (both sides)	1	1
Leg	6	6
Foot	2	2

*Adapted from Long and Finaly[29]

Table 4: FTU guidelines for children*

Guidelines for children				
Anatomic area	**FTU required**	**Amount needed for twice daily regimen in g**		
	3–6 months	**1–2 years**	**3–5 years**	**6–10 years**
Face and neck	1/1	1.5/1.5	1.5/1.5	2/2 g
Arm and hand	1/1	1.5/1.5	2/2	2.5/2.5
Leg and foot	1.5/1.5	2/2	3/3	4.5/4.5
Anterior trunk	1/1	2/2	3/3	3.5/3.5
Posterior trunk and Buttocks	1.5/1.5	3/3	3.5/3.5	5/5

Courtesy *Adapted from Long CC, Mills CM, Finaly AY. Br J Dermatol 1998;138:293–6.

In practice once or twice daily application is recommended for most conventional TC preparations.[16] Some newer formulations have been prepared for once daily application.[31] Even for the former, more frequent administration does not provide better results.[32] In atopic dermatitis a well-documented steroid responsive dermatosis, 10 randomized controlled trials compared once daily versus more frequent applications of ten within the same potency group were reviewed. The findings are summarized in UK Health Technology Assessment report and guidance from the National Institute for Health and Clinical Excellence (NICE).[33] None of the studies found clear evidence that applying TC more than once a day produced better overall clinical outcomes in eczema. On the other hand, frequent use of TC leads to several local and systemic side effects. A change to once daily application was suggested several years ago. Perhaps the biggest barrier to this has been our habit.[34]

It is also a well known fact that the stratum corneum acts as a reservoir for TC. An ultra-potent TC such as clobetasol propionate 0.05% cream was found to persist in stratum corneum till day four.[35] Due to this cumulative depot effect, an alternate or even twice a week application of TC can be advocated. Once a condition is in remission or under desired control weekend TC separated by weekdays of emollients or steroid sparing agents also is quite rewarding. By doing so, the benefits of the therapy can be maximized, the cost can be reduced, and local and systemic adverse effects of TC can be decreased.[14,36] All these factors will improve the patient compliance. For an individual patient, the optimal dosing schedule can be determined by trial and error, titrating to the minimum frequency of application that still provides relief.

Generally most of the TC, regardless of the potency, should not be used for more than 2–4 weeks duration at a stretch. If there is worsening of the lesions or no change noticed, the product needs to be discontinued and re-evaluation of the diagnosis is needed. Super potent and potent preparations are specifically recommended for a maximum duration of only 2 weeks followed by a tapering regimen for maintenance to avoid adverse effects.[4,16]

Adverse effects of TC

TC are used primarily for their anti-inflammatory properties. Paradoxically, the same mechanisms which mediate their anti-inflammatory properties and underlie their usefulness are also responsible for their adverse effects.[37] Besides the cutaneous and systemic adverse effects [Table 5], the phenomenon of steroid addiction, tachyphylaxis, and contact dermatitis (CD) due to TC also needs to be borne in mind.

Local effects

They are encountered more frequently and have become more prevalent with the introduction of high potency TC.[30] These side effects depend on potency of steroid, duration of use (i.e. extended period), volume of the product applied (i.e. excessive amount), site of application, age of the patient and occlusion (if present).

Table 5: Common adverse effects of topical corticosteroids*

Topical corticosteroids (adverse effects)		
	Cutaneous	**Systemic**
Striae distensae	Milia	Hypothalamic-pituitary-adrenal axis suppression
Cutaneous atrophy	Masking fungal infection (tinea incognito), worsening of herpes, demodex, scabies, candidiasis	
Stellate pseudoscars		Cushing's disease
Telangiectasia		Femoral head osteonecrosis
Purpura		Cataracts
Erythema	Granuloma gluteale infantum	Glaucoma
Perioral dermatitis	Hypertrichosis	Decreased growth rate
Rosacea	Photosensitisation	Hyperglycemia
Acne	Hypopigmentation	Hypertension
Rebound erythema	Hyperpigmentation	Hypocalcemia
Steroid addiction	Contact dermatitis	Peripheral edema
Topical steroid dependent face	Tachyphylaxis	

Courtesy *Adapted from Hengge *et al*.[38]

These include, atrophy, striae, telengiectasis, purpura, hypopigmentation, acneiform eruptions, rosacea-like perioral and periorbital dermatitis, and hypertrichosis.[38-53] The normal presentation of superficial infections can be altered when TC are inappropriately used to treat bacterial or fungal infections. A typical example of this is seen when someone applies a TC to an itchy groin rash. If this is a fungal infection, the rash gets redder, itchier, and spread more extensively than a typical fungal infection. The resulting rash is a bizarre pattern of widespread inflammation with pustules called tinea incognito [Figure 1].

Due to inappropriate and uncontrolled use of TC, an under reported and under stressed entity has evolved, namely TC addiction. Convincing arguments have been put to consider several erythema syndromes such as red face syndrome, post-peel erythema, red scrotal syndrome, vulvodynia, perianal atrophoderma, chronic actinic dermatitis, and chronic recalcitrant eczemas under the umbrella of steroid addiction.[54,55] Prolonged and continuous uses of TC on face lead to the development of dermatoses which has been named variously by different workers. In our scenario, it is called "topical corticosteroid-induced rosacea-like dermatitis" (TCIRD)[10] or "topical steroid-dependent face" (TSDF).[11] This has a distinct clinical presentation. Patients are mostly females who keep on using the steroidal cream till they get magical response and continue it later to prevent rebound flare till finally the lesions become persistent [Figure 2].

Systemic effects

Topically applied high and ultra high potency TC can be absorbed well enough to cause systemic side-effects. Hypothalamic-pituitary-adrenal suppression, glaucoma, hyperglycemia, hypertension, and other systemic side-effects have been reported, though rare.[54-58]

Most of the adverse reactions may be reversible to some extent upon discontinuation, with the exception of atrophic striae [Figure 3], which are not reversible.[4,16] Rebound of pre-existing dermatoses has also been reported to occur with abrupt discontinuation, especially with potent preparations. TCIRD/TSDF is very difficult to manage due to a compromised epidermal barrier as well as due to rebound flare up of skin lesions.[10,11]

It has been suggested that corticosteroid effects are due to their action on gene expression by two different mechanisms; transrepression responsible for most therapeutic effects and transactivation which mediates a large proportion of adverse effects. Selective novel glucocorticoid receptor agonists are being developed that exhibit relative dissociation between transrepression and transactivation. This may in future lead to development of a novel class of TC devoid of significant adverse effects.[59]

Tachyphylaxis

It is the tolerance that skin develops to the vasoconstrictive action of TC. After repeated use of topical steroids, the capillaries in the skin do not constrict well, requiring higher dose or more frequent application of the steroid. The ability of the blood vessels to constrict returns four days after stopping therapy.[60,61]

It is now suggested that either poor patient compliance or the natural course of disease activity (unrelated to the therapy) may be the main reason behind tachyphylaxis.

For this reason, instituting, "weekend therapy" or "pulse therapy" may at least resolve the compliance issue. If a TC loses its effectiveness, it should be discontinued for 4–7 days and then restarted.[16]

Cross sensitization and cross reactivity

Contact dermatitis due to TC is not uncommon. The

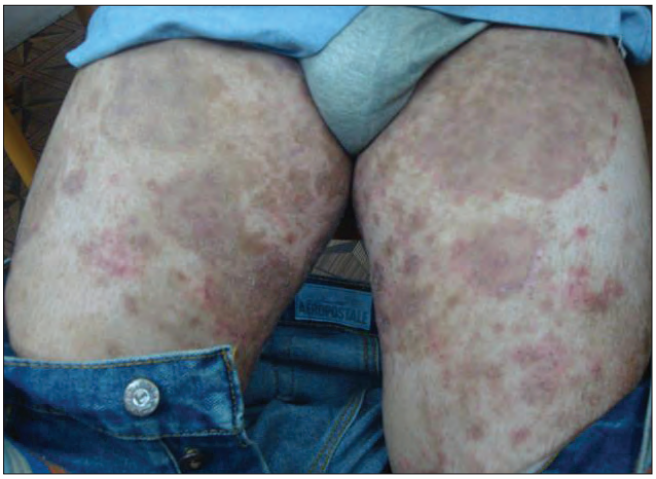

Figure 1: Bizarre pattern of tinea cruris (tinea incognito)

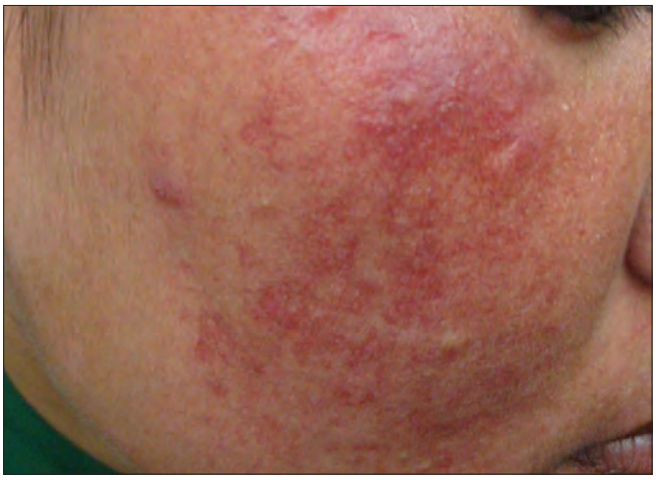

Figure 2: Erythema with papulo-pustules on face (TCIRD)

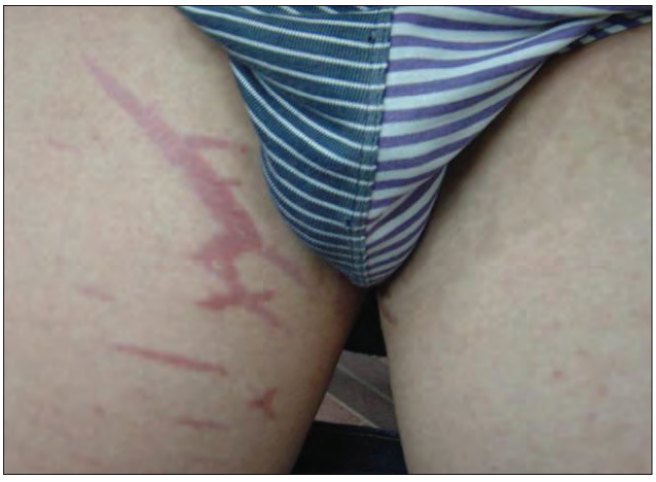

Figure 3: Atrophic striae on groin

estimated prevalence was found to be in the range of 0.2–6% in previous studies.[62-67] Nonfluorinated corticosteroids are more likely to cause CD. It should be considered whenever there is no satisfactory resolution, or worsening of lesions after excluding exacerbation of an undiagnosed infection. Sometimes worsening of a longstanding chronic expanding eczematous rash despite TC use may be due to the phenomenon of corticosteroid addiction, a well-defined entity which may be mediated by an underlying increase in serum nitric oxide levels.[68] It is worthwhile to know whether there is true sensitivity to the TC itself or to one of the constituents or preservatives present in the vehicle. A skin patch test can be used to detect and confirm sensitivity to corticosteroids.

Know the patients

It helps to keep in mind the age, sex, underlying special physiological conditions like pregnancy, lactation, and also the expectation of the patient besides the site and extent of involvement when prescribing TC.[1,4,30]

TC have to be used with caution in children and elderly due to larger surface area to body weight ratio and poor skin barrier function in the former and skin fragility in the latter, respectively.[69] Female patients are more prone to steroid adverse effects due to their tendency to use TC indiscriminately. Since there are no well-controlled studies of the teratogenic potential of most of the TC in pregnancy, they are categorized as pregnancy category C and thus recommended to be used only if the potential benefit justifies the potential risk to the fetus.[38] During lactation, they are to be used with caution. It is known that peer pressure, rapid feel good effect, and ignorance about harmful effects of TC also lead to continuation of treatment beyond prescribed time.[9] Time spent in educating on these points will prevent mishaps. It will also take care of the other extreme of excessive fear of using TC which leads to inadequate usage and poor clinical results.

In normal healthy skin, absorption of TC varies from region to region. Penetration varies between the eyelids and the sole by nearly 300 folds.[70] In diseased states, due to defective epidermal barrier, the penetration of TC can be two to ten folds higher. Areas with thick stratum corneum, such as palms and soles need to be treated with high potency preparations.[4,30] Conversely, areas with thin stratum corneum such as eye lid or areas of occlusion like groin and axilla and other intertrigenous areas need to be treated with medium to low potency preparations.[1,4,30] In the flexural areas, as mentioned before there will be the additional physical effect of occlusion by skin folds that will also enhance absorption. When large surface areas are involved, treatment with a low to medium potency preparation is needed because of the increased risk of systemic absorption. Monitoring of all these variables is constantly required for treatment with TC to be safe and effective.

Conclusions

We will quickly realize that despite the best efforts undertaken at our level, many of these problems will continue to persist because they were not contributed by us alone. To address them, interventions have to be multidimensional,

involving political, educational and legal approaches.[9] Opportunity may have to be seized by the leadership of Indian Association of Dermatologists, Venereologists and Leprologists at every available forum. Political leaders and government officials should be repeatedly apprised of the prevailing situation and the need to curb this menace. Use of media for public education on topical steroid misuse is warranted, and the involvement of general practitioners, nurses. and pharmacists is needed. The legal approach should include the enforcement of the existing legislation related to the control of these drugs, so that TC are not sold without proper prescriptions. Pharmaceutical companies should be made to ensure proper labeling of TC products which should include inserts containing clear "finger tip unit" instruction, preferably with images and chart to show the numbers of unit required for specific areas of the body.[71] This will greatly help in optimal and safe use of TC. The legal aspect should also include measures aimed at strengthening the ethical responsibilities of pharmacists in correctly advising patients about the safety of medicines bought over the counter. Once the measures are in place and working, we hopefully may see the beginning of the reversal of the misuse/abuse of TC and the consolidation of the well-established benefits of this wonderful group of drugs.

Optimizing the use of TC

- To prescribe for the appropriate dermatoses.
- To use appropriate potency and strength of TC to achieve disease control.
- To maintain with a less potent preparation or reduce frequency of application after satisfactory response.
- To taper off the treatment upon complete remission of skin diseases.
- To be extra careful when prescribing topical steroid over certain locations (e.g. scrotum, face, and flexures).
- To be especially considerate when prescribing to the elderly and children.
- To be aware of the adverse effects and act immediately to counteract them.
- To avoid home-made dilutions of TC and prescribing TC in combination with antimicrobial and antifungal.
- To resist temptation to use TC for an undiagnosed rash; this makes the possibility of correct diagnosis even bleaker in the future.

What is new?

1. Abuse or misuse of TC becoming a great cause concern due to their dramatic clinical effects, peer pressure to use them for cosmetic purpose, easy availability of products, inadequate information of their adverse effects, and phenomenon of steroid addiction.
2. TCIRD, TSDF newly defined TC-specific adverse effects.
3. Attempts are ongoing to develop the ideal TC having increased potency without significant adverse effects. Esterification found to improve the safety profile.
4. Evidence-based studies suggest once daily application at par with more frequent applications even in the cases of conventional TC. Weekend or pulse therapy with TC prevents tachyphylaxis.
5. Intervention to prevent steroid addiction, misuse, or abuse has to be multidimensional.

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Announcement

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Cutaneous Manifestations of Internal Malignancy

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Abstract

Background: Many malignancies affecting the internal organs display cutaneous manifestations which may be either specific (tumor metastases) or nonspecific lesions. **Aims:** The study is aimed at determining the frequency and significance of cutaneous manifestations among patients with internal malignancy. **Materials and Methods:** 750 cases of proven internal malignancy, who attended a cancer chemotherapy center in South India, were studied. Specific infiltrates were confirmed by histopathology, fine needle aspiration cytology (FNAC) and marker studies. **Results:** Out of the 750 patients with internal malignancy, skin changes were seen in a total of 52 (6.93%) patients. **Conclusion:** Cutaneous metastases (specific lesions) were seen in 20 patients (2.66%): contiguous in 6 (0.8%), and non-contiguous in 14 (1.86%). Nonspecific skin changes were seen in 32 patients (4.26%). None of our patients presented with more than one type of skin lesions. Herpes zoster was the most common nonspecific lesion noticed in our patients, followed by generalized pruritus, multiple eruptive seborrheic keratoses, bullous disorder, erythroderma, flushing, purpura, pyoderma gangrenosum, insect bite allergy and lichenoid dermatitis.

Key Words: *Cutaneous metastases, internal malignancy, contiguous, non-contiguous*

What was known?
Internal malignancy spreads to skin either by contiguous or non-contiguous mode. Cutaneous metastases (specific lesions) generally occur in later stages. Skin coloured nodules at multiple sites are the most common clinical presentation of Cutaneous metastases . Non-specific skin lesions can also manifest in cases of internal malignancy.

Introduction

Cutaneous metastasis from an internal malignancy is rare and it indicates the later stage. Malignancies which affect internal organs may display cutaneous manifestations, which may be the presenting symptoms and signs of the underlying malignancy.

The aims of the study were to determine the frequency and significance of cutaneous manifestations of internal malignancies among the patients attending a cancer chemotherapy center.

Materials and Methods

Seven hundred and fifty patients with internal malignancies involving various organs, attending the Cancer Chemotherapy Department of Government General Hospital, Chennai, were recorded for a period of 3 years from 2005 to 2008. In our Institution, during the study period, it was not considered mandatory to obtain approval of Ethical Committee for conducting clinical study, and hence it was not obtained.

Data regarding history about the duration of the malignancy and the duration between the onset of malignancy and the skin changes, relapse of malignancy and the symptoms of cutaneous lesions were obtained. Clinical examination including the cutaneous and systemic examination, hematological, radiological and cytological investigation was done to confirm the nature and site of malignancy. Histopathology of the cutaneous lesions, suggestive of metastasis from an internal organ, was obtained. Fine needle aspiration cytology (FNAC) and T cell marker studies were done wherever necessary.

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Results

Out of the 750 patients studied, 52 (6.93%) had cutaneous manifestations, 20 (2.66%) had cutaneous metastases (specific lesions) and 32 (4.26%) had nonspecific skin lesions.

65% were males and 35% were females. The most common age group affected was in fifth and sixth decades of life. Overall, the most common malignancies were leukemia and lymphomas (19.2%), followed by carcinoma breast (13.46%), carcinoma stomach (11.5%), carcinoma cervix (5.76%), carcinoma of the prostate (5.76%) and carcinoma of the buccal mucosa (5.76%). The other malignancies encountered in our study in descending order of frequency were malignant melanoma, seminoma, carcinoma esophagus, carcinoma pharynx, hepatocellular carcinoma, astrocytoma, pheochromocytoma, secondaries in the neck with unknown primary.

In males, non-Hodgkin's lymphoma (NHL) (26.47%) [Figure 1] was the most common malignancy producing skin lesions, followed by leukemias (14.7%) and carcinoma stomach (14.7%).

In females, the most common malignancy was carcinoma

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breast (38.88%) [Figure 2a, b], followed by leukemia (27.77%), carcinoma cervix (16.66%), NHL (5.55%), carcinoma stomach (5.55%) and astrocytoma (5.55%).

Of the specific skin infiltrates, contiguous cutaneous metastases were seen in 6 (11.53%) patients and non-contiguous metastases in 14 (26.92%) patients [Tables 1 and 2]. Skin-colored nodules were the most common, followed by erythematous and hyperpigmented papules and plaques.

Of the nonspecific lesions, herpes zoster was the most common (11 patients) followed by generalized pruritus, multiple eruptive seborrheic keratoses, bullous disorders, erythroderma, flushing, purpura, systemic lupus erythematosus, pyoderma gangrenosum, insect bite allergy and lichenoid dermatitis.

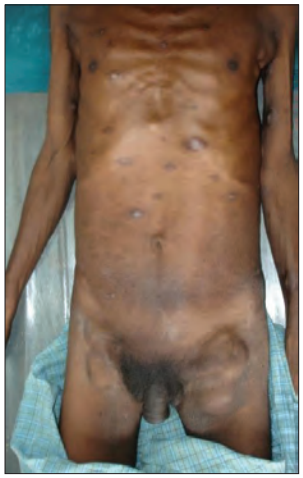

Figure 1: A case of non-Hodgkin's lymphoma having inguinal nodes and skin-colored nodules over chest and abdomen

Table 1: Contiguous metastases

Skin lesions	Sites	Type	No. of patients
Nodules, ulcer, papule	Chest wall	Carcinoma breast	3
Plaque, ulcer	Right nipple	Carcinoma right breast	1
Plaque	Left cheek	Carcinoma buccal mucosa	1
Nodules, plaque	Right neck and chest	Amelanotic melanoma – right cheek	1

Discussion

Skin often mirrors changes in the internal milieu. Skin metastases may herald the recurrence of malignancy after treatment. Cutaneous metastasis can arise at any age. However, most cutaneous metastases occurred during or after the fifth decade as in the present study.[1] The period of interval between the onset of symptoms of the primary malignancy and the onset of cutaneous metastases ranged from 2 months to 5 years. The shortest duration was 2 months in the case of acute myleoid leukemia and the longest was 5 years in the case of carcinoma breast.

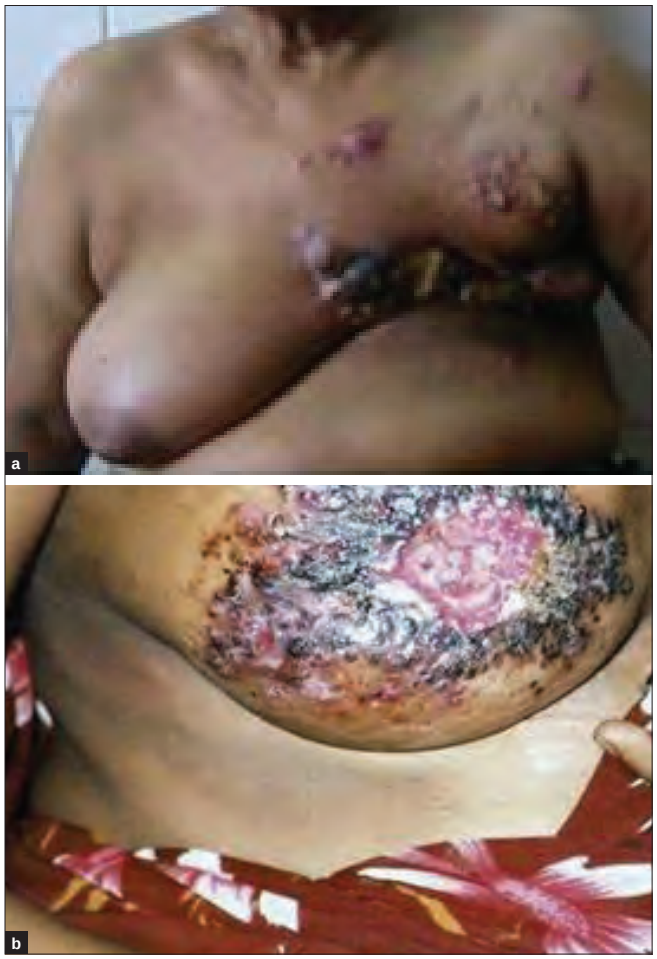

Figure 2: (a) Metastatic carcinoma breast showing multiple nodules and papules following surgery. (b) CA breast (right) with ulcerative plaque eroding nipple and areola

Table 2: Non-contiguous metastases

Type of skin lesion	No. of lesions	Sites	Type of malignancy	No. of patients
Papules, plaques, nodules	Multiple	Upper limb, chest, abdomen	Acute myeloid leukemia	2
Plaque	Single	Lower limb	Chronic lymphocytic leukemia	1
Papules, ulcers, nodules	Multiple	Upper limb, chest, abdomen, face, neck, pelvis, lower limb	Non-Hodgkin's lymphoma	5
Nodules	Multiple	Scalp, face, chest, abdomen	Carcinoma stomach	2
Plaque	Single	Face, abdomen	Carcinoma esophagus	2
Nodules	Multiple	Abdomen, back, lower limb	Carcinoma pharynx	1
Nodules	Multiple	Neck, chest	Malignant melanoma	1

Cutaneous metastatic lesions are usually multiple and may range from 1 to 100.[2] In our study, 5 out of 6 cases with contiguous metastases and 11 out of 14 cases of non-contiguous metastases had multiple lesions. Skin-colored nodules at multiple sites were the most common clinical presentation of cutaneous metastases. We also encountered plaques, papules, and ulcers in decreasing order of frequency. The site of localization of metastasis depends upon mode of spread of the primary tumor, whether it is by lymphatics or hematogenous.

The common malignancies that give rise to cutaneous metastases are carcinoma of the lung and colon in males and carcinoma of the colon and ovary in females. Overall, melanomas are the most common, followed by carcinoma breast, carcinoma oral cavity, lungs, colon, and ovary.[3] In this study, NHL was the most common neoplasm to produce cutaneous metastases, followed by carcinoma breast and leukemia. However, this observation could not be taken as actual reflection of prevalence in South India, as our hospital is a tertiary referral center.

Contiguous spread was more common in females (66.6%) than males (33.3%), while non-contiguous metastases were more common in males (85%) than females (15%). This difference could be because the malignancy encountered in both sexes is different.

In the present study, carcinoma breast was the most common (66%) neoplasm causing direct extension to skin, followed by carcinoma buccal mucosa and amelanotic melanoma [Figure 3a, b]. This finding corroborates with the literature reports.[4] NHL was the most common neoplasm to produce non-contiguous metastases, followed by gastrointestinal malignancies (28.5%) [Figure 4a, b] and leukemia (21.4%), especially acute myeloid leukemia. The most common sites involved by cutaneous metastases in their order of occurrence were as follows:
Anterior chest wall, anterior abdominal wall, lower limb, neck, back, upper limb, face, pelvis, scalp.

This finding corroborates with similar findings reported by Brownstein *et al*.,[3] Rajagopal *et al*.[5] and Tharakaram[6] [Table 3].

Among the nonspecific skin manifestations with internal malignancy, herpes zoster (27%) came first. Carcinoma breast was the most common malignancy associated with herpes zoster, while carcinoma cervix

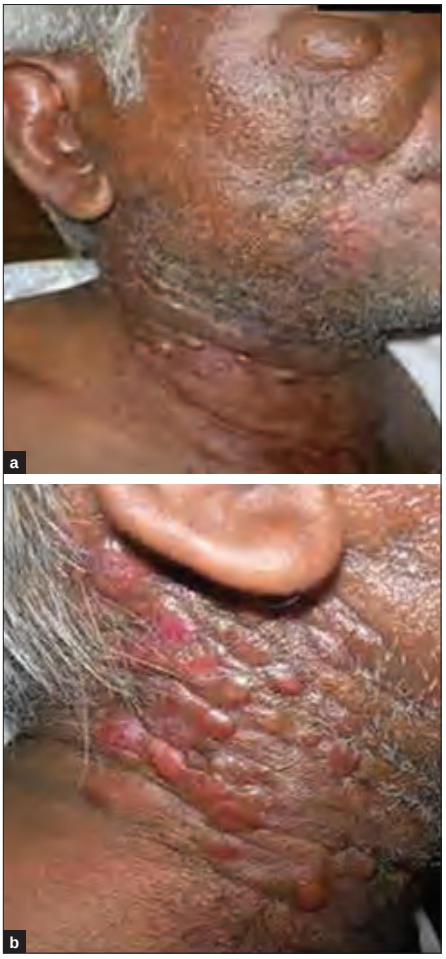

Figure 3: (a, b) Amelanotic melanoma over right cheek with multiple nodules over neck

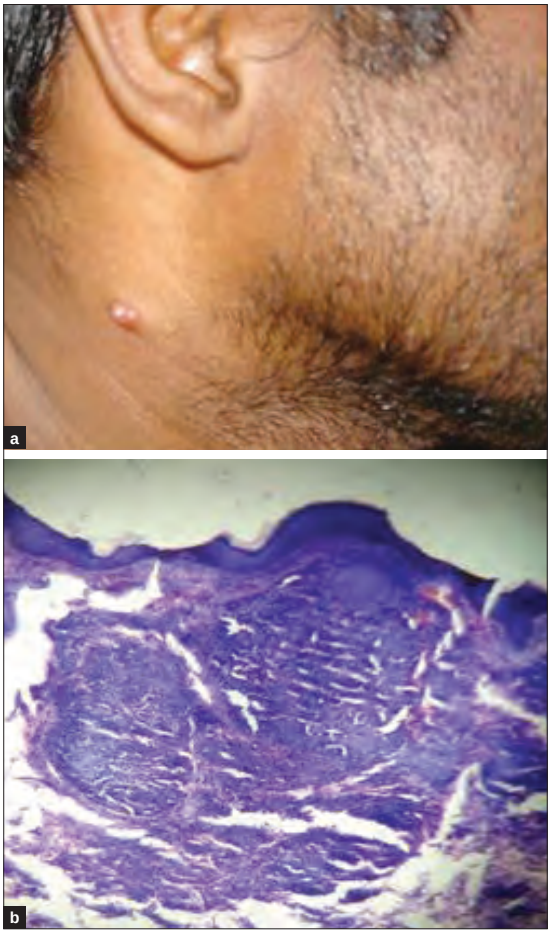

Figure 4: (a) A case of carcinoma stomach showing a single nodule over neck. (b) Histopathology of the nodule shows collection of atypical epithelial cells in upper dermis

Table 3: Comparison of sites of cutaneous metastases

Sites	Brownstein *et al.* (%)	Tharakaram *et al.* (%)	Rajagopal *et al.* (%)	Present study (%)
Scalp	5	8	10	4
Face	6	5	14	9
Neck	12	6	5	11
Upper limb	6	10	10	9
Lower limb	4	11	19	13
Chest	31	26	32	21
Abdomen	20	16	-	17
Back	8	15	5	11
Perineum	8	3	5	5
Total	100	100	100	100

(18%) was the second. Among 11 patients, 6 had single dermatomal involvement, 2 had disseminated and 3 had multidermatomal involvement. According to literature, disseminated herpes zoster is commonly associated with underlying malignant disease.[7]

We encountered paraneoplastic pemphigus in two patients. One of them had NHL which was reported as the most common neoplasm associated with paraneoplastic pemphigus in a study by Anhalt *et al*.[8] The other patient had paraneoplastic pemphigus in association with secondaries in the neck. In this patient, FNAC of the neck showed atypical squamous cells. Both the patients expired. Skin manifestation as the first sign of internal malignancy was noted in another two patients. One of them was a case of hepatocellular carcinoma presenting with pruritus. Another was an elderly man who presented with erythroderma and was diagnosed to have Sézary syndrome on further systemic examination and investigations. One of our patients with carcinoma prostate developed bullous pemphigoid which is also reported in the literature.[4] In the present study, generalized pruritus was noticed in three patients with hepatocellular carcinoma, polycythemia vera and carcinoma stomach. Pruritus was observed as a common manifestation among patients with internal malignancy compared to controls in the study by Rajagopal *et al*.[5] Three patients had multiple eruptive seborrheic keratoses and the most common malignancy associated was carcinoma stomach which corroborates with the literature reports.[4] We encountered a patient with pronounced flushing involving the face and chest, associated with pheochromocytoma, and similar association is reported in literature.[4] A known case of acute myeloid leukemia presented with purpura, which is a well-known association.[4]

Survival period in patients with cutanenous metastasis is said to be around 3 months.[9] Early death in these patients could be due to undetected secondaries in visceral organs and high-grade malignant nature of the primary tumor. In our study, 23 out of 52 patients (44%), were lost to follow-up, and among the remaining 29 patients, 13 (44%) succumbed to their illness during the study period. Seven patients (54%) showing specific cutaneous metastasis expired in the period of 2–6 months, whereas 6 patients (37%) showing nonspecific cutaneous changes expired during the period of 14 days to 8 months [Table 4].

Table 4: Period of survival

Primary neoplasm	Period of survival after the onset of skin manifestation (in months)
Carcinoma breast – contiguous metastasis	4
Carcinoma breast – contiguous metastasis	6
Carcinoma stomach – non-contiguous metastasis	3
NHL – non-contiguous metastasis	4
Carcinoma pharynx – non-contiguous metastasis	4
NHL relapse – non-contiguous metastasis	2
Malignant melanoma – non-contiguous metastasis	6
Nonspecific manifestations	
Paraneoplastic pemphigus – secondaries in the neck	6
Paraneoplastic pemphigus – NHL	8
Herpes zoster – carcinoma stomach	5
Herpes zoster disseminated – chronic lymphocytic lymphoma	3
Pruritus – ca stomach /secondaries in the liver	2
Pruritus – hepatocellular carcinoma	0.5

Shortest survival period (2 months) was seen in a patient who had a recurrence of NHL. Two patients with carcinoma breast, who developed recurrence of malignancy after surgery, expired in 4 months and 6 months, respectively. Shortest survival period in patients showing nonspecific cutaneous metastases was 14 days in a patient with hepatocellular carcinoma. Both the paraneoplastic pemphigus patients expired within 6 months and 8 months, respectively.

Conclusion

Cutaneous metastases indicating a sign of recurrence and widespread metastases have poor prognosis and the survival period is reduced. Though the skin is an infrequent site for metastasis and is only the 18th most common site, skin lesions offer easily accessible tissue for biopsy and histopathologic examination.[10] Systemic response to any particular chemotherapeutic agent can be assessed by the visible regression of skin metastasis. Cutaneous metastases are important to recognize because they may precede internal visceral metastases and early recognition helps in prolonging the survival of the patient.

What is new?
Non Hodgkin's Lymphoma is the most common neoplasm that produces cutaneous metastases followed by carcinoma breast and leukemia. Herpes zoster is the commonest non-specific lesion in internal malignancy.

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Announcement




Department of Dermatology, Venereology & Leprosy and Department of Pathology, Father Muller Medical College

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Netherton Syndrome in One Chinese Adult with a Novel Mutation in the Spink5 Gene and Immunohistochemical Studies of Lekti

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Abstract

Background: Netherton syndrome (NS) is a severe autosomal recessive ichthyosis. It is characterized by congenital ichthyosiform erythroderma, trichorrhexis invaginata, ichthyosis linearis circumflexa, atopic diathesis, and frequent bacterial infections. The disease is caused by mutations in the SPINK5 (serine protease inhibitor Kazal-type 5) gene, a new type of serine protease inhibitor involved in the regulation of skin barrier formation and immunity. We report one Chinese adult with NS. The patient had typical manifestation of NS except for trichorrhexis invaginata with an atopic diathesis and recurrent staphylococcal infections since birth. **Aims:** To evaluate the gene mutation and of its product activity of SPINK5 gene in confirmation of the diagnosis of one Chinese adult with NS. **Materials and Methods:** To screen mutations in the SPINK5 gene, 33 exons and flanking intron boundaries of SPINK5 were amplified with polymerase chain reaction (PCR) and used for direct sequencing. In addition, immunohistochemical staining of LEKTI (lymphoepithelial Kazal-type-related inhibitor) with specific antibody was used to confirm the diagnosis of NS. The results were compared with that of healthy individuals (twenty-five blood samples). **Results:** A G318A mutation was found at exon 5 of patient's SPINK5 gene which is a novel missense mutation. The PCR amplification products with mutation-specific primer were obtained only from the DNA of the patients and their mother, but not from their father and 25 healthy individuals. Immunohistochemical studies indicated there was no LEKTI expression in NS patient's skin and there was a strong LEKTI expression in the normal human skin. **Conclusion:** In this report, we describe heterozygous mutation in the SPINK5 gene and expression of LEKTI in one Chinese with NS. The results indicate that defective expression of LEKTI in the epidermis and mutations of SPINK5 gene are reliable for diagnostic feature of NS with atypical clinical symptoms.

Key Words: *Mutation, Netherton syndrome, SPINK5 gene*

What was known?
The defective gene for NS has been cloned on chromosome 5q32 and it is termed SPINK5.

Introduction

Netherton syndrome (NS; MIM 256500) is a rare severe autosomal recessive disease characterized by congenital ichthyosiform erythroderma (CIE), ichthyosis linearis circumflexa (ILC), "bamboo hair" (trichorrhexis invaginata, TI), and atopic diathesis with high serum IgE levels. Most patients with NS are typically born with a severe scaly erythroderma which can persist throughout life or vary into a milder phenotype known as ILC.[1,2] ILC is characterized with migratory, polycyclic or serpiginous patches with double-edged scaling borders. The defective gene for NS has been cloned on chromosome 5q32 and it is termed SPINK5 (serine protease inhibitor Kazal-type 5).[3] The SPINK5 gene consists of 33 exons and encodes a putative serine protease inhibitor called LEKTI (lymphoepithelial Kazal-type-related inhibitor) which harbors 15 potential inhibitory domains.[3] LEKTI is a new type of serine protease inhibitor with antitrypsin activity. It is expressed in epidermal and mucosal surfaces, tonsils, and thymus. In the epidermis, LEKTI is strongly expressed in the uppermost spinous and granular layers, and is considered to play an essential role in skin barrier formation through inhibiting activities of several proteases[4,5] and may play a role in local anti-inflammatory and/or antimicrobial effects. Chavanas *et al*., reported pathogenic mutations of SPINK5 in NS.[3] To date, more than 40 pathogenic mutations of NS have been reported in the SPINK5 gene,[3,4,6-9] resulting in premature termination codons. Such mutations often cause extensive degradation of the SPINK5 transcripts probably due to nonsense-mediated mRNA decay[3,6] which is predicated to lead to LEKTI deficiency.

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Materials and Methods

Subjects

An 18-year-old Chinese girl with scaly erythroderma came to our hospital in 2006. At her birth, she had generalized erythroderma with exfoliative scaling which accentuated in the cheeks, scalp and the flexor surface of elbows and knees. However, the generalized erythroderma disappeared gradually in five months after her birth and remained in the palmoplantar regions. The patient had profuse amount of fine, dry, flaky, branny desquamation, involving the entire scalp and ILC remained localized along with

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atopy. The patients didn't display characteristic hair shaft abnormalities, particularly trichorrhexis invaginata (bamboo hair) and torsion twists. The patient showed good responses to corticosteroid hormone and irritation to acitretin. Laboratory blood tests were normal except for the serum IgE levels (2176 IU/ml) and IgE antibody. No other abnormalities were observed by other physical and radiological examinations. Her parents were unaffected and there was no consanguinity.

Source of DNA

After obtaining signed informed consent from her parents and the approval of the ethics commission in Department of Guangzhou Institute of Dermatology, peripheral leukocyte DNA was prepared from peripheral blood of the patient and her parents using standard protocols. Genomic DNA was also extracted from 25 blood samples obtained from healthy individuals as controls. The study was conducted in accordance with the Declaration of Helsinki guidelines.

Analysis of the SPINK5 gene

The genomic DNA samples from the patients, their parents, and healthy individuals were then subjected to mutation screening by amplifying the segments of SPINK5 gene with PCR. All 33 exons and flanking intron boundaries of the SPINK5 gene were amplified for direct sequencing. The primers for the SPINK5 gene were designed as previously reported[6,10] and synthesized on the basis of intronic sequences. For polymerase chain reaction (PCR) amplification, approximately 200 ng of genomic DNA, 12.8 pmol of each primer, 10 μmol of deoxyribonucleoside, and 1.25 U of Ampli Taq Gold (Perkin Elmer, Roche Molecular Systems, Inc., Branchburg, NJ, U.S.A.) were used in a total volume of 50 μL. PCR reaction were performed at 94°C for 5 min followed by 35 cycles of 94°C for 45 s, annealing 45 s at 60°C and 45 s at 72°C with a final extension at 72°C for 10 min. The amplified PCR fragments were run on 1.5% agarose gels. The PCR products were examined on 2% agarose gel [Figure 1] and purified by QIAquick columns (Qiagen, Chatsworth, CA, U.S.A.) followed by direct DNA sequencing with an ABI 377 automatic sequencer (Advanced Biotechnologies, Columbia, MD, U.S.A.) with both forward and reverse primers.

Immunohistochemistry

All reagents and chemicals were purchased from Sigma (Poole, UK) unless otherwise stated. Formalin-fixed paraffin-embedded skin samples from patient and normal Chinese individual were cut into 5-μm sections and mounted on silane-coated slides. Immunohistochemistry using mouse monoclonal antibodies (Zymed laboratories, South San Francisco, CA) against N-terminal D1-D6 domains of LEKTI was performed by the following protocol described previously.[5] Tissue samples were fixed in 10% neutral buffered formalin. Tissue sample with 4-μm were prepared from paraffin-wax-embedded tissues and their reactivity with LEKTI antibodies was studied by immunohistochemistry. Prior to immunodetection, specimens were deparaffinized, rehydrated and processed as described.[5] Antigen retrieval of dewaxed sections was performed by heat-treatment for 40 min using a water bath at 95°C in 10 mM citrate buffer (pH 6.0) containing 1% Tween 20, or using the Target Retrieval Solution (Dako, Trappes, France). Sections were immunostained for 30 min at room temperature with polyclonal-N (11 μg/ml) or polyclonal-C (4 μg/ml) antibodies diluted in PBS containing 0.3% BSA or with the undiluted-N monoclonal antibody (5 μg/ml). Tissue sections were incubated with the streptavidin-biotin-peroxidase complex (ABC method) using the StrepABComplex/HRP Duet (mouse/rabbit) kit (Dako). Extensive washing with PBS containing 0.3% BSA was performed between each step. Labeling was revealed using diaminobenzidine tetrahydrochloride and hydrogen peroxide, and nuclei were counterstained with hematoxylin. Negative controls were included for each sample by omitting the primary antibody. The specificity of labeling was verified by using the corresponding pre-immune sera at the same concentrations and by competition experiments using 10-fold excess (weight) of the recombinant antigens.

Results

Genomic DNA from the patient and her parents were used for DNA sequencing of all exons and exon-intron boundaries of the SPINK5 gene. It was found that a novel mutation was heterozygous G-A transition (318 G-A) in exon 5 of the SPINK5 gene which generated a premature termination codon (D106X) [Figure 2]. The PCR amplification products with mutation-specific primer were obtained only from the DNA of the patients and their mother, but not from their father and 25 healthy individuals. The patient's mother was a heterozygote for this mutation without phenotype of NS. The sequencing analysis of the parents' DNA indicated that the 318 G-A mutant allele was inherited from her mother. Allele-specific PCR performed by using either a wild-type-specific or a mutation-specific reverse primer, and a common forward primer, was used to confirm that the mutation is not a polymorphism.

Monoclonal antibodies against the N-terminal region of LEKTI did not detect LEKTI in the skin of the patient [Figure 3a]. In contrast, a positive staining in the granular layer of the epidermis was obtained in control skin [Figure 3b].

Discussion

In this study, we identified heterozygous mutation in the SPINK5 gene of one Chinese girl affected with NS. She had generalized erythroderma, ichthyosis linearis circumflexa, and radioallergosorbent tests were positive to cow's milk and egg IgE antibodies. The patients didn't display characteristic hair shaft abnormalities, particularly trichorrhexis invaginata (bamboo hair) and torsion twists which is different from the reported case that most patients later display characteristic

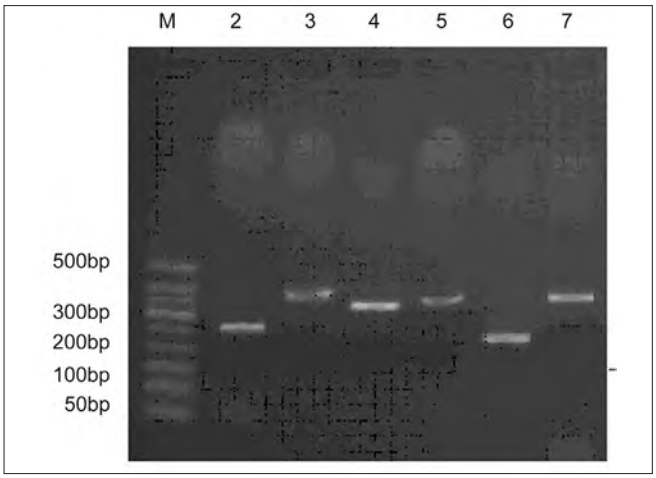

Figure 1: Result of exons of SPINK5 by PCR

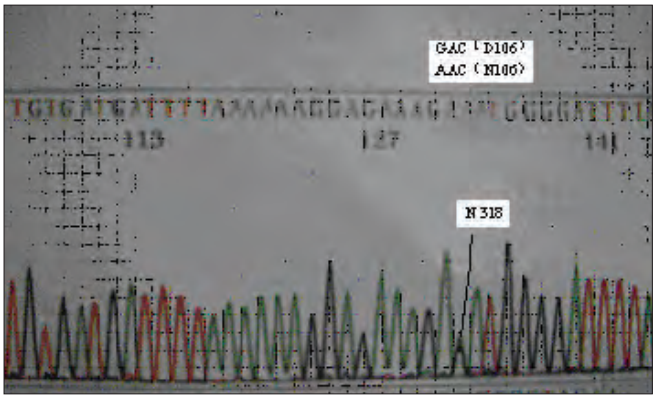

Figure 2: G318A missense mutations was found at exon 5 of SPINK5 gene

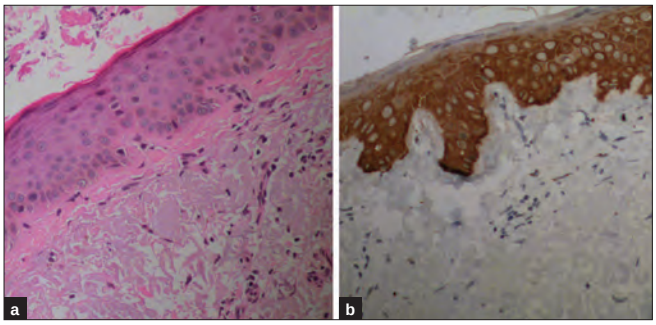

Figure 3: (a) Patient skin showed absent staining indicating a dramatic reduction of epidermal LEKTI (hematoxylin and eosin, ×200). (b) Normal skin showed a predominantly cytoplasmic, partially pericellular presence along the stratum granulosum (DAB stain, ×200)

hair shaft abnormalities, particularly trichorrhexis invaginata (bamboo hair) and torsion twists (pili torti).[7] In addition, the expression of bamboo hairs is often delayed.[7] Medical treatment started after the age of two years and the patient had a good response to corticosteroid hormone. But the lesions were aggratated by acitretin therapy. We screened the gene mutations in the SPINK5 gene, all 33 exons and flanking intron boundaries of SPINK5 were amplified by PCR for direct sequencing. Immunohistochemical staining of LEKTI with specific antibody was used to confirm the diagnosis of NS.

Immunological detection of LEKTI in normal skin was confined to the granular layer giving a predominantly cytoplasmic reaction occasionally mixed with a pericellular signal. Recent studies have revealed that LEKTI deficiency influenced several other molecules in the epidermis of patients with NS[11] and SPINK5-knockout mice.[12,13] It is consistent with previous reports.[5,7,11] Immunohistochemistry using anti-LEKTI antibodies showed there was no LEKTI in patient's skin sample. Our studies show the identified D106X is sense mutation. Bitoun *et al.*, reported that there was no clear correlation between mutation and phenotype in NS.[6] The protein analyses with anti-LEKTI antibodies supported their suggestion because LEKTI was not detected in most skin samples of patients with NS regardless of location of mutations.[5,11,14,15] We have shown that there is no LEKTI expression in epidermis of the case. The result demonstrated that loss of LEKTI expression is the major molecular mechanism underlying NS. Because we had no cell cultures of NS patient available, we could not evaluate the effect of the novel mutation at mRNA level. Our immunohistochemistry analysis of NS skin confirmed that there is no SPINK5 gene product in NS patient analyzed. In contrast, normal or slightly reduced levels of LEKTI were detected in normal human skin.

In this study, we identified heterozygous mutations in the SPINK5 gene of one Chinese adult with NS. The 318 G-A (D106X) is a novel mutation and it is hasn't been found in Europe[3,6,14] and Asia.[4, 6-9,14] Together with previous reports, 15 of 44 mutations reported to date have been located between exons 22 and 26 of the SPINK5 gene indicating that this region would be one of the largest mutation clusters for NS. But in our study, we identified the 318 G-A (D106X) is a novel mutation which was located at exon 5 of the SPINK5 gene of one Chinese adult affected with NS.

Conclusion

In this report, we describe heterozygous mutation in the SPINK5 gene from one Chinese adult and confirm the diagnosis of NS with Immunohistochemistry. The study reveals that defective expression of LEKTI in the epidermis and mutations of SPINK5 gene are reliable for diagnostic feature of NS with atypical clinical symptoms.

Acknowledgement

The authors are deeply grateful to Dr. Guodong Liu form Department of Chemistry and Molecular Biology for his kind suggestions.

What is new?
A G318A mutation was found at exon 5 of the Chinese patient's SPINK5 gene.

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Original Article

A Clinico-Epidemiological Study of Macular Amyloidosis from North India

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Abstract

Background: Macular amyloidosis (MA) is the most subtle form of cutaneous amyloidosis, characterized by brownish macules in a rippled pattern, distributed predominantly over the trunk and extremities. MA has a high incidence in Asia, Middle East, and South America. Its etiology has yet to be fully elucidated though various risk factors such as sex, race, genetic predisposition, exposure to sunlight, atopy and friction and even auto-immunity have been implicated. **Aim:** This study attempts to evaluate the epidemiology and risk factors in the etiology of MA. **Materials and Methods:** Clinical history and risk factors of 50 patients with a clinical diagnosis of MA were evaluated. Skin biopsies of 26 randomly selected patients were studied for the deposition of amyloid. **Results:** We observed a characteristic female preponderance (88%) with a female to male ratio of 7.3:1, with a mean age of onset of MA being earlier in females. Upper back was involved in 80% of patients and sun-exposed sites were involved in 64% cases. Incidence of MA was high in patients with skin phototype III. Role of friction was inconclusive**.** Lymphohistiocytic infiltrate in the dermis and in perivascular distribution was seen in almost all the histopathology sections studied. Focal disruption of basal layer with pigmentary incontinence was present in a small number of patients. Amyloid deposits could be detected better with Congo red staining viewed under polarized light**. Conclusion:** Lack of clear-cut etiological factors makes it difficult to suggest a reasonable therapeutic modality. Histopathology is not specific and amyloid deposits can be demonstrated only in a small number of patients. For want of the requisite information on the natural course and definitive etiology, the disease MA remains an enigma and a source of concern for the suffering patients.

Key Words: *Epidemiology, macular amyloidosis, risk factors*

What was known?
MA is a common pigmentary disorder, mostly of young women involving interscapular area, exposed sites and those amenable to friction. Rarely, other sites like clavicles, face, breast, neck and axilla may be involved. Despite the implication of various factors such as race, female gender, genetic, sun exposure, friction and atopy, exact etiology and consequently the treatment are still an enigma.

Introduction

Macular amyloidosis (MA) represents a common variant of primary localized cutaneous amyloidosis (PLCA). Macular form of cutaneous amyloidosis was first described by Palitz and Peck in 1952.[1] MA has a characteristic female preponderance[2-7] with the age of onset ranging between 21 and 50 years.[7] Clinically, MA presents as poorly delineated hyperpigmented patches of grayish-brown macules with a rippled pattern,[8] associated with deposition of amyloid material in the papillary dermis.[9] The sites most commonly involved are the interscapular area,[10] extremities (shins and forearms),[11,12] although involvement of the clavicles, breast, face, neck, and axilla[2] have also been reported. Various risk factors such as, race,[2,8] female gender,[3,6,10] genetic predisposition,[13] sun exposure,[12] atopy[14] and friction[12,15-17] have been implicated in the etiopathogenesis of MA. On the basis of a patient of PLCA having sarcoidosis and IgA nephropathy and increasing number of reports suggesting immune mediated factors, the possibility of autoimmune basis in a group of patients with extensive disease was also proposed.[18] Yet, its etiology still remains an enigma.

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It is the most subtle form of cutaneous amyloidosis and tends to persist unchanged for many years. The natural course of the disease is not well described. Though the exact incidence of MA is not known, it is by no means an uncommon disease. In our study comprising 50 patients from Northern India, we studied the possible etiological and risk factors of MA.

Materials and Methods

Fifty patients with a clinical diagnosis of MA attending the out-patient clinic of a tertiary care dermatology center were enrolled in the study. The study design was approved by the Institute's Ethics Committee and written informed consent was obtained from patients prior to enrollment. Complete history and physical examination to exclude any associated systemic disorder or drug usage leading to cutaneous pigmentation was obtained. The age of onset, gender, skin type, duration, sites of involvement, pruritus, history of friction, sun exposure, personal and family history of MA and/or atopy were recorded. Punch biopsies of 4-mm diameter from 26 randomly selected patients were fixed in 10% formalin and processed as required for light microscopy. All the slides were stained with Hematoxylin and Eosin (H&E) and Congo red, to study the location of amyloid and its extension to

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adjoining vessels and appendages under light microscope and polarized light.

Results

The prevalence of MA in our out-patient clinic was observed to be 0.03% of all dermatological patients with a characteristic female preponderance. Forty-four of the 50 patients were females (88%), with a female to male ratio of 7.3:1.The age of onset of MA for all patients ranged between 16 and 59 years. The mean age of onset was 34.6±10.5 years, being earlier in females (34.2±10.9 years) compared to males (38±6.78 years). Half the patients (50%) experienced pruritus of varying degrees, and only three patients experienced severe pruritus. Only 16 (32%) patients gave a history of use of nylon scrubs and towels. In our study, there was a wide variation in the duration of the disease ranging from 1 month to 12 years. More than one site was involved in 30 (60%) patients. The most common sites of involvement were the upper back (interscapular area) seen in 40 (80%) patients [Figure 1]. The other sites of involvement in decreasing order of frequency were extensor aspect of arm(s) in 30 (60%) and extensor aspect of legs in 17 (34%) patients [Figure 2]. Bony prominences such as clavicular and scapular regions were involved in three patients each, with rare sites like the buttocks being involved in one patient. Clinically, the lesions in all of our patients presented as hyperpigmented macules, predominantly in a rippled pattern. Coalescence of the macules was observed in 20 (40%) patients. A biphasic pattern comprising both macular and lichen amyloidosis was seen in three (6%) patients. Family history of MA was present in 10 (20%) patients. More than half of our patients, 32 (64%) had involvement of sun-exposed sites, comprising upper back, extensor aspect of arms and legs, whereas 13 (26%) patients had lesions on both sun-protected and sun-exposed sites and only five (10%) patients had involvement of sun-protected sites.

Thirty-nine (78%) patients in our study had skin phototype III; the rest were of skin phototype IV. The average age at onset of MA in patients with skin phototype III was 30.8 years and was lower than that observed in patients with skin phototype IV (34.4 years). Various systemic and cutaneous diseases in association with MA in our patients were chronic urticaria, diabetes mellitus, acne vulgaris, generalized xeroderma, hypothyroidism, hypertension and idiopathic hirsutism.

Histopathological findings from the 26 biopsies undertaken and studied are summarized. Epidermis was essentially normal in most of the sections. Mild to moderate thinning of the epidermis was seen in seven (27%) patients [Figure 3]. There was mild hyperkeratosis of the epidermis in three (11.5%) specimens which showed moderate degree of acanthosis with broadening and elongation of the rete ridges. These changes did not always correlate with the deposition of amyloid and extended well beyond the areas of amyloid deposits. Necrotic keratinocytes were seen in the suprabasal region and in the basal layers of the epidermis in five (19%) sections. Occasionally, more number of necrotic keratinocytes were found overlying the subepidermal amyloid deposits. Focal disruption of the basal cell layer with pigment incontinence and melanophages in the papillary dermis were seen in four (15%) biopsy specimens. Predominant perivascular lymphocytic infiltrate was seen in majority of sections (23 out of 26 (88%).

In the sections stained with H&E and Congo red, amyloid deposits could be visualized in three and four specimens respectively on light microscopy [Figure 3]. On viewing, the Congo red-stained sections under polarized light, amyloid deposits with apple green birefringence were detected in seven biopsy specimens [Figure 4]. The amyloid was localized to the subepidermal zone and not scattered or localized around blood vessels or appendages.

Discussion

Amyloidosis is an extra-cellular deposition of the fibrous protein either involving multiple organ systems (systemic amyloidosis) or restricted to a single-tissue site (localized amyloidosis).[8,19] The various localized forms of amyloidosis confined to the skin are lichen amyloidosis, MA and the rare nodular or tumefactive amyloidosis.[8,19] Not infrequently, features of lichen and MA may coexist and are termed as biphasic amyloidosis.[8,20] In primary localized cutaneous amyloidosis (PLCA), amyloid deposits are seen in previously normal skin, with no evidence of deposits in internal organs.[19]

MA clinically presents as small (2-4 mm) brownish macules with a characteristic reticulated or rippled pattern, which may coalesce to form poorly circumscribed hyperpigmented areas.[10] The common sites of occurrence are upper back[3,10] (interscapular areas) and extremities (shins and forearms).[3,11] Less commonly, the clavicles, breast, face, neck, axilla[2] and ribs are involved.[19-22] MA has a high incidence in Asia, Middle East and South America, but is rarely seen in European and North American countries.[2,8] Although most cases of PLCA are sporadic, 10% of cases have been reported to be familial.[3,23] Female preponderance has been consistently reported in the literature,[3,6,14] except for a study by Black *et al.* which reported more males to be affected.[24] We observed a similar female prevalence with a female to male ratio of 7.3:1. It has been suggested that female preponderance maybe due to medical attention sought earlier by women for the cosmetically disturbing pigmentation.[3,10,24,25] The role of female sex hormones has also been hypothesized although conclusive studies are lacking.[7]

The patients' ages ranged between 16 and 59 years similar to the previous reports,[7,24,26] with a mean age of onset of 34.6±10.5 years. The mean age of onset of MA was lower in women, compared to men, which was contrary

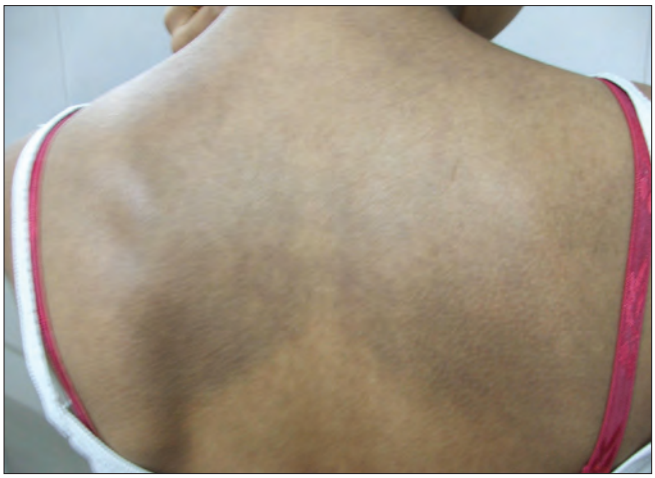

Figure 1: Macular amyloidosis on the upper back

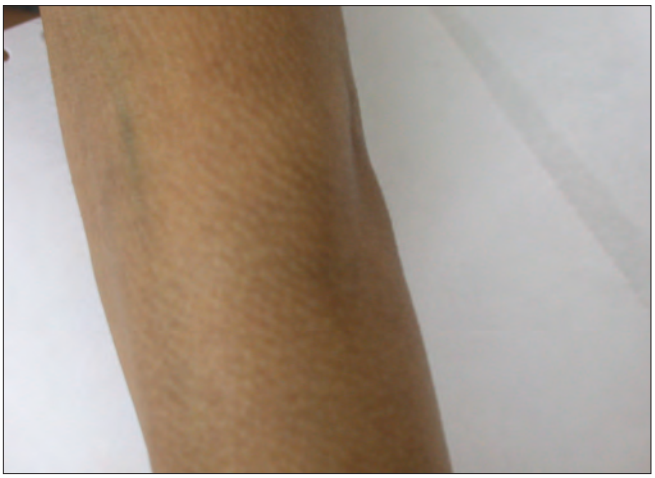

Figure 2: Macular amyloidosis on the extensor aspect of the arm

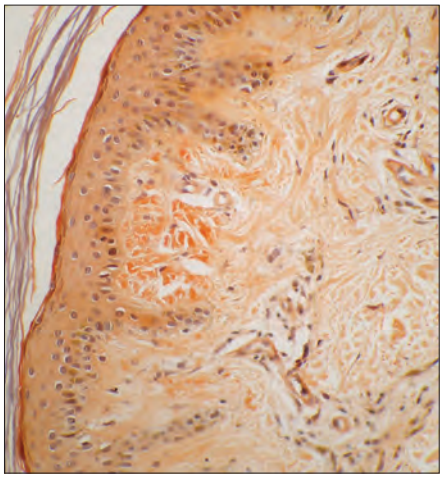

Figure 3: Microphotograph showing mild epidermal thinning and congophillic material in the papillary dermis (Congo red ×280)

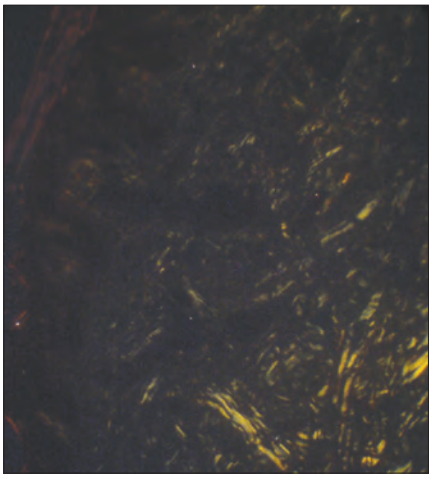

Figure 4: Microphotograph showing apple birefringence with congophillic material (polarized light ×540)

to a report by Rasi *et al*.,[7] where a higher mean age on onset for females was reported. In our study, there was a wide variation in the duration of the disease at the time of presentation (1 month-12 years), and about half of the patients presented within 2 years of appearance of the lesions. This may be attributed to the nonavailability of a satisfactory treatment. Apart from the considerable cosmetic disability, patients occasionally complain of troublesome pruritus. Twenty-two patients (44%) in our study complained of itching which was minimal to moderate in intensity with only three patients complaining of severe itching. Although itching is a frequent symptom in PLCA, it is not a universal finding and has been reported to be absent in 20% of patients. In a study by al-Ratrout and Satti,[3] six of the 10 patients complained of mild to moderate pruritus which increased in intensity in two patients during conditions of high humidity. We did not observe such a pattern in our study.[10,26-28]

Mechanical trauma such as that induced by nylon fibers and bristles has been considered in the etiology of MA and has been reported under various names, such as friction amyloidosis, towel melanosis and nylon clothes friction dermatitis.[17,27,29] Only 16 (32%) of our patients gave a history of using nylon scrubs or towels, but the perceived excessive friction did not correlate with the sites having pigmentary lesions. Similar observations were made in studies by Rasi *et al*.[7] and Eswaramoorthy *et al*.[6] As in previous studies, we could not find any correlation between the use of cosmetics, shampoos, soaps and creams and MA.[6] Personal history of atopy was present in seven of our patients, of whom three had family history of atopy. However, the relationship if any between history of atopy and MA has not been either confirmed or explained.[24] Frequent involvement of back, extensor aspects of upper limbs and clavicular areas compared to sun-protected sites like lower back, legs, thighs, buttocks and breast would point to exposure of ultraviolet (UV) rays as an etiological factor in MA. Moreover, sunny weather contributing to increased pigmentation in PLCA has previously been reported.[17] Sun-protected sites were involved in only 10% of our patients with sun-exposed sites being involved in a higher number of patients (64%). Upper back was involved in 40 patients.

Hence, sunlight could be incriminated as a risk factor in the causation of MA in our patients. Eswaramoorthy *et al.*[6] and Rasi *et al.*,[7] however, did not find any correlation between sun exposure and MA in their studies. Epidemiologically, PLCA is prevalent in populations which generally have a high skin phototype (IV and V).[3,17] This might explain its rarity in western countries. In our study, majority of patients had skin phototype III (78%), which is common phototype in North India and rest had phototype IV.

MA classically presents in a rippled pattern or as reticulate pigmentation.[3,10] Unusual presentations of MA, such as nevoid like hyperpigmentation, widespread diffuse pigmentation, poikiloderma like, incontinentia pigment like and linear MA have frequently been reported in the literature.[22,30-33] A rippled pattern of pigmentation was present in all of our patients without any special pattern or distribution.

There is no convincing explanation for the origin of the amyloid protein in the skin. Two theories, fibrillar body theory and secretory theory, have been proposed.[34] The fibrillar body theory states that damaged keratinocytes undergo filamentous degeneration by apoptosis and transformation by dermal fibroblasts and histiocytes and are converted into amyloid which deposits in the papillary dermis.[35] Secretion theory describes the deposition of amyloid from the degenerated basal keratinocytes at the dermoepidermal junction which eventually drops into the papillary dermis through the damaged lamina densa of basal layer.[36] Chang *et al.*[9] suggested that keratinocyte destruction in cutaneous amyloidosis may occur as an initial result of apoptosis as apoptotic keratinocytes were seen in the spinous layer and the dermoepidermal junction just above the amyloid deposits.[37] In our study, we found necrotic keratinocytes with pyknotic nuclei in five specimens overlying subepidermal amyloid, but their contribution toward the formation/localization of amyloid remains a matter of speculation. Additionally, there was focal disruption of the basal layer with pigmentary incontinence in only a few cases. No amyloid was detected around blood vessels or other cutaneous appendages. Similar features of thinning of epidermis, moderate acanthosis and hyperkeratosis, focal distribution of the basal layer with pigmentary incontinence as observed by us have been consistently described.[24,27,38,39] Amyloid on H&E stain shows amorphous eosinophilic masses and small deposits of amyloid can be missed with routine H&E stains.[39] Congo red produces an apple green birefringence under a polarizing microscope and is the most specific stain for detection of amyloid.[3,19] We observed an increased rate of detection of amyloid with Congo red and polarized light confirming its superiority for staining amyloid on histological sections

The hyperpigmentation which sometimes involves large surface areas of the upper back, arms and legs poses an important aesthetic problem. In general, the treatment of PLCA is disappointing. Topical corticosteroids with or without occlusive dressings and photoprotection can be used to treat mild cases. A topical application of 10% dimethyl sulphoxide (DMSO) has been advocated for treatment but results have been equivocal.[40,41] Ultraviolet B (UVB) therapy has also been used with some success in the treatment of both macular and papular amyloidosis.[42] Etretinate and acitretin therapy has been beneficial in some cases,[43,44] but the condition seems to relapse after the treatment is stopped.[45] Treatment modalities like cyclophosphamide, cyclosporine[46] and dermabrasion[47] have a limited therapeutic efficacy. The Q-switched Nd-YAG laser (532 nm and 1064 nm) has shown positive response in the reduction of pigmentation in MA. In a study by Ostovari *et al.*,[48] 90% of patients with MA demonstrated more than 50% reduction in their pigmentation with the Q-switched Nd-YAG laser. A recently discovered cytokine, interleukin (IL)-31, has been proposed to play a role in itching[49] and has been implicated in the pathophysiology of itchy dermatosis such as PLCA (sporadic and familial).[50] This hypothesis has led to research of newer pharmacological therapies targeting IL-31 receptor in the management of PLCA and various other itchy dermatoses. A study by Clos *et al.* on a mouse model of cutaneous amyloidosis describes the use of conformational antibodies directed against amyloid, to facilitate antibody-mediated clearance of amyloid deposits in the skin. It is achieved by direct intradermal injection of these antiamyloid antibodies.[51]

Conclusion

The parameters collected and collated by us on this chronic, persistent and cosmetically disfiguring disease support the findings of the previous workers in relation to adult age of onset, preponderance of female sex, earlier onset in women and more frequent involvement of upper back and extensors of arms and the presence of symptoms of itching. Sun exposure did seem to play an important role in the localization of disease. Contrary to previous reports, MA in our study was observed in a majority of patients of comparatively lighter skin than in those with a higher skin phototype. The observation about the role of friction could not be conclusively supported or negated. Histopathology of the tissue specimens corroborates previous studies that the use of special stains increases the sensitivity of detecting amyloid in more specimens. Lack of clear-cut etiological factors makes it difficult to suggest a reasonable therapeutic modality. For want of the requisite information on the natural course and definitive etiology the disease, MA remains an enigma and a source of concern for the suffering patients and physicians.

What is new?
In this study MA was observed in a majority of patients of comparatively lighter skin than in those with a higher skin phototype.

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Announcement

Leprosy in 2012: Achievements and Future Challenges

Call for Papers

The last three decades brought success in leprosy control worldwide due to impressive contributions of WHO, national governments, NGOs, and voluntary role of civil society and the private sector in leprosy-affected countries. However, leprosy continues to be a challenge to health care worldwide, with about 2,50,000 new leprosy cases being detected annually. A third of newly diagnosed patients have nerve damage and might develop disabilities. A major shift in leprosy control strategies is a change from a well-supported, specialized programme to one that is now integrated within general health and social services. Sustainability is a challenge to all leprosy activities. We hope that researchers and funding will be available to take up these challenges.

Priorities for strengthening research and work in leprosy in the twenty-first century will range from basic sciences to health services. We invite health care workers/investigators to contribute original/review articles that will stimulate the continuing efforts to sustain gains made by leprosy programmes and provide an insight into remaining challenges in disease control. We are particularly interested in articles dealing with effective tools for detection of early infection, to identify markers for predicting nerve damage and reactions and evolving strategies for management of neuritis and reactions. Also renewed efforts are required for deciding strategies regarding chemoprophylaxis of contacts, delays to diagnosis, discrimination, and stigma of disease in society. Potential topics include, but are not limited to:

- Current trends of leprosy epidemiology
- Neuritis and reactions in leprosy: immunopathogenesis and treatment
- Neuropathic pain
- Resistance and relapse in current context
- Deformities in leprosy: tools for early detection, trends, and management
- Community-based rehabilitation of leprosy patients
- Impact of amalgamation of specialized leprosy services into the general health services (vertical to horizontal)
- Role of chemoprophylaxis and vaccines
- Recent advances in immunology and immunodiagnosis of leprosy

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Manuscript Due	–	Friday, 31st August 2012
First Round of Reviews	–	Friday, 23rd November 2012
Publication Date	–	Friday, 18th January 2013

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Original Article

Pattern of Pediatric Dermatoses in a Tertiary Care Centre of South West Rajasthan

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Abstract

Background: The evaluation for skin disorders forms an important component of primary health care practice for all including children. The prevalence of certain skin diseases in children can reflect status of health, hygiene, and personal cleanliness of a community. **Aims:** This study was planned to evaluate the magnitude of skin diseases, pattern of various dermatoses, factors contributing to these dermatoses and concurrent systemic disease among children up to five years of age. **Materials and Methods:** Consecutive 1000 children, aged up to five years, attending the Dermatology OPD of RNT Medical College and MB Government Hospital, Udaipur were the subjects of this study. A detailed general, systemic and cutaneous examination followed by relevant investigations were carried out. The findings were recorded in a proforma for analysis and interpretation of data. **Results:** One thousand twenty seven (1027) diagnoses were made in 1000 children. Etiological analysis revealed that majority (417; 40.60%) of dermatoses belonged to infection and infestation group followed by eczematous (358; 34.86%) and hypersensitivity (105; 10.22%) groups. Of the infection and infestation group, bacterial infection (141; 13.72%) was the most common entity followed by scabies (107; 10.42%), fungal (67; 6.52%), and viral infection (35; 3.40%). **Conclusion:** This study provides a preliminary baseline data for future clinical research. It might also help to assess the changing trends of pediatric dermatoses.

Key Words: *Bacterial infections, fungal infections, pediatric dermatoses, scabies, viral infections*

What was known?
The prevalence of certain skin diseases in children reflects status of health, hygiene, and personal cleanliness of a community.

Introduction

The pattern of skin disease is a consequence of poverty, malnutrition, overcrowding, poor hygiene, illiteracy, and social backwardness in many parts of India.[1] The evaluation for skin disorders is an important component of primary health care practice for all, including children.[2] Status of health, hygiene and personal cleanliness of a society can be judged from the prevalence of certain skin diseases in the children of the community.[3]

Wide range of primary skin disorders are seen during childhood and skin is often a marker of underlying systemic diseases and hereditary syndromes.[4] The pattern of skin diseases varies from country to country with pyoderma and malnutrition being more prevalent in developing countries, while eczemas are more common in developed countries. This can be attributed to differing climatic, cultural and socio-economic factors.[5] Dermatological problems account for about 30% of primary and secondary reasons for pediatric clinic visits and 30% of all visits to dermatologists involve patients of pediatric age group.[6] The incidence of skin diseases in children has been reported to be 9%-37% in various studies.[2,5,7-10]

This study was carried out to share our experience about various dermatoses prevalent among children up to five years of age attending skin OPD at RNT Medical College and MB Government Hospital, Udaipur.

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Materials and Methods

Consecutive 1000 children, aged up to five years, attending the Dermatology outpatient department of RNT Medical College and MB Government Hospital, Udaipur were the subjects of this study. A detailed general, systemic and cutaneous examination was done. Relevant investigations were carried out whenever deemed necessary. The findings were recorded in a proforma for analysis and interpretation of data.

Results

Out of total 46,321 patients examined, 1000 (2.16%) patients were children up to five years of age. Males slightly outnumbered females; the male: female ratio was 1.23:1.

Some of the patients had more than one dermatosis. A total of 1027 dermatoses were recorded in 1000 patients. The majority (417; 40.60%) of dermatoses belonged to infection and infestation group followed by eczematous (358; 34.86%) and hypersensitivity (105; 10.22%) groups. The pattern of other dermatoses is depicted in Table 1.

Amongst the infective dermatoses, bacterial infection (141;

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13.72%) was the most common entity followed by fungal (67; 6.52%) and viral infection (35; 3.40%). Out of bacterial infections, impetigo (84; 59.57%) was the commonest entity followed by secondary pyoderma (38; 26.95%). The pattern of bacterial infections is shown in Table 2. Of the infestation group, scabies was the most common entity recorded in 107 (10.42%) patients. Molluscum contagiosum (21; 60%) was the commonest viral infection followed by warts (7; 20%). Out of various fungal infections, tinea capitis was seen in majority (47; 70.15%) of the cases followed by tinea faciei (7; 10.45%) and tinea corporis (7; 10.45%).

Pattern of eczematous disorders [Table 3] revealed atopic dermatitis to be the commonest (198; 55.31%) followed by seborrhoeic dermatitis (60; 16.76%) and pityriasis alba (29; 8.10%). Twenty four patients of atopic dermatitis had atopic background. Among the hypersensitivity disorders, papular urticaria formed the largest (62; 59.05%) group followed by urticaria (34; 32.38%) as shown in Table 4.

Keratoderma (13; 50%) and ichthyosis (9; 34.62%) were the two most common keratinization disorders. Pigmentary disorders were recorded in 21 patients, of which post inflammatory hypopigmentation was the commonest (14; 66.67%), followed by vitiligo (6; 28.57%). Lichen striatus (6; 35.29%) and lichen nitidus (5; 29.41%) were the commonest entities amongst papulosquamous disorders. No case of lichen planus was recorded. Among the vascular lesions, hemangioma (11; 78.57%) was the most frequent. Out of the 10 patients of nevi, naevus depigmentosus and epidermal nevi were seen in 5 and 4 patients, respectively. Among the miscellaneous disorders, xerosis (19; 45.24%) constituted the largest group followed by acrodermatitis enteropathica (7; 16.67) and miliaria (4; 9.52%).

A pattern of seasonal variation was observed in six common dermatoses. Patients with impetigo and dermatophytic infections were recorded mainly in rainy and summer seasons, while scabies was mostly seen in winter and rainy seasons. Atopic dermatitis and seborrhoeic dermatitis were documented more in winter season and papular urticaria presented predominantly in rainy season.

Discussion

The pattern of skin diseases in pediatric age group vary from one country to another and within the same country from one state to another due to various climatic, cultural and socio-economic factors.[5] The infants are mostly confined to their household, while preschool children aged one to five years are exposed to their neighborhood. Thus, childhood age may be considered as a surrogate marker for environmental risks.[11]

Table 1: Pattern of dermatoses (*n*=1027)

Conditions	Male		Female		Total	
	No.	%	No.	%	No.	%
Neonatal	4	0.71	2	0.43	6	0.58
Infections and infestations	227	40.11	190	41.21	417	40.60
Eczematous	207	36.57	151	32.75	358	34.86
Pigmentary	8	1.41	13	2.82	21	2.04
Papulosquamous	9	1.59	8	1.74	17	1.66
Bullous	3	0.53	3	0.65	6	0.58
Vascular lesions and vasculitis	3	0.53	11	2.39	14	1.36
Nevi	5	0.88	5	1.08	10	0.97
Keratinization	14	2.47	12	2.60	26	2.53
Hypersensitivity	67	11.84	38	8.24	105	10.22
Hair disorders	1	0.18	4	0.87	5	0.49
Miscellaneous	18	3.18	24	5.21	42	4.09
Total	566	55.11	461	44.89	1027	100

Table 2: Pattern of bacterial infections (*n*=141)

Entity	Male		Female		Total	
	No.	%	No.	%	No.	%
Impetigo	46	63.89	38	55.07	84	59.57
Secondary pyoderma	19	26.39	19	27.54	38	26.95
Folliculitis	5	6.94	8	11.59	13	9.22
Furuncle	2	2.78	1	1.45	3	2.13
Paronychia	0	0	1	1.45	1	0.71
Scrofuloderma	0	0	2	2.90	2	1.42
Total	72	51.06	69	48.94	141	13.73

Table 3: Pattern of eczematous disorders (*n*=358)

Entity	Male		Female		Total	
	No.	%	No.	%	No.	%
Atopic dermatitis	120	57.97	78	51.66	198	55.31
Seborrhoeic dermatitis	33	15.94	27	17.88	60	16.76
Pityriasis alba	17	8.21	12	7.95	29	8.10
Infective eczematoid dermatitis	6	2.90	9	5.96	15	4.19
Nummular dermatitis	6	2.90	8	5.30	14	3.91
Pompholyx	0	0	2	1.32	2	0.56
Contact dermatitis	5	2.42	3	1.99	8	2.23
Diaper dermatitis	0	0	3	1.99	3	0.84
Intertrigo	10	4.83	4	2.65	14	3.91
Prurigo	6	2.90	2	1.32	8	2.23
Photo dermatitis	3	1.45	2	1.32	5	1.40
Id eruption	1	0.48	1	0.66	2	0.56
Total	207	57.82	151	42.18	358	34.86

Table 4: Pattern of hypersensitivity disorders (*n*=105)

Entity	Male		Female		Total	
	No.	%	No.	%	No.	%
Urticaria	23	34.33	11	28.95	34	32.38
Angioedema	1	1.49	0	0	1	0.95
Aquagenic itch	1	1.49	0	0	1	0.95
Papular urticaria	39	58.21	23	60.53	62	59.05
Insect bite	1	1.49	3	7.89	4	3.81
Blister beetle dermatitis	2	2.99	0	0	2	1.90
Drug induced pruritus	0	0	1	2.63	1	0.95
Total	67	63.81	38	36.19	105	10.22

Pattern of pediatric dermatoses has varied in different studies. In this study, majority (417; 40.60%) of dermatoses belonged to infections and infestations group followed by eczemas (358; 34.86%) and hypersensitivity (105; 10.22%) groups. A similar pattern of dermatoses has also been reported in several other studies.[2,5,8,9,12-16] However, in a few studies,[17-20] eczema group has been the predominant dermatoses.

Of the infective dermatoses, bacterial infections (141; 13.72%) were the most common followed by fungal (67; 6.52%) and viral infections (35; 3.40%). Similar pattern has been observed in some other studies as well.[2,9,16,21] Sayal *et al.*,[5] reported fungal infections to be more common, while viral infections out-numbered bacterial and fungal infections in a study by Wenk and Itin[18] and Gul *et al*.,[20] The variation among infective dermatoses can possibly be attributed to the region of study, prevalent environmental factors, type of population studied, and hygiene and nutritional status. Impetigo was the commonest (84; 59.57%) bacterial infection followed by secondary pyoderma (38; 26.95%). Most studies[2,5,10-12,17] report impetigo as the commonest bacterial infection. Molluscum contagiosum (21; 60%) was the commonest viral infection followed by warts (7; 20%). A similar observation has been made in several studies. [5,9,16,21] Nanda *et al*.,[17] however in their study recorded higher prevalence of warts compared to molluscum contagiosum. Tinea capitis was the most frequent fungal infection seen in majority (47; 70.15%) of cases followed by tinea faciei (7; 10.45%) and tinea corporis (7; 10.45%). This is in accordance with other studies[10,13,16] in which tinea capitis was the most common. However, in a study by Sharma and Mendiratta,[21] candidal intertrigo was the most common fungal infection (39.47%) with maximum incidence in infants (63.6%), followed by tinea capitis (34.3%) and tinea corporis (19.15%). This could be due to the pediatric population recruited for the study. Scabies was the most common infestation seen in 107 (10.42%) patients in our study. Almost a similar occurrence (10.61%) has been reported by Sardana *et al*.[16]

Of the eczema group, atopic dermatitis was the commonest (198; 55.31%) followed by seborrhoeic dermatitis (60; 16.76%) and pityriasis alba (29; 8.10%), a finding similar to other studies.[17,18] However, Hayden[2] documented diaper dermatitis (16%) to be more common followed by atopic dermatitis (9%) and seborrhoeic dermatitis (6%), while Sardana *et al*.,[16] found infantile seborrhoeic dermatitis (10.49%) to be more common compared to pityriasis alba (5.85%) and atopic dermatitis (5.27%). The incidence of eczemas' primarily depends upon genetic constitution, individual predisposition, and environmental threats/allergens. Papular urticaria was the commonest hypersensitivity disorder (62; 59.05%) followed by urticaria (34; 32.38%). Sayal *et al.*,[5] and Sardana *et al*.,[16] also noticed a frequent occurrence of papular urticaria compared to urticaria, while in some studies,[9,17] urticaria has been reported to be more common than papular urticaria.

Of the nutritional disorders, acrodermatitis enteropathica was the only entity recorded in seven (0.68%) patients. A higher incidence (3.6%) of acrodermatitis enteropathica has also been reported in a study from Karachi by Javed *et al*.[10] Interestingly, there was only one case of psoriasis and no case of lichen planus found in our study. There was no significant association of various dermatoses with systemic diseases in our study except for a single case of pyoderma in whom hypothyroidism was associated.

The prevalence of certain dermatoses may be influenced by seasonal and climatic changes. This was quite evident in our study in which atopic dermatitis and seborrhoeic dermatitis were noted predominantly in winters while papular urticaria was seen more frequently in rainy season. Dhar *et al*.,[22] in a large series of 672 children of atopic dermatitis documented disease aggravation during winters in 67.14% and 58% of infantile and childhood atopic dermatitis cases, respectively. Banerjee *et al*.,[23] studied seasonal variations in pediatric dermatoses and found scabies and seborrhoeic dermatitis to be more prevalent during winter, while impetigo, furunculosis, and miliaria during summer and rainy seasons. Papular urticaria was more frequent in the rainy season. Almost a similar observation was documented in our study also.

This study provides a preliminary baseline data for future epidemiological and clinical research. It might also help to assess the changing trends of pediatric dermatoses.

What is new?

Majority of dermatoses belonged to infection and infestation group followed by eczematous and hypersensitivity groups. Of the infection and infestation group, bacterial infection was the most common entity followed by scabies, fungal, and viral infection. This study points towards the changing trends of pediatric dermatoses.

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Announcement

Dermatologic & Aesthetic Surgery International League (DASIL)

1st Annual Congress

Call For Abstracts

The Dermatologic & Aesthetic Surgery International League (DASIL) is currently accepting abstracts for consideration to be presented at the organization's 1st Annual Congress to be held in Malta during October 31 - November 4, 2012. Please email DASIL President Dr. Michael Gold at drgold@thedasil.org with submission information. All topics in dermatologic surgery, basic and advanced, will be included in this scientific forum. All submissions should include the following:

- Abstract title and topic
- Corresponding authors and contact information including email

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Efficacy of 2% Metronidazole Gel in Moderate Acne Vulgaris

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Abstract

Background: Acne vulgaris is an inflammatory disease of the pilosebaceous units. Various systemic and topical options are available for its treatment. **Aims:** This study aimed to evaluate the efficacy of 2% metronidazole gel in acne vulgaris. **Materials and Methods:** Double-blind, randomized, placebo-controlled, split-face clinical trial. Seventy young adults with moderate acne vulgaris received 2% metronidazole gel on the right side of their face and placebo on the left side of their face twice daily for 8 weeks. The number of inflamed and noninflamed facial lesions and side effects of treatment were documented on weeks 1, 2, 4, and 8. The patients' overall satisfaction was recorded at the end of the study. For statistical analysis we used the repeated-measures analysis, the chi-square test, Fisher's exact test, and the independent-samples *t*-test as appropriate. **Results:** Counts of inflamed and noninflamed facial lesions were comparable between the two sides at baseline. The number of the lesions was significantly lower on the metronidazole-treated side at all follow-up visits. Erythema and oily face decreased by 85.7% and 87.1%, respectively, on the metronidazole-treated side. Mild burning sensation and dryness on the metronidazole-treated side was reported by 3.4% and 22.9% of the patients, respectively. Eighty-eight percent of the patients were satisfied with the results of treatment on the metronidazole-treated side. **Conclusions:** Metronidazole gel (2%) is an effective, safe, and well-tolerated topical medication for moderate acne vulgaris.

Key Words: *Acne vulgaris, efficacy, 2% metronidazole gel*

What was known?
1. There is only limited number of studies with application of topical metronidazole in acne vulgaris with heterogeneous results.
2. Propionibacterium acnes has traditionally been considered a metronidazole-resistant microorganism.

Introduction

Acne vulgaris is a common dermatologic disease that is usually managed by application of topical preparations, systemic medications, or a combination of the two.[1-3] Antibiotics play a pivotal role in treatment. However, the emergence of new resistant strains or cross-resistance, development of various side effects, and poor tolerability are factors that sometimes limit their usefulness.[4-8] Successful management of acne needs careful selection of anti-acne agents according to clinical presentation and individual patient needs.[9] Today, different topical therapies are available for patients with acne vulgaris, including comedolytic agents, anti-inflammatory medications, antibiotics, and even herbal preparations.[10-16] Metronidazole is an antibacterial agent that is available in the form of an aqueous gel for topical application. Its mechanism of action in acne vulgaris is thought to be associated with its anti-inflammatory, immunosuppressive, and/or antimicrobial properties.[17,18] There is a very limited number of studies on the topical use of metronidazole in acne vulgaris.[19,20] This study aimed to evaluate the efficacy of 2% metronidazole gel in moderate facial acne vulgaris.

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Materials and Methods

Study design and participants

In this double-blind, placebo-controlled, split-face clinical trial conducted at a referral teaching clinic of dermatology, 78 young adults (age range: 18–30 years) with moderate facial acne vulgaris (acne grade III)[21] were recruited from September 2010 through July 2011. Reasons for exclusion were: acne secondary to other problems; pregnancy or intention to become pregnant; breastfeeding; another dermatological disease of the face; significant systemic disease, especially colitis; treatment with oral isotretinoin within the previous 1 year; taking any other acne treatment; history of having taken any medication that could interact with metronidazole within the previous 3 months; and known hypersensitivity to the study medication. The study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences. The study was conducted in accordance with the Declaration of Helsinki and good clinical practices guidelines. All patients provided written informed consent before participation.

Procedures

Type of facial skin was determined by a Sebumeter® SM 815 (Courage and Khazaka, Cologne, Germany) on five

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different sites of the face and, according to previously established criteria,[22] The patients were classified into two groups based on their skin type; with normal/dry (non-oily) skin or with oily skin. Topical 2% metronidazole gel was applied on the right side of the face twice daily for 8 weeks in all patients, while a similar-appearing water-based neutral gel (placebo) was simultaneously applied on the left side of the face in the same fashion. The metronidazole gel and placebo were filled in similar tubes that were marked 'right' or 'left,' indicating the side on which they should be applied. During the study period, only a caregiver who was not involved in the experiment was aware of the contents of the tubes; the patients and the examiner were blind to the topical compounds.

The 2% metronidazole gel was prepared in the Tabriz University Department of Pharmacy. Carbomer, as the gelifiant, was added to preserved water with methyl alcohol and propylparaben. Twenty-four hours later, the other components, including glycerin and polyethylene glycol, as well as metronidazole, were added to the prepared solution. The organoleptic and physical stability of both preparations were tested and confirmed.

The patients came for follow-up examinations on day 2 and weeks 1, 2, 4, and 8. All patients completed the study period. Counts of inflamed and noninflamed lesions, presence of erythema, the facial skin type (oily or not), and any possible complications/side effects were assessed and documented on each visit by a skilled dermatologist. On the last visit, the patients were asked about their satisfaction with the treatment.

Statistical analysis

Statistical evaluation was done using SPSS® for Windows v 18.0 (SPSS Inc., Il, USA). Data were shown as frequency (percentage) or mean±standard deviation (SD). The repeated-measures analysis, the Chi-square test, Fisher's exact test, or the independent-samples *t*-test were used as appropriate. $P \leq 0.05$ was considered statistically significant.

Results

Seventy patients, 26 males (37.1%) and 44 females (62.9%), with a mean age of 22.6±4.28 years (range: 18–30 years) were enrolled in this study. The mean duration of acne in the study population was 3.03±1.54 years (range: 2–5 years). Counts of inflammatory, noninflammatory, and overall (inflammatory plus noninflammatory) facial lesions are summarized and compared between the two sides on different occasions in Table 1. The two sides were comparable with regard to the baseline counts. On the other occasions, decrease of the mean lesion counts was significantly more on the right side of the face than on the left side (repeated-measures analysis, $P<0.001$ on all occasions). At the last visit, the number of cases with erythema and oily skin on the metronidazole-treated side had decreased by 85.7% and 87.1%, respectively ($P<0.001$), whereas there was no change on the contralateral side. The side effects on the metronidazole-treated side were mild burning sensation in 22 patients (31.4%) and mild dryness of skin in 16 other patients (22.9%). However, none of these side effects led to discontinuation of treatment and all the participants completed the study. At the last visit, 88% of the patients stated that they were satisfied with the results of treatment on the right side, whereas none reported satisfaction with the treatment results on the left side ($P<0.001$).

Table 1: Counts of the lesions on both sides of the face at the different visits

Lesion	Week	Metronidazole (*n*=70)	Placebo (*n*=70)	*P* value
Inflammatory	0	24.31±5.12	22.66±4.43	0.55
	1	18.37±4.79	21.81±4.25	0.04*
	2	13.17±5.80	22.42±5.23	<0.001*
	4	9.01±4.86	23.58±4.44	<0.001*
	8	4.49±3.12	21.19±5.74	<0.001*
Noninflammatory	0	17.62±4.35	16.19±5.01	0.62
	1	12.57±4.91	16.41±5.62	0.03*
	2	9.23±3.06	15.32±4.49	<0.001*
	4	6.80±2.49	16.12±5.11	<0.001*
	8	3.40±2.92	16.67±4.47	<0.001*
Total	0	37.69±4.06	36.82±4.32	0.97
	1	31.12±5.59	35.23±5.18	0.02*
	2	23.38±4.83	36.79±4.47	<0.001*
	4	16.08±5.29	39.61±5.16	<0.001*
	8	7.41±4.12	39.32±4.89	<0.001*

Data are presented as mean±standard deviation; *Statistically significant

Discussion

In the present study, 2% metronidazole gel was shown to be an effective and safe topical medication for treating moderate acne vulgaris. There are only limited numbers of studies that have similarly examined the effect of metronidazole topical application on acne vulgaris, and the results have been variable. While Tong *et al*. found no significant benefit of 0.75% metronidazole gel over placebo in reducing counts of inflamed and noninflamed lesions in mild to moderate acne vulgaris,[19] Bannatyne reported significant efficacy of the drug in a similar setting.[20] Nielsen compared 2% metronidazole and 5% benzoyl peroxide cream in acne vulgaris and reported that 2% metronidazole cream was significantly better than the 5% benzoyl peroxide gel. It was also shown that 2% metronidazole and 5% benzoyl peroxide cream were both equal in efficacy to systemic oxytetracycline therapy.[23] Our findings are in concordance with the results of Nielsen's study. The high efficacy of 2% metronidazole gel is despite the fact that *Propionibacterium acnes* has traditionally been considered a metronidazole-resistant microorganism.[24-27] So, mechanisms other than microbicidal action may underlie the therapeutic effect of metronidazole, such as

anti-inflammatory, immunosuppressive, and anti-itching actions, as well as the inhibition of free radical generation by human neutrophils.[28] Nevertheless, development of resistant strains is always a worry and the use of therapeutic regimens that incorporate agents with complementary but different mechanisms of action is a possible strategy in this regard.[29] Recurrence of acne after drug withdrawal is another important issue that should be examined in future studies.

What is new?
In patients with moderate acne vulgaris, 2% metronidazole gel is an effective, safe and well-tolerated topical medication.

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Efficacy of Suction Blister Epidermal Graft without Phototherapy for Locally Stable and Resistant Vitiligo

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Abstract

Introduction: Surgical methods for treatment of vitiligo include punch grafts, blister grafts, follicular grafts and cultured melanocyte grafts. The aim of this study was to determine the efficacy of suction blister grafts for treatment of vitiligo, without the use of phototherapy. **Materials and Methods:** This clinical trial study was conducted on 10 patients with vitiligo that was resistant to usual treatments and with limited involvement in the affected sites. We used cryotherapy and a manual suction device for blistering at the recipient and donor sites, respectively. The blister was separated and fixed with sutures and a dressing to the recipient site. Repigmentation of lesions was evaluated monthly for 6 months after treatment. Repigmentation rates higher than 90%, between 71%–90%, from 51%–70%, and less than 50% were graded as complete, good, moderate, and poor, respectively. **Results:** Ten patients (five females with a mean age of 23.2±3.96 years and five males with a mean age of 30.60±4.15 years) were enrolled in the study. Reponses to treatment after a 6-month follow-up were 'complete,' 'good,' and 'moderate' in 7 (70%), 1 (10%), and 2 (20%) patients, respectively. **Conclusion:** With this technique, patients with restricted sites of involvement, that did not respond to the usual treatments showed very good repigmentation without any additional phototherapy over a 6-month follow-up; moreover, there were no side effects such as scarring.

Key Words: *Blister graft, PUVA, repigmentation, vitiligo*

What was known?
Suction Blister graft without PUVA Therapy is an effective treatment for stable Vitiligo.

Introduction

Vitiligo is an acquired pigmentary disorder that is caused by loss of melanin, resulting in depigmented skin, mucous membrane, eyes, and sometimes hair bulbs. It occurs worldwide, with a prevalence of 0.1%–2% in various populations.[1,2] A number of therapeutic options for regimentation are available. Narrow-band UVB is effective and considered by many to be the first choice for most patients.[3–6] Psoralens and UVA treatment is the most important treatment for generalized vitiligo that affects more than 10%–20% of the cutaneous surface. For localized vitiligo, topical corticosteroids or calcineurin inhibitors are the most valuable treatments.[4]

Surgical techniques have also been introduced for stable, segmental and unresponsive vitiligo. A number of dermatosurgery techniques are available to promote repigmentation of vitiligo in adults and children, such as mini- or punch grafts, split-thickness skin grafts, cultured epidermal sheets, cultured melanocyte suspensions, follicular grafts and suction blister grafts.[7–18] Among these methods, the highest success rates have been achieved with split–thickness skin grafts and epidermal blister grafts. For better results, phototherapy or photochemotherapy of donor sites can also be performed after or before grafting.[19–21] Because phototherapy is not without limitations and side effects, the aim of the present study was to evaluate treatment of stable vitiligo in Iranian patients using suction blister grafting, without phototherapy either before or after grafting.

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Materials and Methods

The patients enrolled in this study had limited vitiligo that was stable but resistant to common treatments. They were admitted to the dermatology ward of the Imam Reza Hospital, Mashhad, Iran. Patients excluded from the study included those with unstable disease and those under 18 years (because of the pain associated with surgical procedures). All patients were advised to discontinue previous treatments at least 1 month before the grafting procedure to minimize any possible drug effects.

The day before surgery, relatively intense cryotherapy was done at the vitiligo-affected recipient site. Cryotherapy was performed with liquid nitrogen and a cotton swab through two cycles of 15–20 seconds, with 20 seconds intervals. On the day of surgery, a donor site was selected on the medial aspect of the thigh (with normal skin) and the area was cleaned first with povidone iodine and then with normal saline. After local anesthesia, the site was attached to the vacuum device and the device piston was

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pulled steadily to produce a high negative pressure. For blister induction at the donor site, we used a YUEXIAO™ vacuum device (made in China) that is originally intended for relieving muscle and joint pain [Figure 1]. After about 3–4 hours of application of suction, the blister was ready and was removed by scalpel or scissors and placed in a dish containing normal saline. The donor site was dressed with antibiotic ointment and Vaseline gauze. After removing the roof of the donor and recipient site blister, donor graftable epidermis was placed on the recipient site, sutured with 6-0 nylon and then covered with antibiotic ointment and Vaseline gauze. To prevent shifting of the graft, wet sterile cotton was applied over the area and covered with sterile gauze, with the dressing firmly bound in place with a compression bandage. After surgery, a 7-day course of antibiotic (cephalexin 500 mg qid orally) was given and the patient was advised to keep the site immobilized for a week. The dressing was changed after a week and sutures were removed after 2 weeks. Finally, repigmentation rates were evaluated by comparing images of the lesions every month for 6 months after surgery. Repigmentation rates >90%, 71%–90%, 51%–70%, and <50% were graded as 'complete,' 'good,' 'moderate,' and 'poor,' respectively.

Results

In this study, 10 patients (5 female and 5 male) with stable vitiligo were evaluated for response following suction blister grafting, without pre- or post-graft phototherapy. The mean ages of our male patients and female patients were 30.60±4.15 and 23.20±3.96, respectively. Responses to treatment at different follow-up evaluations are presented in Table 1. No gender differences were noted in the response to treatment, although 'complete' responses were more common in men and 'moderate' responses were more common in women. Responses to treatment were mild, moderate, good, and complete in 20%, 20%, 40%, and 20% of patients, respectively, after 1 month of follow-up. After 5 and 6 months of follow-up, moderate, good, and complete responses were found in 20%, 10%, and 70% of patients, respectively [Figure 2].

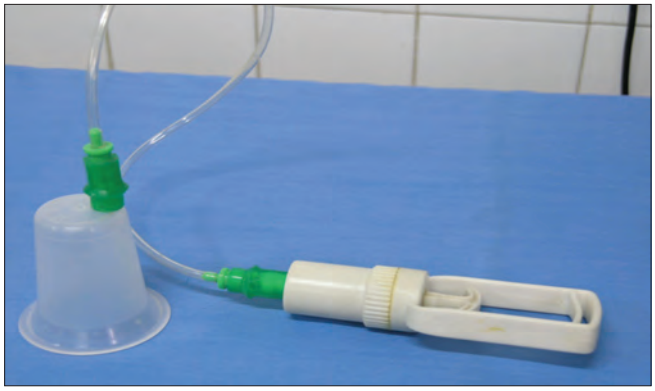

Figure 1: The vacuum device that was used for this study

Discussion

Vitiligo should initially be treated with medical therapy. When the therapy fails in spite of all appropriate interventions, surgical treatment may be indicated.[3] Autologous skin grafts can be obtained from uninvolved skin using several techniques, including a number of dermatosurgery techniques.[1] Each method has its advantages and disadvantages. The mini-graft is the simplest, least expensive, and most commonly used, but it has the highest rate of adverse effects, with 35% risk of cobblestone appearance at the recipient site and hypopigmentation and keloid formation at the donor site.[22,23] Thin split-thickness grafting has the highest mean success rate (87%) according to a systematic review by Njoo *et al*.[19] Transplantation of cells cultured *in vitro* from a small piece of donor skin is also used for treatment of large areas by expanding the melanocyte population; however, this method is very expensive and requires special and advanced laboratory facilities that is now available only at a few academic centers.[3] Suction blister grafting is accomplished by suction of viable epidermis from dermis and pigmented epidermis is used for coverage of achromic areas. In most studies in the literature, when epithelization was completed (usually after 1 week) phototherapy was used to induce proliferation and migration of melanocytes in the recipient sites.[24–26] The repigmentation rate in

Table 1: Responses to blister graft surgery at different follow-up evaluations in female (F) and male (M) patients.

Follow-upvisit (month)	Responses to treatment			
	Mild F/M	Moderate F/M	Good F/M	Complete F/M
1 month	0/2	1/1	2/2	2/0
2 month	0/0	0/3	2/0	3/2
3 month	0/0	0/2	2/0	4/2
4 month	0/0	0/2	1/1	4/2
5 month	0/0	0/2	0/1	5/2
6 month	0/0	0/2	0/1	5/2

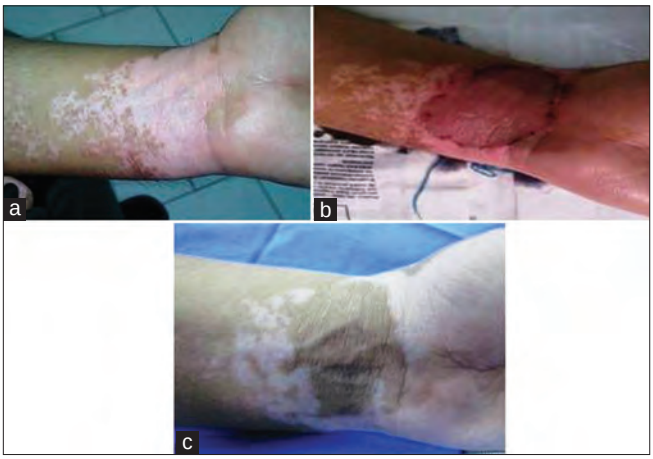

Figure 2: (a) before the blister graft, (b) 1 month after graft surgery, and (c) 6 months after graft surgery

these studies, according to the review by Njoo *et al*., was 87%, whereas Ozdemi *et al*. reported rates between 25%–65%.[19,27] In a similar study in our region, Maleki *et al*. evaluated ten patients with refractory vitiligo who were treated by suction blister graft and subsequent PUVA therapy and reported over 90% repigmentation in seven patients.[28] Nanda *et al*. evaluated six patients with resistant eyelid vitiligo who underwent suction blister grafting without phototherapy (as performed in the present study) and reported repigmentation in all cases.[29]

In our study, blister grafting without phototherapy showed excellent results in 70% of our patients. The advantages of this technique include low cost, absence of scarring and the possibility of reusing the donor site. The disadvantages are that it is time consuming, painful and not suitable for large areas, uneven surfaces and the palm. Our study shows that this technique is effective and safe for treating stable and limited vitiligo especially when phototherapy is not available.

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What is new?
This study shows our technique is a simple, low cost and effective treatment especially when phototherapy is not available.

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Chronic Bullous Disease of Childhood with IgG Predominance: What is the Locus Standi?

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Abstract

Linear IgA disease (LAD) is an acquired, autoimmune, subepidermal, blistering disease, characterized by linear deposition of IgA along the dermoepidermal junction on immunofluorescence. Some cases known as 'mixed immunobullous disease' show weak staining with other immune reactants like IgG, IgM or C3. We report a rare case of a child having typical manifestations of LAD (chronic bullous disease of childhood), but with IgG predominance rather than IgA. Obviously it is improper to term this as linear IgA disease. Such cases are reported in literature as variants of LAD, with a multitude of terms like mixed immune bullous disease, linear IgG / IgA disease, linear IgA / IgG disease, and so on. In view of the tremendous confusion that these multiple terms cause in the absence of any practical benefit, we propose that the broad term 'chronic bullous disease of childhood' be applied to all childhood cases, irrespective of the nature of the immune deposits.

Key Words: *Chronic bullous disease of childhood, linear IgA disease, linear IgG / IgA disease, mixed immunobullous disease*

What was known?

1. Linear IgA disease is a subepidermal immunobullous disease having childhood and adult variants, both of which show characteristic linear deposition of IgA at basement membrane zone on direct immunofluorescence.
2. Rarely, "mixed immunobullous disease" can occur in LAD, with weak deposition of IgG, IgM or C3 in addition to IgA.

Introduction

Linear IgA disease (LAD) is defined as an acquired, autoimmune, subepidermal, blistering disease of unknown etiology, characterized by linear deposition of IgA along the dermoepidermal junction on immunofluorescence.[1,2] The target antigens are BP 180 / collagen XVII and its shed ectodomain [97 kD], BP 230 or LAD285.[3] The disease occurs with slightly different clinical patterns in adults and children, and is also called 'chronic bullous disease of childhood' in the latter.[3] Until 1975, this entity was confused with bullous pemphigoid or dermatitis herpetiformis, especially in adults, due to the overlapping clinical features. The distinction between LAD and bullous Pemphigoid / dermatitis herpetiformis is mainly based on the characteristic linear deposition of IgA along the basement membrane zone on immunopathology in the former.[1] Some cases known as 'mixed immunobullous disease' show other immune reactants like IgG, IgM or C3, albeit with weaker staining.[2,4] However, there are very few reports of cases presenting with typical clinical manifestations of LAD, but showing a predominant deposition of IgG rather than IgA.[5] Obviously it is improper to term these as linear IgA disease. Whether to consider this as a distinct entity or a variant of bullous pemphigoid is controversial. Alternatively, these cases have been termed by some authors as 'linear IgG / IgA disease'.[2,4] One such rare case of a child having typical manifestations of chronic bullous disease of childhood showing predominant deposition of IgG rather than IgA is reported here. Also, the discrepancy in the terminology of this uncommon entity is discussed.

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Case History

A five-year-old boy presented with recurrent, multiple, itchy, blisters all over the body since two months. The lesions burst open within two to three days, forming erosions with serous discharge and crusting, again followed by new blisters appearing around the healing erosion. There was no history of mucosal involvement, photosensitivity, prior drug intake, trauma, consanguinity or similar lesions in the family. A general physical and systemic examination was normal. On cutaneous examination, multiple grouped vesicles, bullae, and erosions were present all over the body, particularly more over the perioral, perineal, and lower trunk areas [Figure 1]. The palms, soles, external genitalia, and mucosae were spared. The characteristic annular arrangement of the vesicles / bullae around a crusted, erythematous plaque, described as 'string of pearls sign' or 'cluster of jewels', was seen in many sites [Figures 2 and 3].

Routine hematological and biochemical parameters, Gram stain, and Tzanck smear did not reveal any significant abnormality. Histopathology showed subepidermal bulla with predominantly neutrophilic infiltration within the bulla and the dermis [Figure 4]. Direct immunofluorescence of the perilesional skin revealed linear deposition of IgG [+++], IgA [++], and C3, along the basement membrane

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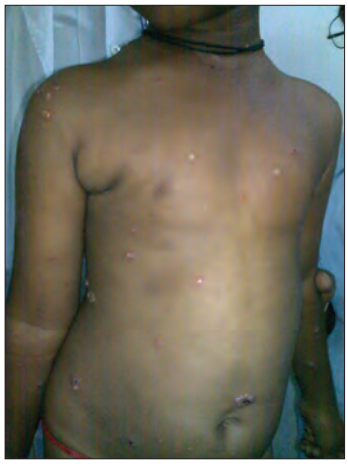

Figure 1: Multiple vesicles, bullae, and erosions present all over the body

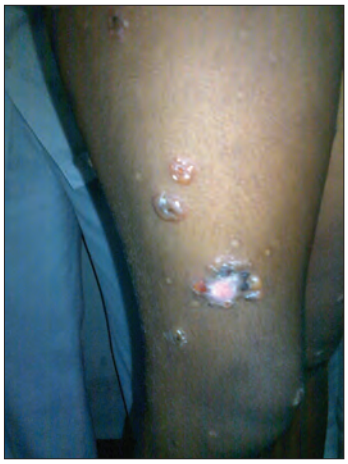

Figure 2: Characteristic annular arrangement of vesicles / bullae around a crusted, erythematous plaque, appearing as a 'string of pearls' or 'cluster of jewels'

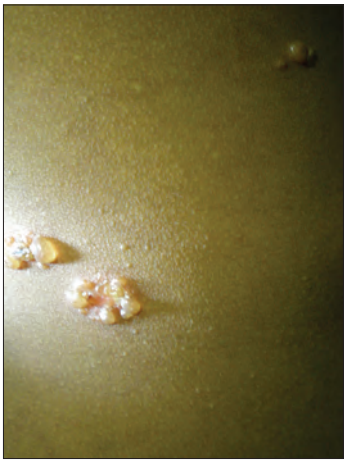

Figure 3: The 'string of pearls' or 'cluster of jewels' sign, pathognomonic of chronic bullous disease of childhood

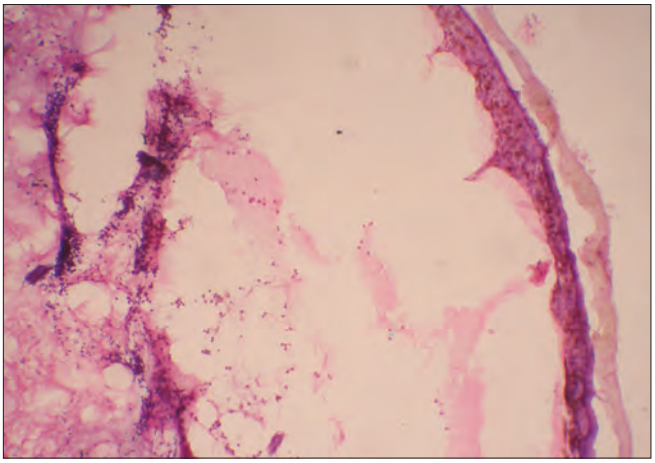

Figure 4: Subepidermal bulla with predominantly neutrophilic infiltration within the bulla and the dermis [H and E, 10×]

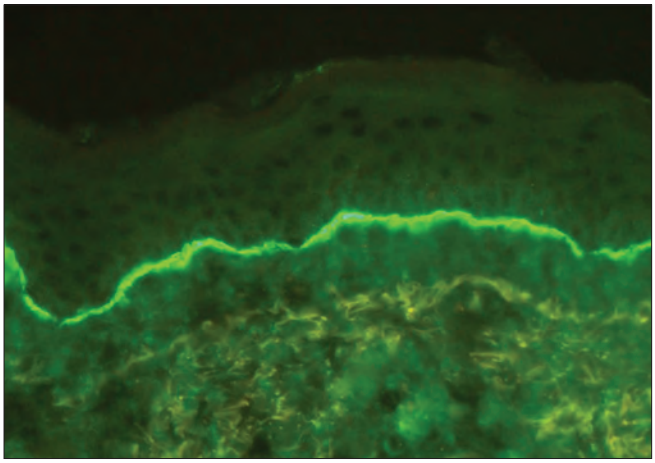

Figure 5: Linear deposition of IgG, IgA, and C3 along the dermoepidermal junction on direct immunofluorescence

zone [Figure 5]. Based on the clinical, histopathological, and immunopathological features, a diagnosis of chronic bullous disease of childhood, but with IgG predominance was made.[3] Dapsone 25 mg / day (body weight was 15 kg) was given, apart from potassium permanganate compresses and symptomatic therapy.[3,4] The patient showed excellent response within 15 days, with minor and short lasting recurrences thereafter for a few months.

Discussion

Linear IgA disease occurs in two different clinical patterns depending on the age of onset. In children, the onset is usually below five years of age. In adults, the peak age of onset is in the fifth decade.[6] The childhood disease (chronic bullous disease of childhood) manifests with an abrupt onset of itchy vesicles or large tense bullae. The annular arrangement of vesicles / bullae around a crusted, erythematous plaque, described as 'string of pearls sign' or 'cluster of jewels sign' is pathognomonic.[3] There is a predilection for perioral, perineal and lower trunk areas.[3] On the other hand, linear IgA disease of adults shows considerable variation in the morphology and distribution of the lesions. Scattered tense blisters resembling bullous pemphigoid are much more common than the cluster of jewels appearance. Perineal and perioral involvement is

less common than in children.[6] Mucosal erosions or ulcers can occur in both the age groups. The childhood disease undergoes spontaneous remission in most cases by the age of six to eight years, whereas, the adult type is more protracted in nature.[3,6]

The current consensus is to consider both the childhood and adult cases with linear deposition of IgA at the basement membrane zone as age wise variants of a single entity termed, 'Linear IgA disease'.[6] However, confusion arises when immune deposits other than IgA are predominant. Adult cases showing predominant IgG or C3 deposition are usually considered as bullous pemphigoid rather than LAD in view of the overlapping clinical features. However, in children, cases with IgG predominance cannot be included under bullous pemphigoid if the typical 'string of pearls' lesions are present. Hence, such cases are considered to be variants of LAD and recorded with a multitude of terms like mixed immune bullous disease, linear IgG / IgA disease, linear IgA / IgG disease, and so on.[2,4]

Powell *et al.* observed that irrespective of whether IgA or IgG is predominantly deposited, the clinical features, response to treatment with dapsone, and prognosis of the childhood disease remain the same.[7] This was true in the case described by us too, as the child had a typical 'string of pearls' sign and showed excellent recovery with dapsone, despite IgG predominance. Therefore, the classical cases with predominant IgA deposition (linear IgA disease) as well as mixed immune bullous disease (linear IgG / IgA disease or linear IgA / IgG disease) seem to be practically the same entity. The division of this clinically homogeneous entity into the classical form and variants, based on the immunopathology seems artificial, futile, and confusing. Considering all these factors, indiscriminate use of terms like linear IgA disease, linear IgA bullous dermatosis of childhood, mixed immune bullous disease, linear IgG / IgA disease, linear IgA / IgG disease, and so on, should best be avoided in childhood cases.[7,8] Hence, we propose that all cases showing the typical clinical picture of 'cluster of jewels' or 'string of pearls' sign should be included under the broad term 'chronic bullous disease of childhood,' irrespective of the nature of the immune deposits. By implication, probably the childhood disease is a separate entity with variable immune deposits, but with unique clinical features as the unifying factor, as opposed to the linear IgA disease of adults, where the clinical features are variable, but the linear deposition of predominantly IgA is an essential factor.

What is new?
A rare case of a child having typical manifestations of chronic bullous disease of childhood but showing predominant deposition of IgG rather than IgA at basement membrane zone is reported here.

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Announcement

Android App

A free application to browse and search the journal's content is now available for Android based mobiles and devices. The application provides "Table of Contents" of the latest issues, which are stored on the device for future offline browsing. Internet connection is required to access the back issues and search facility. The application is compatible with all the versions of Android. The application can be downloaded from https://market.android.com/details?id=comm.app.medknow. For suggestions and comments do write back to us.

Tinea Capitis in the form of Concentric Rings in an HIV Positive Adult on Antiretroviral Treatment

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Abstract

Dermatophyte infection may present in the form of concentric rings caused by Trichophyton concentricum, known as Tinea Imbricata. In immunosuppressed patients, there are reports of lesions in the form of concentric rings caused by dermatophytes other than Trichophyton concentricum too, mostly by *Trichophyton tonsurans*, known as Tinea indesiciva or Tinea pseudoimbricata. We report a case of tinea capitis in a HIV-positive adult woman on antiretroviral therapy, who presented with concentric rings of papules and pustules with slight scaling on the scalp along with diffuse thinning of hair. Both Potassium hydroxide mount and culture showed the presence of Dermatophytes. Tinea capitis is considered rare in adults, but new cases are being reported in immunocompromised as well as in immunocompetent patients. The pertinent features of this case are: HIV-positive adult female on antiretroviral therapy, presenting with tinea capitis in the form of concentric rings; culture from the lesion grew *Microsporum audouinii*; responding to oral Terbinafine.

Key Words: *Tinea imbricata, tinea indecisive, tinea pseudoimbricata*

What was known?

Tinea imbricata manifest as multiple concentric rings of fungal infection of skin, caused by Trichophyton concentrcum. Cell mediated immunity is considered to be the main mechanism of defense against fungal organisms. Decreased or negative delayed type hypersensitivity response is known to occur in patients suffering from Tinea Imbricata, which might be responsible for concentric rings of infection

Introduction

Tinea imbricata or Tokelau is fungal infection of the skin, which manifest with multiple concentric rings of erythematous papules, pustules, scaling and crusting, caused by Trichophyton concentricum, an anthrophphillic dermatophyte. Tinea pseudoimbricata or tinea indecisiva are the terms given for similar clinical presentations caused by fungal agents other that Trichophyton concentricum, like Trichophyton tonsurans, mainly in patiets with prolonged use of steroid and anti fungal topical medications or inadequate treatment with anti fungal agents leading to re-infection by the same pathogen, forming concentric rings. Genetic, environmental and immunological factors play a major role in development of this disease. Decreased immune response to Trichophyton concentericum is well known in patients of Tinea imbricata. Diagnosis can be easily made by clinical examination because of its characteristic appearance. Scrapings from the affected skin show fungal hyphae and culture on Sabouraud's dextrose agar or Mycosel agar (Sabouraud's medium plus cycloheximide and chloramphenicol to inhibit bacterial growth) grow fungal colonies in 8-15 days. Many treatments have been used for managing Tinea Imbricata. General guidelines include use of combined systemic and topical anti fungal agents.

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Case Report

A 35-year-old HIV-positive woman presented to us with concentric rings of pustules and papules, with multiple rings of scaling present on almost the entire scalp, extending on to the forehead anteriorly, along with diffuse thinning of hair [Figures 1 and 2]. Her CD4 lymphocyte count was 99cells / (mm)^3 and she was receiving treatment with zidovudine, efavirenz, and cotrimoxazole, for the last 15 days. There was no family history of any skin complaint. Scraping from the lesion showed fungal hyphae on Potassium hydroxide (KOH) examination, and culture from the sample taken from the scalp grew *Microsporum audouinii*. The patient was treated with terbinafine 250 mg daily for three weeks and she had complete clinical and microbiological clearance at three weeks.

Discussion

Tinea capitis is considered rare in adults and usually accounts for less than 3% of all tinea capitis cases,[1-3] although reports of incidence as high as 11% are reported in the literature.[4] Tinea capitis is considered rare after puberty because of certain protective factors,[3,5-8] namely the fungistatic property of the increased sebum, sweat, greater thickness of hair, and presence of *Pityrosporum ovale* as a competing agent in this age group. The clinical presentation of tinea capitis varies in adults. In HIV patients, the rarity of tinea capitis has been explained by some[9] as being due to the increase in colonization of their

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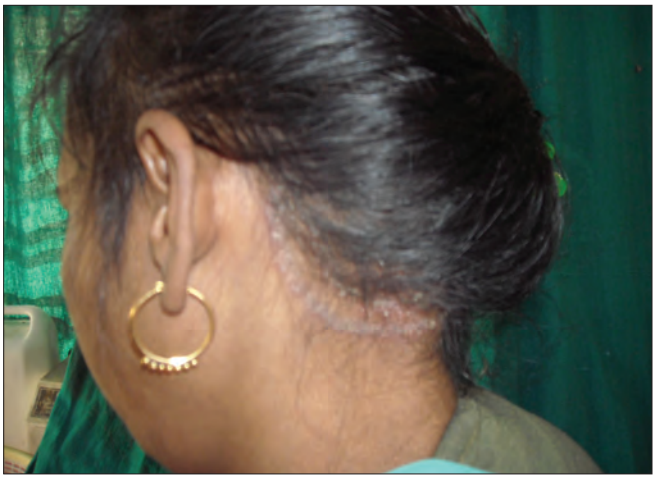

Figure 1: Concentric rings of papules and pustules with scaling

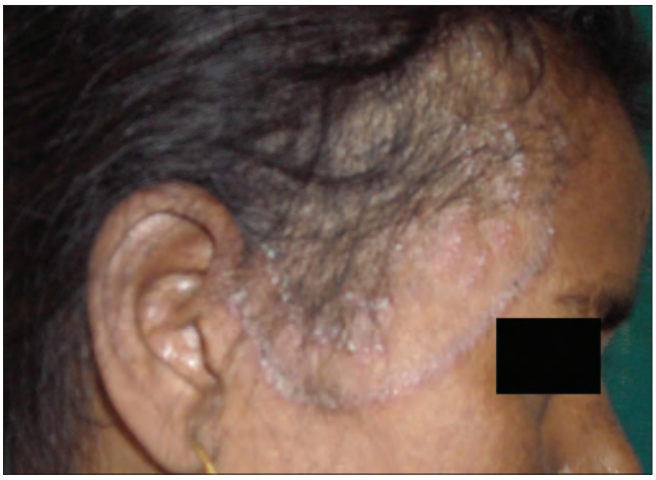

Figure 2: Concentric rings of tinea capitis extending to the face

scalp by *Malassezia* spp, thus competitively inhibiting the dermatophytes. Predisposing factors for tinea capitis in adults have been thought to be; impairment of health, source of fungal infection somewhere else on the body, children, zoophilic sources like pets, hormonal changes as in postmenopausal women, and so on.

However, unusual presentations are not uncommon in HIV-positive patients. A high degree of clinical suspicion and a careful mycological study are essential to diagnose it. The current patient presented with concentric rings of pustules and papules limited to the scalp. The KOH examination showed fungal hyphae. A culture on Sabouraud's dextrose agar with antibiotics grew *Microsporum audouinii*. An asymptomatic adult carrier state is also not a rare event.[6]

Tinea Imbricata manifests in the form of concentric rings on the body caused by Trichophyton concentricum. The occurrence of concentric rings has been explained in literature as being due to a negative, delayed-type hypersensitivity to the Trichophyton concentricum cytoplasmic antigen and T-lymphocyte hyporeactivity,[10] thus leading to a ring- within-a-ring formation. There are reports of patients presenting with tinea in the form of concentric rings caused by dermatophytes other than *Trichophyton concentricum*, mostly by *Trichophyton tonsurans* and *Microsporum gypseum*.[11-13] In all such cases reported as Tinea pseudoimbricata or Tinea indecisiva, patients were either systemically or locally immunosuppressed. Perhaps these cases simulated the mechanism of T-cell hyporeactivity and lack of delayed-type hypersensitivity to *Trichophyton concentricum* as seen in Tinea Imbricata. The current patient, who was HIV positive and had a CD4 count of 99 cells / $(mm)^3$, presented with a similar clinical presentation on the scalp, however, the culture grew *Microsporum audouinii.*

Cell-mediated immunity is the primary defense against fungal infections, although patients with tinea capitis usually develop specific antifungal antibodies, but these have a minor role. The clinical resemblance of such cases may be due to similar immunosuppressive processes involving the T cells. As in Tinea Imbricata, T-cell hyporeactivity allows sequential waves of infection and immune response, leading to a ring-within-a-ring formation. The same process might explain the current case also, as T-cells are the major target in HIV infection.

The treatment of tinea capitis in HIV-positive adults is not more difficult than in immunocompetent patients.[5] However, it is well known that in HIV-infected patients, adverse drug reactions are more common and a lower gastric acidity in such immunosuppressed patients causes diminution of drug absorption. Our patient has been clinically and microbiologically (post three weeks of treatment, KOH and culture were negative) treated with Terbinafine 250 mg daily for three weeks, but some have reported difficulty in treating cases of tinea capitis in HIV patients.[14] Prolonged treatment may be necessary and also due to the presence of achlorhydria, the dose of the anti-fungal may have to be increased. Relapses are also known to be more frequent in HIV-infected patients. Thus, not only can tinea capitis in immunosuppressed patients have atypical presentations, but it can also be refractory to treatment, with frequent relapses.

What is new?

In our knowledge, Microsporum audouinii has never been reported in the past to cause Tinea capitis, manifesting as Tinea pseudoimbricata or Tinea indecisiva. Such a presentation in immunocompromised patient, in this case, HIV positive female, strengthens the idea of T cell hyporeactivity as a factor in causing concentric rings of fungal infection, irrespective of the organism. HIV patients are known to have atypical clinical presentations of infectious disease (s). Management of such infections can also be difficult.

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Announcement

Dermatosurgery Registry of ACS(I)

Association of Cutaneous Surgeons (I) (www.acsinet.net) is happy to announce the launch of its online Dermatosurgery registry (www.acsiregistry.in). This registry has been created to obtain data on dermatosurgical procedures being performed by our members across the country. This is the first-of-its-kind effort to accumulate real-time scientific data online w.e.f 1st June 2012. Nine different commonly performed procedures have been selected for the purpose of documentation. The feedback from members of ACS(I) registered with the website will be pooled in the registry and various information on these dermatosurgical procedures will be available as a ready reference. The registry is password protected; the registry can't be accessed by anyone not registered in the site.

We request participation by all to make this unique project successful and pave the way for an entirely new era of real-time online documentation of scientific data on a large scale and nationwide basis.

Announcement

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In-Transit Metastases from Squamous Cell Carcinoma Penis

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Abstract

An in-transit metastasis is one that is located between the primary tumor and the closest lymph node region and results from tumor emboli getting trapped in the lymphatic channels. A 65-year-old male patient who had undergone partial amputation of the penis and bilateral inguinal lymph node resection for squamous cell carcinoma of the penis 4 months earlier developed multiple cutaneous metastatic lesions in the pubic region and scrotum. The case is reported for the uncommon presentation of in-transit metastases.

Key Words: *In-transit metastasis, inguinal lymph nodes, squamous cell carcinoma, penis*

What was known?
In-transit metastases, which manifest after resection of primary tumor and draining lymphnodes, are often mistaken for lymphangectasia, as in the present case.

Introduction

Cutaneous metastases are of diagnostic importance as they may be the first manifestation of an undiscovered internal malignancy or the first indication of metastasis from a supposedly adequately treated malignancy.[1] As a rule, cutaneous metastases usually appear in the skin close to the primary tumor. Most regional metastases probably occur through the lymphatic system, while distant metastases are more likely to occur via the hematogenous route.[2]

In-transit metastases are cutaneous metastatic foci located between the tumor and the closest regional lymph nodes. A case of squamous cell carcinoma (SCC) of the penis with numerous in-transit metastases in the pubic region and scrotum is reported for its rarity.

Case Report

In May 2010, a 65-year-old male patient presented at our hospital with complaints of numerous papules and nodules in the pubic and suprapubic region and the scrotum. According to him the lesions had been present for the last 4 months. In October 2009, he had undergone partial amputation of the penis at a tertiary care hospital for an ulceroproliferative growth involving the glans penis, which was histologically proven to be a moderately differentiated SCC.

A fine needle aspiration cytology (FNAC) of the left inguinal nodes at the same teritiary care hospital where patient underwent surgery, revealed well-differentiated metastatic SCC on the left side and reactive lymphoid hyperplasia on the right side. Bilateral block resection of inguinal lymph nodes, wth skin grafting from a donor site from the thigh, was performed. However, 4 months later he developed edema of both lower limbs, scrotum, and the suprapubic region. He also developed multiple painless papules and nodules in the above areas, with some of the lesions discharging a clear fluid. A diagnosis of post-lymphadenectomy lymphangiectasia, was entertained at that time at the tertiary care hospital and the patient was treated conservatively and reassured.

He presented at our hospital in May, 2010, with multiple papules and nodules (some of them ulcerated) on the scrotum and the pubic and suprapubic regions. Local examination revealed edema of the scrotal skin and suprapubic region, a short stump of the amputated penis, postsurgical scars in both inguinal regions, and postinflammatory pigmentary changes – both hypo- and hyperpigmentation – at the donor site on the thigh [Figure 1]. There were multiple firm papules and nodules of about 2–3 mm in size, some of them ulcerated and discharging serous fluid, in the pubis, suprapubic region, and scrotum. A biopsy from one of the papules revealed a metastatic deposit. [Figure 2] Roentgenogram of the chest and ultrasonogram of the abdomen did not reveal any metastatic deposits. Other than anemia (with hemoglobin of 8.1 gm%), the routine hematologic and biochemical investigations did not reveal any abnormality.

A diagnosis of SCC with in- transit cutaneous metastasis was made and the patient was referred back to the tertiary hospital for further management. However, he was later lost to follow-up.

Discussion

Carcinomas arising from modified skin such as the glans penis and the vulva and from the oral mucosa have a rather high rate of metastasis unless they are recognized and adequately treated at an early stage.[3] Carcinomas arising in sun-damaged skin have a very low propensity

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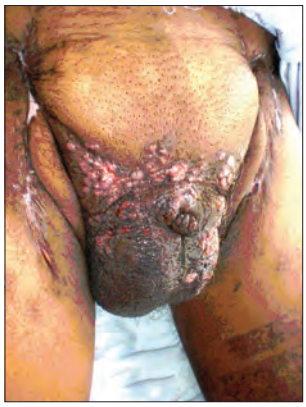

Figure 1: Edema of the scrotal skin and suprapubic region, the short stump of the amputated penis, and postsurgical scars in both inguinal regions.

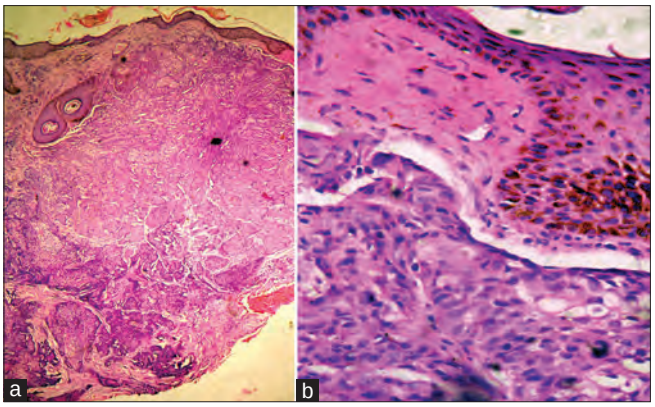

Figure 2: Islands of metastatic squamous cell carcinoma with a clear zone between the deposit and the epidermis. Overlying stratified squamous epithelium is normal (H and E; A ×200, B ×400)

to metastasize, the incidence being only about 0.5%.[4] The rate of metastases is higher in adenoid and mucin-producing SCC of the skin than in the common type.[3] However, in our patient, details about the histological type of the primary lesion were unavailable. Dissemination may take place via the lymphatics or the blood stream.[1]

In-transit metastases are cutaneous metastatic foci located between the tumor and the closest lymph node region. Analogous to in-transit metastasis found in melanoma, these represent metastatic spread along lymphatic vessels and/or nerves and their presence is an indicator of poor prognosis.

In the present case, in view of the innumerable papulonodules and the previous history of regional (i.e., inguinal) lymph node involvement as proved by FNAC study, lymphatic spread was probably the reason for these in transit metastases.

A case of penile cancer has been reported earlier where the patient presented with primary high-grade penile squamous carcinoma and secondary skin metastases, in addition to metastases to liver, lungs, and other organs.[5] However, in our patient there was no clinical or radiological evidence of involvement of other organs.

Overall, in-transit metastases occur most frequently from SCC risk stratified as high-risk lesions; however, all SCC that occur in immunosuppressed patients have the potential for distant spread. Ninety percent of metastatic SCC occurs within 3 years of diagnosis of the primary tumor. In our patient, however, the metastasis occurred within a much shorter period of 4 months. It is possible that the tumor emboli were already lodged in the lymphatic channels at the time the inguinal node resection was undertaken and hence this early recurrence.

Clinically, in-transit metastasis are nondescript, subtle, waxy, gray-white or flesh-colored papules of about 2–6 mm diameter and are not contiguous with the primary lesion.[6] This was the picture in our patient, who had multiple such nondescript papules. An erroneous diagnosis of postsurgical sequelae and lymphangiectasia is often made. Such a diagnosis was entertained in the present case also at the tertiary care hospital 3 months prior to his visit to our hospital.

In a review of 21 cases with in-transit metastases, Carucci *et al*. reported that patients presented most commonly with discrete dermal papules distinct from, but in the vicinity of, the primary tumor site.[6] In their series, histologic differentiation was variable. These findings are similar to the features in our patient.

Local control of in-transit metastasis should be achieved with Mohs surgical technique or some other surgical method, where the surgical margins are rigorously evaluated for residual tumor, perineural extension, or intravascular invasion (e.g., excision with intraoperative frozen section control or excision with postoperative margin assessment). Postoperative radiation should be strongly considered. The radiation field often involves the primary tumor site, the in-transit metastatic site, and the draining lymph node basin. Our patient was referred for further treatment to the same tertiary care hospital where he had earlier undergone surgery for his SCC penis, but he was lost to follow-up.

This case is presented because of the uncommon presentation of 'in-transit' metastases after the primary tumor and the regional lymph nodes were resected.

What is new?
The case is reported to highlight the importance of correct diagnosis which can be arrived at only by histopathological examination of the lesion, in view of the vast difference in prognosis.

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Announcement

Retraction Notice

1. Jalel A, Soumaya GS, Hamdaoui MH. Dermatology life quality index scores in vitiligo: Reliability and validity of the Tunisian version. Indian J Dermatol 2009; 54(4):330-3 (http://www.e-ijd.org/article.asp?issn=0019-5154;year=2009;volume=54;issue=4;spage=330;epage=333;aulast=Jalel)

Based on the report of a fact finding committee as appointed by the editorial board of Indian Journal of Dermatology and in consultation with the journal Ombudsman last year (2011) the above article was retracted (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3108510/) from the online and offline version of Indian Journal of Dermatology and the authors were barred from submitting their manuscript(s) to IJD® for the next 5 years on the charges of plagiarism as the presented patients, data, results and discussion were identical with those of an article published in BMC Dermatology in 2004 cited below.

Aghaei S, Sodaifi M, Jafari P, Mazharinia N, Finlay AY. DLQI scores in vitiligo: reliability and validity of the Persian version. BMC Dermatology; 4: 8. Published online 4 August 2004

2. Jalel A, Yassine M, Hamdaoui MH. Oxidative stress in experimental vitiligo C57BL/6 mice. Indian J Dermatol. 2009;54(3):221-4 (http://www.e-ijd.org/article.asp?issn=0019-5154;year=2009;volume=54;issue=3;spage=221;epage=224;aulast=Jalel)

It has come to our notice that almost the same set of authors in that same year published another article (as above) which contains identical introduction, identical table and most of the discussion of an article published in Acta Dermatovenerol Alp Panonica Adriat in 2008 cited below.

Arican O, Kurutas EB. Oxidative stress in the blood of patients with active localized vitiligo. Acta Dermatovenerol Alp Panonica Adriat. 2008 Mar; 17(1):12 -6.(http://www.zsd.si/ACTA/PUBLIC_HTML/acta-apa-08-1/2.pdf)

In the background of serial academic dishonesty, the authors were initially served with a show-cause notice and on receipt of their clarification (deemed inadequate), based on unanimous decision of the Editorial Board, a complete restriction on the part of the journal on all future articles in which they are assigned/mentioned as an author/ coauthor was imposed and the corresponding author was communicated accordingly.

Now the second article is also being formally retracted from the online and offline version of the journal.

IJD® maintains a strict principle of absolute zero tolerance in matters like these.

- Editor, IJD®

Congenital Calcinosis Cutis of the Foot

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Abstract

Calcinosis cutis is a rare disease characterized by deposition of insoluble calcium salts in the skin. Subepidermal calcified nodule is a form of idiopathic calcinosis cutis that commonly affects children but rarely presents at birth. Herein we describe a healthy 10-month-old boy who had a solitary hard nodule on the left foot since birth. Surgical excision of the nodule was done and histopathology confirmed the diagnosis of subepidermal calcified nodule.

Key Words: *Subepidermal calcified nodule, idiopathic calcinosis cutis, congenital presentation*

What was known?
Calcinosis cutis is characterized by presence of calcium deposits in skin. Metastatic, dystrophic, iatrogenic and idiopathic are the four forms of calcinosis cutis.

Introduction

Calcinosis cutis is a group of disorders characterized by the presence of calcium deposits in the skin. There are four forms of calcinosis cutis: metastatic, dystrophic, iatrogenic, and idiopathic.[1] Metastatic calcification occurs in normal tissues secondary to abnormal calcium and phosphate metabolism. The dystrophic type of calcinosis cutis, the commonest form, manifests secondary to tissue damage. The iatrogenic type occurs following treatment. In the idiopathic type, calcinosis presents in the absence of either tissue damage or abnormal mineral metabolism. Idiopathic scrotal calcinosis, tumoral calcinosis, and subepidermal calcified nodule are grouped under idiopathic calcinosis. We present a case of congenital subepidermal nodule.

Case Report

A 10-month-old boy was brought to our department for an asymptomatic solitary, 3-mm size, firm white nodule over the heel of the left foot that had been present since birth [Figure 1]. The nodule had slowly grown in size during the first few months of life and then remained static. There was no discharge from the nodule. The infant had been delivered normally. The family history and medical history were unremarkable. General and systemic examination was normal. The infant had normal serum mineral values and renal function tests.

The nodule was excised and sent for histopathological study. Microscopic examination revealed massive compact hyperkeratosis and acanthosis of the epidermis. Dark basophilic-stained granular calcium deposits were found within cystic spaces in the dermis [Figure 2]. Von Kossa stain confirmed the presence of calcium [Figure 3]. Based on the clinical features and histopathology, we arrived at a diagnosis of subepidermal calcified nodule. On follow-up there has been no recurrence.

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Discussion

Solitary congenital nodular calcification was first described by Winer in 1952.[2] There are only a few case reports of subepidermal calcified nodule from India. Subepidermal calcified nodule, also called cutaneous calculi, predominantly affects children, and in some cases it is present at birth.[2–4] It is extremely rare in adults. Males are more commonly affected than females.[1] The majority of cases of subepidermal calcified nodule present as an asymptomatic small solitary nodule. Occasionally, there may be a few to numerous nodules.[3] Congenital calcinosis may also occur in a bilateral distribution. There may be a surrounding erythematous halo. Lesions are often present over the ears, eyelids, nose, fingers, and feet.[2,4,5] Occasionally, there may be involvement of the mucosa of lip, gingiva, hard palate, and tongue.[6] The surface can be smooth or warty. Younger lesions may have surface ulceration, whereas older lesions can be warty.[7] These nodules are not associated with systemic or cutaneous disorders. Subepidermal nodule can be considered as one of the differential diagnosis for wart or molluscum contagiosum in children.

The etiology remains uncertain. These lesions do not appear to arise from sweat glands or a preexisting nevus. It is hypothesized that subepidermal calcified nodule represents dystrophic calcification following needle stick injury during the neonatal period.[8] Some authors speculate that congenital calcinosis could be induced by trauma during gestation.[4]

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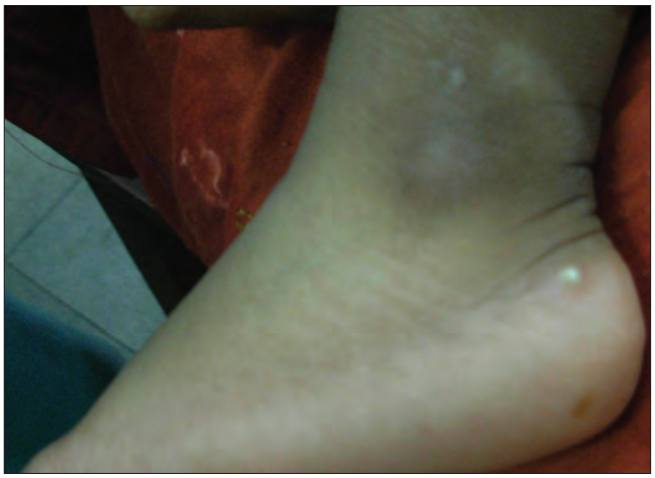

Figure 1: Photograph showing a single white nodule over heel of left foot

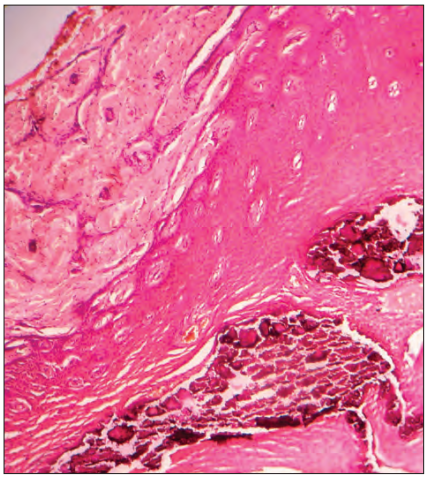

Figure 2: Photomicrograph shows massive compact hyperkeratosis, acanthosis and basophilic calcium granules within cystic spaces (H & E × 200).

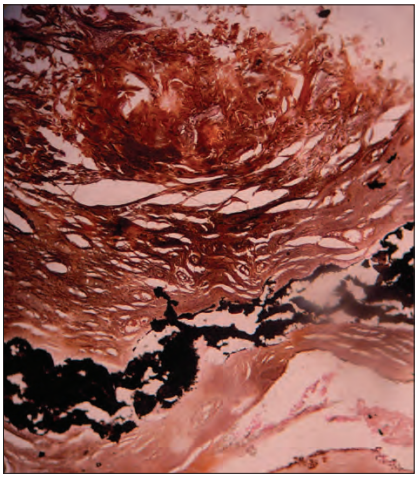

Figure 3: Photomicrograph showing calcium granules that have taken up black color (vonKossa X 200).

Histopathological examination shows calcium deposits predominantly in the upper dermis, though in large nodules they may be seen in deeper dermis.[2] Calcium is present as closely aggregated globules. Occasionally, there are few foreign body giant cells around the deposits. Calcium granules may be found within the epidermis, indicating transepidermal elimination.

The treatment of choice is surgical excision. If small and multiple, electrodessication or CO2 laser ablation may be done.[9] Recurrence following surgical excision is uncommon.[10]

This case is reported because of the rarity of congenital calcinosis cutis, especially that involving the foot.

What is new?
There are only a few case reports of idiopathic sub epidermal calcified nodule involving the foot from india

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Syphilis D' Emblee

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Abstract

A 28-year-old male patient presented to Skin, V.D. and Leprosy outpatient with a single gray white plaque on the left side of the lower lip for last 8 months and multiple papulosquamous lesions all over the body for last 6 months. There was history of blood transfusion for anemia 1 year back. Histopathology of lip lesion and reactive VDRL and TPHA tests confirmed the diagnosis as syphilis. We report this rare case of Syphilis d' emblee.

Key Words: *Blood transfusion, syphilis d' emblee, VDRL*

What was known?
Syphilis can be transmitted by blood transfusionand in this condition, no primary lesion appears.

Introduction

Syphilis is an infectious disease caused by Treponema pallidum. Syphilis, 'the great imitator', is among the most fascinating of skin disease. It may present to the dermatologist as a sexually acquired, contagious disease or as a congenitally acquired infection. Syphilis can be transmitted by blood transfusion, but it is very rare now and in this condition, no primary lesion appears. This is called Syphilis d' emblee. We present a patient with secondary syphilis who acquired the infection during blood transfusion.

Case Report

A 28-year-old unmarried male, office worker, presented to the Skin, V.D. and Leprosy department with a grayish white painless plaque on the left side of the lower lip for last 8 months and multiple papulosquamous non-pruritic lesions all over the body including palm and sole.

There was history of transfusion of 3 U of stored blood in to the patient for severe anemia 1 year back, in a local nursing home. The patient did not have history of any type of sexual contact. There was no history of hypertension, diabetes, tuberculosis or drug eruption. Similarly there was no history in the family members. On examination, lip lesion was grayish white in color, oval in shape and size was about 4 cm in diameter, soft and non-tender [Figure 1]. There was generalized lymphadenopathy and lymph nodes were palpable, mobile, non-tender and rubbery. There were also multiple papulosquamous non-pruritic lesions all over the body including trunk [Figure 2], upper and lower limbs, palms and soles but sparing oral mucosa and the genital. There was no loss of scalp hair. There was no scar of any previous lesions on the genital.

Hematological examination showed moderate anemia (8.2 gm%) and all biochemical parameters were within normal range. Serological tests for syphilis were positive (VDRL in 1:32 dilution and reactive TPHA) and ELISA for HIV-1 and 2 were negative. Incisional biopsy of the lip lesion was sent for histopathological study, which showed dense infiltration of plasma cells and few lymphocytes in the dermis, in and around blood vessels in the form of perivasculitis and intimal proliferation in few of the arteries and veins (endarteritis obliterans) [Figure 3]. Silver staining of the lip lesion showed multiple spirochetes.

The patient showed hypersensitive reaction during intradermal testing with benzathine penicillin. Then patient was put on oral azithromycin 1 gm stat and doxycycline 100 mg twice daily and partial regression of lesion was observed after nearly 3 weeks of treatment.

Discussion

Syphilis is a chronic disease with a waxing and waning course, the manifestations of which have been described for centuries. The causative organism is T. pallidum. The rate of primary and secondary syphilis, the most infectious stages of the disease decreased throughout the 1990s and in 2000 reached an all time low.[1] The primary mode of transmission is by sexual contact, and the next most common is transfer across the placenta.[2] Kissing, blood transfusion and accidental inoculation have also been reported as routes of transmission, but are of minor importance today. The risk of transmission through blood is negligible due to improved donor selection, uniform serological testing of all blood donor, and a shift from transfusion of fresh blood to transfusion of refrigerated blood components.[3,4] Transmission via blood products is nonetheless theoretically possible since organism

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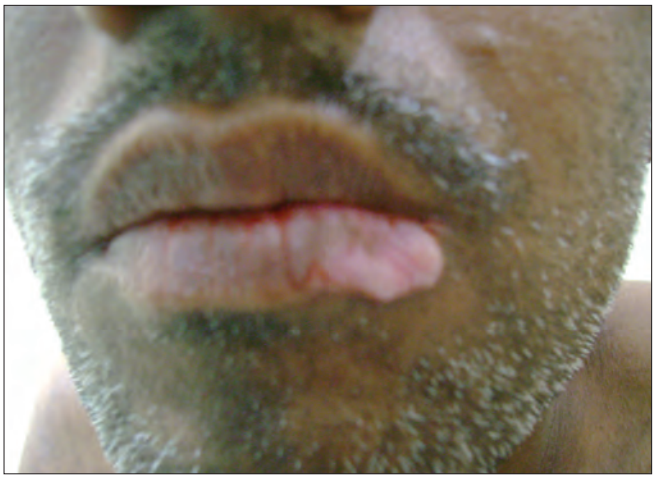

Figure 1: Lesion of secondary syphilis-flat papule (condyloma lata) on lip

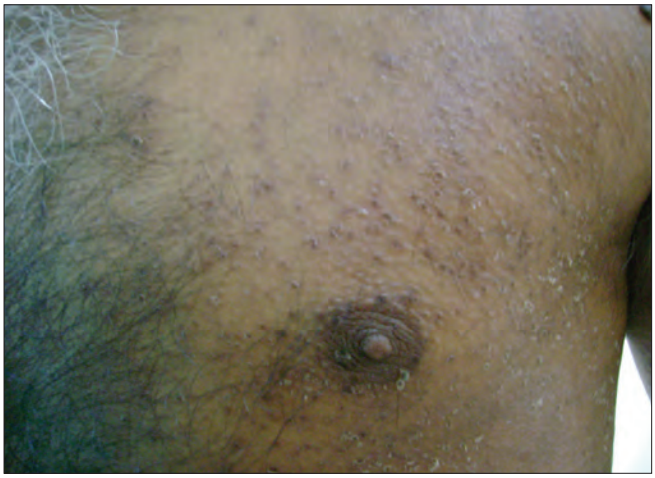

Figure 2: Lesions of secondary syphilis-papulosquamous lesions on trunk

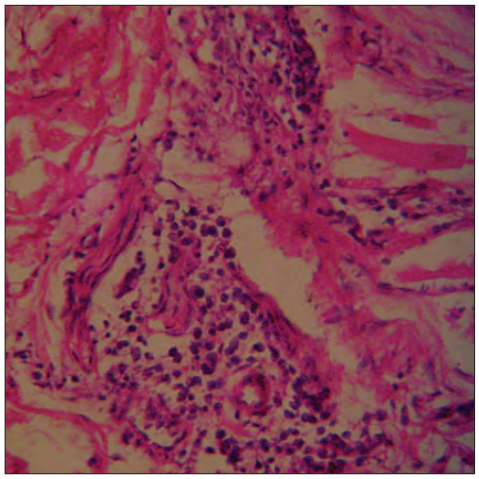

Figure 3: Histopathology of lip lesion(condyloma lata) showing plasma cell infiltration in dermis and endarteritis obliterance (H and E Stain ×400)

may survive for up to 5 days in refrigerated blood.[5] Needle sharing probably does not play a significant role in syphilis, but remains unclear.[6] Our patient developed lesions of secondary syphilis after transfusion of stored whole blood.

The disease has been arbitrarily divided into three stages. The primary stage is defined by a chancre at the site of inoculation. The secondary stage is characterized by a polymorphic rash, lymphadenopathy and other systemic manifestations. The tertiary stage is the most destructive and is marked by cardiovascular and neurologic sequelae and gummatous involvement of any organ system. Our patient presented with lesions of secondary syphilis including soft, non-tender plaque on the left side of lower lip, papulosqumaous lesions on the trunk, palms and soles and lymhadenopathy. The confirmed diagnosis of primary, secondary or early congenital syphilis are made by demonstration of organism by dark ground microscopy.[7] Serological test for syphilis include VDRL, T. pallidum immobilization test, fluorescent treponemal antibody absorption(FTA-ABS) test, T. pallidum hemagglutination assay (TPHA) test and EIA (Treponemal enzyme immunoassay) test.[8-11] In this case VDRL and TPHA tests were reactive. The characteristic histopathological findings of syphilis are perivascular infiltration of plasma cells and lymphocytes and intimal proliferation of both arteries and veins (endarteritis obliterans), which was seen in the biopsy of lip lesion of our case. The differential diagnosis of our case were Chancre, Squamous cell carcinoma lip, Lichen planus, Actinic granuloma, Leukoplakia, Psoriasis, Drug eruption and Graft versus Host Disease. Theoretically, the possibility of chancre of lip could not be ruled out but strongly denied of any type of sexual contact by the patient and history of blood transfusion indicate syphilis d' emblee.

Many antibiotics, with notable exceptions of the aminoglycosides and sulphonamides, have some treponemicidal activity.[12] Benzathine penicillin is the recommended first-line therapy for syphilis.[13] In patients who are hypersensitive to penicillin, regimens based on tetracycline, doxycycline, erythromycin, azithromycin, ceftriaxone and chloramphenical have all been used. The patient in this case showed hypersensitivity to penicillin so he was put on azithromycin 1 gm single dose and doxycyclin 100 mg twice daily and he had been responding to it.

What is new?
Though extremely rare, but strong clinical suspicion may lead to diagnosis of syphilis d' emblee even in this modern era of blood collection and transfusion.

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Announcement

ASPCR

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Date: 17th-19th May, 2013

Venue: Sydney, Australia

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Cardiofaciocutaneous Syndrome: A Rare Entity

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Abstract

The cardiofaciocutaneous (CFC) syndrome is a condition of sporadic occurrence, with patients showing multiple congenital anomalies and mental retardation and characteristic dysmorphic features. We, thus, report a rare case of this syndrome in a 1-year-old child who presented with typical features of CFC syndrome.

Key Words: *Anomalies, cardiofaciocutaneous syndrome, defects*

What was known?
The cardiofaciocutaneous (CFC) syndromeis a syndrome where patients have multiple congenital anomalies related to mentation, growth, cardiovascular system skin, eyes, gastrointestinal tract and central nervous system.

Introduction

The cardiofaciocutaneous (CFC) syndrome (OMIM 115150) is a syndrome where patients have multiple congenital anomalies or mental retardation, failure to thrive, psychomotor delay, a characteristic face, congenital heart defects, and abnormalities of the skin, eyes, gastrointestinal tract and central nervous system. Occurrence is sporadic, with men and women equally affected. The syndrome was first described 20 years ago by Reynolds *et al*[1] in eight children. Additional reports soon followed and, according to a recent review,[2] about 59 patients have been reported, providing the basis for an accurate delineation of the phenotypic spectrum of the syndrome. Nevertheless, a question has lingered for many years whether CFC is a unique and separate condition, or a variant of the Noonan syndrome (OMIM 163950)[3-9] or of the Costello syndrome (OMIM 218040).[10] A useful diagnostic approach was provided with the creation of a CFC index based on 82 clinical traits and their frequencies in the population with the CFC syndrome.[11] However, matters changed radically only with the discovery of different genes whose mutations cause each one of these syndromes: the protein tyrosine phosphatase SHP-2 gene PTPN11 for Noonan syndrome,[12] HRAS for Costello syndrome,[13] and KRAS, BRAF, mitogen-activated protein/extracellular signal-regulated kinase MEK1 and MEK2 for CFC.[14,15]

Case Report

One-year-old Indian boy was referred to our center at 8 months of age with some dysmorphic features and developmental delay for evaluation. He was a product of a full-term normal delivery with a birth weight of 3.6 kg (more than the 95th percentile). He had transient neonatal jaundice which needed phototherapy but without any complications. Developmental history showed a delay from the beginning with the child unable to crawl, sit or hold objects in hand or produce any sounds like the normal children. Family history revealed the child being the third sibling after two normal children and two early abortions. There was no history of consanguineous marriage. No similar condition existed in the family.

Clinically his weight was 10 kg (90th percentile), height 73 cm (75th percentile), and head circumference 44.5 cm (25th percentile).

Dermatological evaluation showed a dysmorphic child with asymmetrical face, bitemporal narrowing and prominant metopic sutures, epicanthic fold, wide mouth, sparse hair, and absent eye brows [Figures 1a-c]. His skin was dry and mildly hyperkeratotic; eczematous lesions were found on his neck and extremities, keratosis pilaris on his arms [Figure 2], seborrheic dermatitis on his scalp, and miliaria on his back.

There was an evidence of a vascular hemangiomatous plaque measuring 5 cm×3.5 cm involving the medial aspect of right lower limb [Figure 3].

The results of routine hematological examination, blood biochemistry analysis, urinalysis, thyroid function tests, and serum zinc level assessment were within the normal ranges.

Echocardiography was suggestive of small secundum atrial septal defect and patent ductus arteriosus. Ultrasound of the abdomen showed mild hepatosplenomegaly. MRI scanning of the brain showed bifrontal subdural T2 hyperintense areas plus prominence of the frontotemporal subarachnoid space and corpus callosum hypoplasia. There was no

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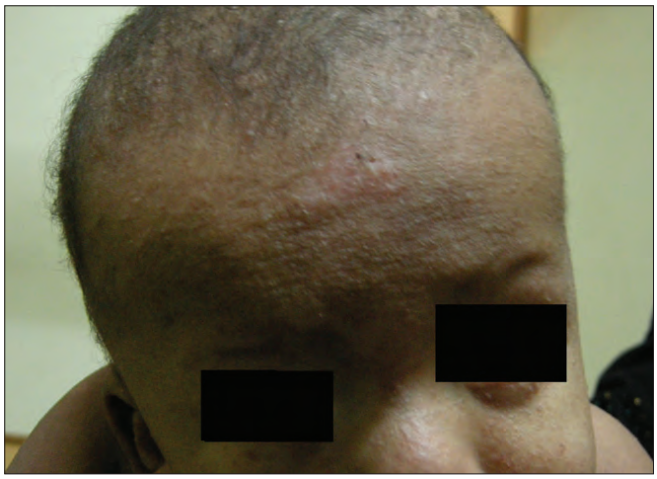

Figure 1a: Dysmorphic face with asymmetry, bitemporal narrowing and prominant metopic sutures, epicanthic fold, wide mouth, sparse hair and absent eye brows

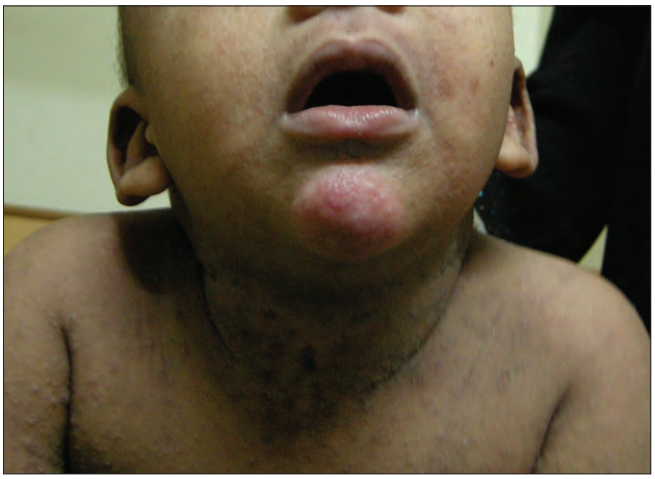

Figure 1b: Close-up view of facial features

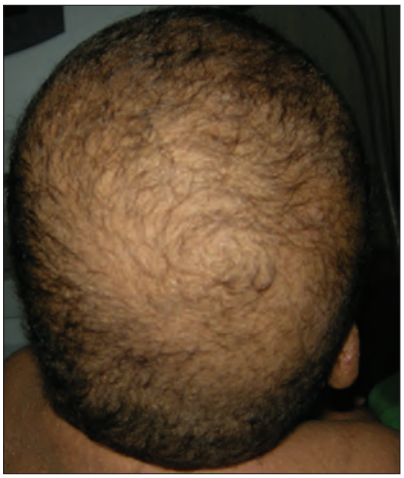

Figure 1c: Sparse scalp hair

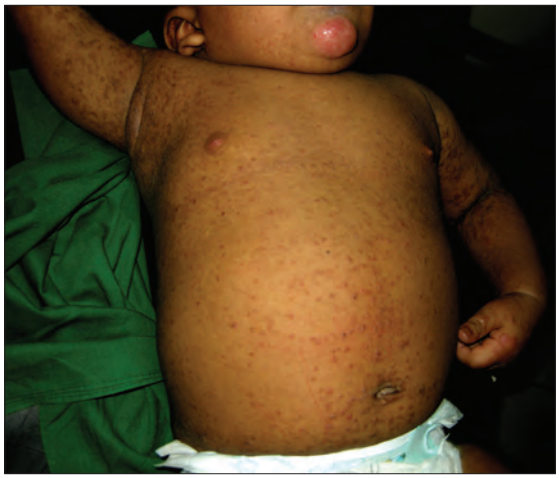

Figure 2: Dry and mildly hyperkeratotic skin. Eczematous lesions found on his neck and extremities, keratosis pilaris on his arms

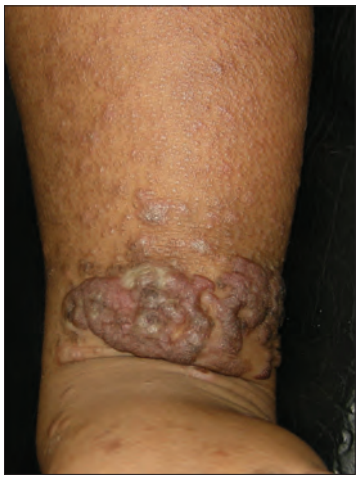

Figure 3: A vascular hemangiomatous plaque involving the right lower limb

evidence of hypoplasia.

Karyotype revealed 46 XY, involving 9p11q21.2 chromosome.

Discussion

CFC syndrome is a sporadic developmental disorder involving characteristic craniofacial features, cardiac defects, ectodermal abnormalities, and developmental delay.[14]

The syndrome is caused by gain-of-function mutations in four different genes BRAF, KRAS, mitogen-activated protein/extracellular signal-regulated kinase MEK1 and MEK2, all belonging to the same RAS extracellular signal-regulated kinase (ERK) pathway that regulates cell differentiation, proliferation and apoptosis.[16]

The diagnosis of CFC syndrome is purely clinical.[11]

It is characterised by failure to thrive, relative macrocephaly, a distinctive face with prominent forehead, bitemporal constriction, absence of eyebrows, hypertelorism, downward-slanting palpebral fissures often with epicanthic folds, depressed nasal root and a bulbous tip of the nose. The cutaneous involvement consists of

dry, hyperkeratotic, scaly skin, sparse and curly hair, and cavernous hemangiomata. Most patients have a congenital heart defect, most commonly pulmonic stenosis and hypertrophic cardiomyopathy. The developmental delay usually is moderate to severe.[16]

Neurological involvement in the CFC syndrome is extensive, and can involve functions of the cortex, brain stem and ventricular system. Mental retardation and global developmental delay are found in most (81%) cases.[17]

We established the diagnosis in our patient based on typical dysmorphic features concordant with CFC syndrome. Noonan syndrome and Costello syndrome, especially the former, can be phenotypically similar to CFC syndrome and should be excluded.[18] Noonan syndrome differs by less severe psychomotor delay bordering to normality, low posterior hairline with thick hair, cubitus valgus, neck abnormalities, ectodermal involvement characterized by nevi, café-au-lait spots, familial occurrence.[4] Costello syndrome differs by the presence of 'coarse' face, nasal and/or anal papillomata and a predisposition to child tumors such as neuroblastoma, redundant skin of hands and feet with deep palmar and plantar creases, elbow joint limitation.[18]

What is new?
Combination of classical clinical features should raise the suspicion of rare entity like this one.

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Announcement

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A free application to browse and search the journal's content is now available for iPhone/iPad. The application provides "Table of Contents" of the latest issues, which are stored on the device for future offline browsing. Internet connection is required to access the back issues and search facility. The application is Compatible with iPhone, iPod touch, and iPad and Requires iOS 3.1 or later. The application can be downloaded from http://itunes.apple.com/us/app/medknow-journals/id458064375?ls=1&mt=8. For suggestions and comments do write back to us.

Multicentric Reticulohistiocytosis: A Rare Case Report

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Abstract

A 58-year-old lady presented with polyarthritis followed by multiple shiny erythematous dome-shaped papulonodules mainly over the face, around joints and coral bead sign on fingers without any mucosal involvement. Characteristic histopathology with well-defined dermal infiltrate consisting of multinucleated giant cells and large macrophages having abundant eosinophilic cytoplasm clinched the diagnosis of multicentric reticulohistiocytosis.

Key Words: *Mutilating arthropathy, multicentric reticulohistiocytosis, histiocytosis*

What was known?
It is a rare entity with cutaneous and bony joint involvement, often associated with internal malignancy.

Introduction

Multicentric reticulohistiocytosis (MRH) is a rare histiocytic proliferative disease in which joints, skin, mucous membranes and internal organs are affected.[1] The most prominent clinical features are distinctive cutaneous nodules and destructive arthritis.[2] Twenty five percent of the patients have an associated internal malignancy at various sites. MRH has few other names in the literature as lipoid dermatoarthritis, giant cell histiocytoma, reticulohistiocytic granuloma. This is a rare condition, fewer than 200 cases have been reported in the world literature[3] and to the best of our knowledge this is the third case reported from India.

Case Report

A 58-year-old female presented with destructive polyarthritis of small joints of the hands, wrists, elbows and knee joints for past one and half years. She also developed multiple papulonodules on the forearm, elbow [Figure 1], face [Figure 2], ears helices and knee for last 6 months. The papulonodules were mildly erythematous, dome-shaped, glistening, translucent and non-pruritic and non-tender. The sizes varied from small papules to large pea-sized. There was a tendency to grouping of the lesions. Many small papules along the nail folds were seen forming the "coral bead sign" [Figure 3]. The surrounding skin was normal. The oral mucosa was free.

An extensive laboratory evaluation including complete hemogram, ESR, lipid profile, chest X-ray, USG abdomen, urinanalysis, stool for occult blood, ANA and X-ray of hand were done. Investigations revealed mild normocytic normochromic anemia (Hb-9.2 g/dl), raised ESR (55mm in 1st hr) and increased triglyceride level (175 mg/dl). USG

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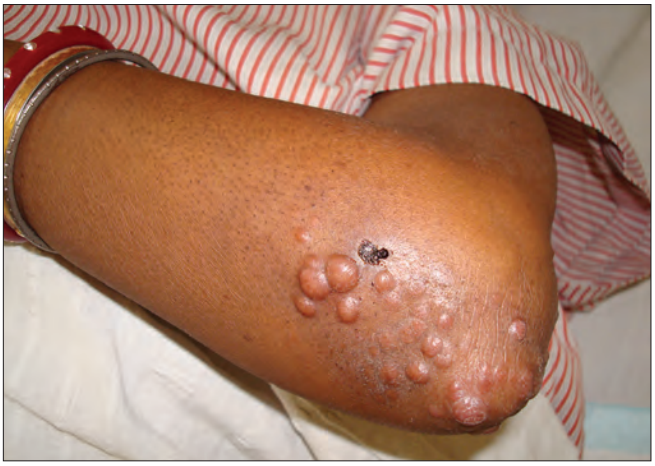

Figure 1: Shows typical erythematous glistening papulonodules around left elbow joint

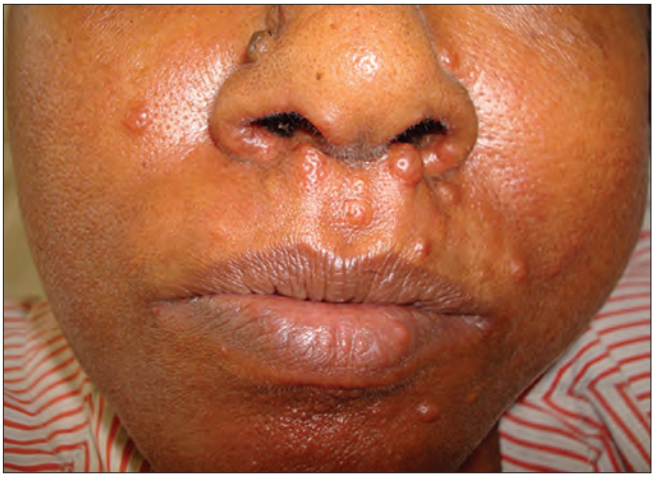

Figure 2: Typical lesions on central part of the face

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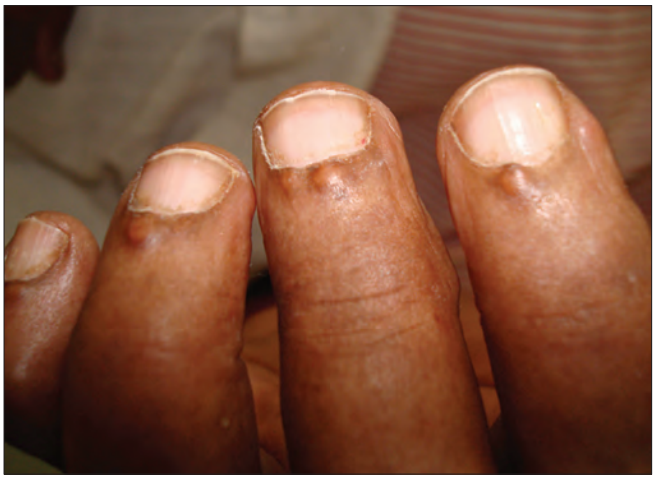

Figure 3: The "coral bead sign" on nail folds

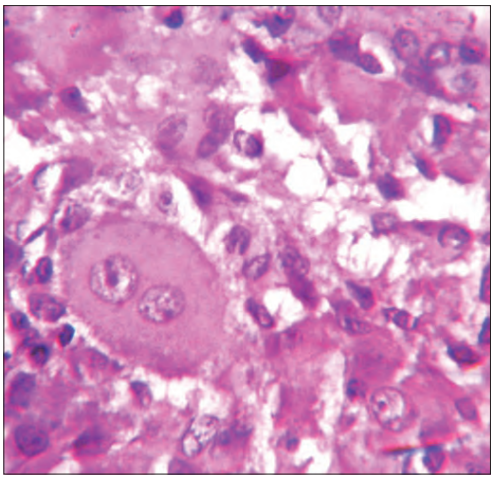

Figure 4: Histopathology showing multinucleated giant cells and macrophages having abundant eosinophilic finely granular cytoplasm in the dermis (H and E, ×200)

abdomen showed mild splenomegaly and X-ray of the chest was normal but X-ray of the hand showed erosion in the proximal and distal interphalangeal joints.

Skin punch biopsy was done from a nodule at the elbow region. The histopathological examination revealed well defined dermal infiltrate consisting of multinucleated giant cells and macrophages having abundant eosinophilic finely granular cytoplasm with ground glass appearance [Figure 4]. These features are consistent with MRH.

Discussion

MRH is a class II or non-Langerhans cell histiocytosis, characterized by local proliferation of resident mononuclear phagocytes other than Langerhans cell.[4]

The onset of MRH is usually insidious and cutaneous manifestations usually follow the articular signs and symptoms.[4]

The typical cutaneous manifestations consist of nonpruritic, flesh colored to reddish brown yellow papules and nodules that may be found anywhere in the body with a predilection for face, hand and around joints.[5] Around nail folds small papules are found which are called coral beads represent typical clinical sign. Differential diagnosis of the cutaneous lesions includes lepromatous leprosy, sarcoidosis, xanthomatosis, histiocytosis X, juvenile and adult xanthogranuloma, generalized eruptive histiocytoma, familial histiocytic dermatoarthritis and neurofibromatosis. The presence of skin manifestations on the face and hands with erosive arthritis usually differentiates MRH from other diseases.

MRH is associated with multiple medical conditions; underlying malignancy is found in about 25% of the cases.[3] Breast and stomach are the most common sites for underlying malignancy but may occur anywhere. Other conditions include hyperlipidemia, tuberculosis, pregnancy and autoimmune diseases. In our case no underlying malignancy or other disorders could be detected.

In conclusion MRH is a very rare disease; only 200 cases are reported worldwide so far. To the best of our knowledge it is the third case reported from India.

What is new?
The present case is not associated with any underlying malignancies like the other two previous cases reported from India

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Not Just Skin Deep: A Case Report of Multiple Endocrine Neoplasia Type 1

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Abstract

Multiple endrocrine neoplasia (MEN) type 1 is characterized by mainly a triad of pancreatic, pituitary and parathyroid involvement. This is a case report of a 41-year-old male in whom recognition of collagenoma and gingival papule led to the identification of MEN type 1. Often the recognition of such dermatological manifestations help in the presymptomatic diagnosis of complex syndromes.

Key Words: *Collagenoma, multiple endocrine neoplasia type 1, systemic manifestation*

What was known?
Multiple endocrine neoplasia type 1 (MEN1) is an Autosomal Dominant disorder with pancreatic and pituitary tumours and hyperplasia of pituitary glands. The cutaneous lesions in MEN1 include angiofibromas, collagenomas, café-au-lait macules, lipomas, confetti-like hypopigmented macules and gingival papules.

Introduction

Many a time the skin acts as a window to a variety of systemic illnesses. Multiple endrocrine neoplasia (MEN) type 1 is a complex hereditary disorder encompassing pancreatic and pituitary tumors and hyperplasia of the parathyroid glands and it has a variety of skin manifestations. This is a case report of a patient with MEN type 1 in whom the search for the systemic manifestations was lead by the recognition of the skin changes.

Case Report

A 41-year-old man was referred to the outpatient clinic of Dermatology, Medical College, Thiruvananthapuram, by surgical gastroenterologist for evaluation. He presented with asymptomatic skin lesions over the abdomen and front of neck of 3-year duration. For the last one and a half year he is having early morning fatigue, tremor, sweating and difficulty in holding objects. He was earlier diagnosed by a neurologist to have absence seizures and was put on anticonvulsants but there was no relief. He also gave a past history of two episodes of ureteric colic 6 years back. General examination was normal except for an increased arm span (height -165 cm, arm span - 179 cm) and an elevated blood pressure of 160/100 mm of Hg.

Dermatological examination revealed multiple discrete skin-colored soft as well as firm dome-shaped smooth papules of 0.5 cm diameter over the abdomen and lateral aspect of trunk [Figure 1]. A single 2 × 1 cm hyperpigmented macule with serrated margins was seen over the right side of chest [Figure 2]. Multiple discrete brownish macules as well as hyperpigmented and erythematous papules were seen over the anterior and lateral aspect of neck and pre-sternal area [Figure 2]. A single whitish papule of 0.5 cm was seen over the right lower gingival mucosa [Figure 3]. Examination of other systems was normal.

With these findings, the possibility of steatocystoma multiplex or neurofibroma or collagenoma with angiofibroma and café-au-lait macules was considered. In view of the late-onset cutaneous tumors and associated systemic symptoms, the patient was subjected to detailed investigations. The routine blood and urine examinations as well as liver and renal function tests were normal. Serum calcium level was 11mg% and serum phosphorus was decreased (1.9 mg%; normal value: 2.5 - 4.5 mg %). Random blood sugar was 51mg%. In view of the repeatedly low blood sugar values, serum insulin was

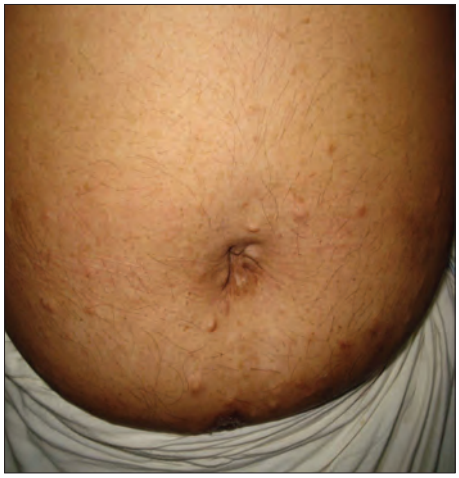

Figure 1: Papules on abdomen

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measured. It was found that serum insulin was elevated (112.47 μIu/ml; normal value: 2-25 μIu/ml) with an increased insulin/glucose ratio (2.205) and a slightly raised C-peptide level (4.16 mg/ml; normal value 1-3 mg/ml). The detection of hyper insulinemia prompted us to do a detailed endocrinological evaluation. Serum parathormone was elevated (151.4 pg/ml; normal value: 15-75 pg/ml) whereas the other hormones like thyroid hormones, cortisol, gastrin and prolactin were normal. Ultrasonographical examination of neck revealed a hypoechoic lesion of 5.3×11 mm seen posterior to the right lobe of thyroid suggestive of parathyroid adenoma. Visual field examination, OGD scopy and X-ray skull were normal. Plain CAT scan of the abdomen showed a tumor involving the body and tail of pancreas and multiple calculi were noted in the left kidney. CAT scan of head was normal but MRI brain showed a space-occupying lesion in the pituitary suggestive of pituitary adenoma [Figure 4].

Skin biopsy of the papules over the abdomen showed normal epidermis with increased dense connective tissue in the dermis which on subjecting to Van Gieson's stain- a mixture of Picric acid and Acid Fuchsin- took up red color confirming the diagnosis of collagenoma [Figure 5]. Erythematous papule on the pre-sternal area for which a provisional diagnosis of angiofibroma was made, showed hyperkeratosis, acanthosis and dilated blood vessels in the upper dermis with perivascular infiltrate which was more in favor of seborrhoeic keratosis rather than angiofibroma. Thus a final diagnosis of MEN type 1 was arrived at. The patient underwent parathyroidectomy and enucleation of the pancreatic tumor. The serum insulin level was normalized and his hypoglycemic symptoms disappeared after the surgical treatment.

MEN type 1 is a complex hereditary disorder encompassing pancreatic and pituitary tumors and hyperplasia of the parathyroid glands. Hyperparathyroidism is the most frequently expressed endocrinopathy in the syndrome which may also include on or more of the following: pancreatic tumors like insulinomas and gastrinomas, pituitary tumors like pinealomas, acromegaly, cushing's syndrome, thyroid tumors, carcinoids and hyperprolactinemia.[1] The term MEN was introduced by Steiner *et al* in 1968 to describe

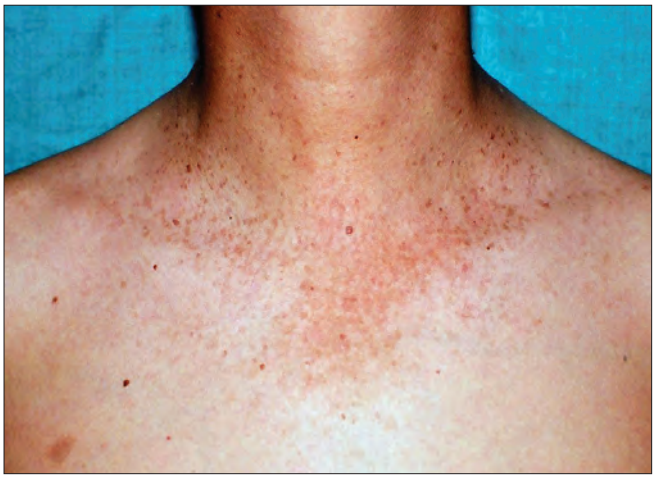

Figure 2: Erythematous papule on chest,hyperpigmented macule on chest

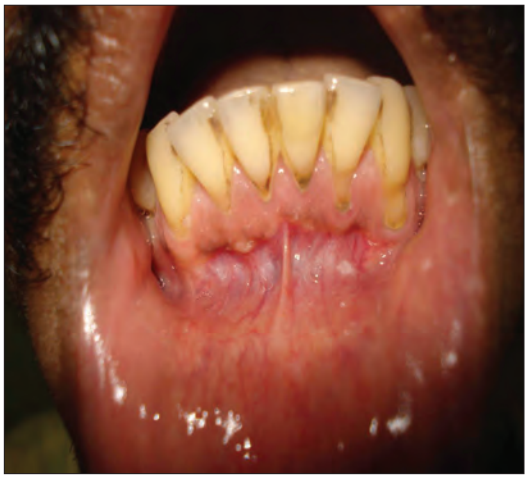

Figure 3: Gingival papule

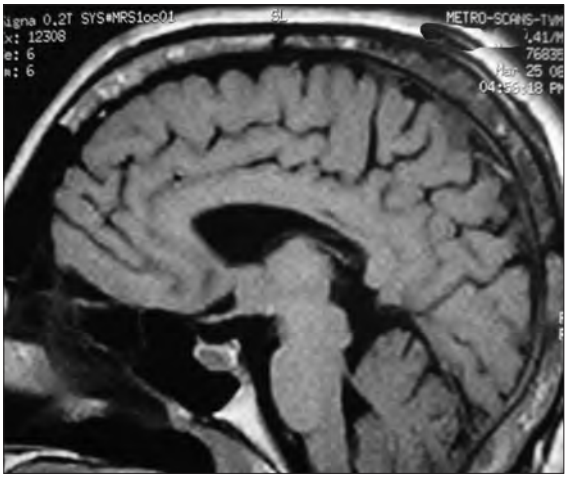

Figure 4: MRI of Brain showing Pituitary tumour

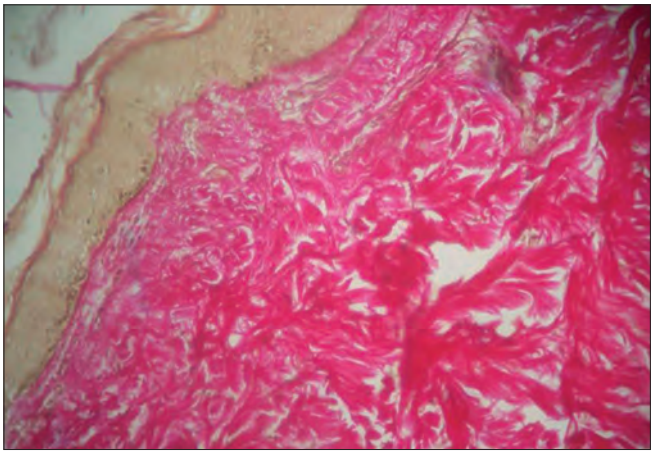

Figure 5: Van Gieson's stained section of skin coloured papule over abdomen consistent with Collagenoma, 40× magnification

disorders with a combination of endocrine tumors. These are complex genetic syndromes caused by activation or inactivation of different types of genes known to be involved in the regulation of cell proliferation and they include MEN 1, MEN 2, von Hippel - Lindau syndrome, Neurofibromatosis type 1 and Carney complex. Steiner and his colleagues also reported that the syndrome could be divided into two classes, MEN 1, (pituitary, pancreatic and parathyroid involvement) and MEN 2 (thyroid, medullary cancer, adrenal medullary and parathyroid disease).[2]

Wermer in 1954 first described the classical triad of pancreatic, pituitary and parathyroid tumors which is now known as MEN 1. Hence MEN 1 is also known as Wermer's syndrome. It is inherited in an autosomal dominant pattern and is caused by inactivating mutation of the tumor suppressor gene MEN 1 on chromosome 11q13 which encodes a peptide called menin. Its prevalence is 1 in 30,000. Among cases showing biochemical expression of MEN 1, 90-97% exhibit primary hyperparathyroidism; pancreatic tumors are manifested in 30-80%, and pituitary tumors are manifested in 15-50%.[1] The cutaneous lesions seen in MEN 1 include angiofibromas (88%), collagenomas (72%), café-au-lait macules (38%), lipomas (34%), confetti-like hypopigmented macules (6%) and gingival papules (6%). Collagenomas are skin-colored to slightly hypopigmented firm, round to oval papules and nodules of 0.2-2cm diameter, mostly located on upper part of trunk and neck and show an increased amount of collagen and normal or decreased elastic fibers on histopathological examination.Other conditions where collagenomas are seen include Tuberous sclerosis, Birt-Hogg-Dubé syndrome, Down syndrome, Chronic myelocytic leukaemia, Syphilis, Cowden's syndrome, Proteus syndrome and Encephalocraniocutaneous lipomatosis.[3]

The constellation of these cutaneous findings like collagenomas, angiofibromas and gingival papules do not establish the diagnosis of MEN 1 as they are also seen in other genodermatoses like tuberous sclerosis (TSC) and Birt - Hogg - Dubé syndrome (BHDS). Figure 5 shows the overlapping clinical features seen in these three disordersBHDS is an uncommon autosomal dominant genodermatosis characterized by a triad of skin tumors - fibrofolliculomas, trichodiscomas and acrochordons - together with an increased risk of renal tumors and spontaneous pneumothoraces. BHDS should be considered, along with tuberous sclerosis and multiple endocrine neoplasia type 1 in the differential diagnosis of multiple facial angiofibromas and collagenomas, particulary when the onset is in adulthood.[4] Angiofibromas seen in MEN 1 are clinically and histologically indistinguishable from those observed in TSC.[5] However, angiofibromas in patients with MEN 1 tend to be smaller and fewer in number than in those with severe TSC. In the former, they also tend to appear on the upper lip and its vermilion border, regions usually spared in patients with TSC.[6] So a thorough search should be made for other associated cutaneous tumors and systemic involvement before arriving at a final diagnosis.

Angiofibromas and collagenomas (single or multiple) have 50-65% sensitivity and 92-100% specificity for MEN 1. The combination criteria of multiple angiofibromas (more than three) and any number of collagenomas had the highest sensitivity (75%) and specificity (95%). This criterion has greater sensitivity than pituitary or adrenal disease and is comparable to hyperparathyroidism in some studies of patients with MEN 1 with gastrinoma.[7] These cutaneous tumors also help in the presymptomatic diagnosis of MEN 1 because, even though the symptoms of endocrine tumors are delayed until the fourth decade, the cutaneous tumors make their first appearance in the teenage years itself. In addition, symptoms of hormone dysregulation may mimic non-endocrine diseases including neurologic or psychiatric disorders. Depression often associated with hyperparathyroidism and hypercortisolism.[8,9] Confusion and abnormal behavior characterize hypoglycemic episodes in patients with insulinomas and they are often unrecognized or mistaken for seizures or psychiatric disorders.[10]

What is new?

The need to consider the possibilities of genodermatoses like Multiple Endocrine Neoplasia type 1, Tuberous Sclerosis and Birt – Hogg –Dubè Syndrome in patients with constellation of cutaneous findings like collagenomas, angiofibromas and gingival papules. Recognition of these cutaneous tumours will help in the presymptomatic diagnosis of MEN1 and similar genodermatoses.

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Announcement

Dr. Badri Narayan Prasad Research Award

Nominations are invited for the above mentioned award initiated by Jharkhand branch of IADVL which carries a cash prize of Rs.20,000.00 (Twenty thousand only) to be given to the main author of the best published research paper during the year 2012. The address for correspondence is:

Dr. Birendra Narayan Prasad, Chairman,
Dr. Badri Narayan Prasad Research Award
Ex. Prof of Dermatology & Ex. President IADVL, Jharkhand
Doranda, Ranchi, Jharkhand-834002.

For any query the second contact detail is:
Dr. Ravishankar Dwivedi
Ph. No. 09835331002
Email: bnpra@shantiskinhospital.com

CRITERIA FOR THE AWARD:

1. Scholar must be up to the age of 45 years as on 31st December 2012 and of Indian origin.
2. The research work should be in any branch of Dermatology, Verenology or Leprology.
3. The research work must be submitted and accepted for publication in any national or international journal in the year 2012 (from 1st January 2012 to 30th September 2012).
4. The nomination must be sent up to 30th September 2012 to the Chairman of the Research Award with five copies of the research paper, proof of the age and letter of acceptance from the editor of the journal.
5. The decision of the best research paper will be taken up by five examiners. The decision of the majority will be final and will not be challenged.
6. The award will be given during the annual conference of Jharkhand Branch of IADVL to be held in the month of December 2012 at Jamshedpur, Jharkhand.

Dr. D. K. Mishra
Secretary, IADVL Jharkhand Branch

Fusarium Solani: A Causative Agent of Skin and Nail Infections

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Abstract

Fusarium spp are non-dermatophytic hyaline moulds found as saprophytes and plant pathogens. Human infections are probably a result of various precipitating predisposing factors of impaired immune status. Immunocompetent individuals of late are also vulnerable to various unassuming saprophytic and plant pathogens. To stress the need to identify correctly and institute appropriate antifungal therapy in newly emerging human fungal infectious agents. Repeated mycological sampling of the skin and nails of the suspected fungal infection were processed as per the standard format including direct microscopy and fungal culture on Sabouraud's dextrose agar. The fungus was isolated as *Fusarium solani*. *Fusarium* is an important plant pathogen and soil saprophyte. Infection is acquired by direct inoculation or inhalation of spores. It is associated with a variety of diseases like keratitis, onychomycosis, eumycetoma, skin lesions and disseminated diseases.

Key Words: *Fusarium solani, onychomycosis, agriculturists, immunocompetent individuals*

What was known?
Fusarium known as a laboratory contaminant and seen widely as an etiology agent in burns cases.

Introduction

Fungal infection may occur following trauma or wound contamination.[1] New opportunistic pathogens have now emerged as a cause of life-threatening infections worldwide. *Fusarium* is associated with a high mortality and may respond to novel therapies. Disseminated fusariosis is seen in high-risk patients with hematological cancers,[2,3] organ transplant recipients and in burns injuries.[4] However, little is known about the pathogenesis, clinical characteristics and management of these infections.[2] We report here three cases of fusariosis in individuals with normal immune status.

Case Reports

The following cases had come to the dermatology OPD of a medical college hospital. All patients were diagnosed based on repeat mycological examination by direct microscopy and fungal culture. Samples of nail and skin plaques previously cleaned with 70% alcohol were collected with a sterilized scalpel. Ten percent KOH wet mount of the sample was examined followed by inoculation onto Sabourauds dextrose agar.

Case 1

A 50-year-old male diagnosed presumptively as onychomycosis presented with a white superficial lesion on the right index finger. The lesions appeared 4 months back. There was no history of itching, pain or discharge from the lesion.

Case 2

A 70-year-old male presented with erythematous scaly plaques on the left little finger since 3 years with no itching, pain and discharge from the lesion.

Case 3

A 45-year-old male presented with interdigital plaques on the right foot since 5-6 years with no itching, pain or exacerbation.

Direct wet mounts revealed hyaline, septate, branched hyphae. Culture on Sabouraud′s dextrose agar grew white, cottony colonies which later turned pink in color. Lactophenol cotton blue mount of colony revealed septate, branched hyphae with microconidia and many sickle shaped macroconidia [Figure 1].

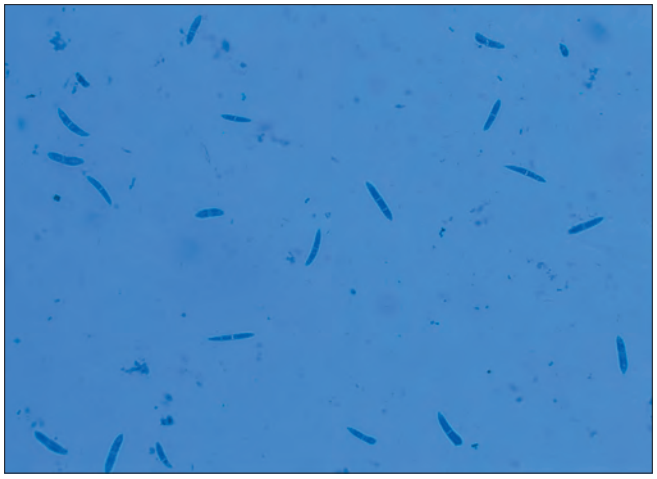

Figure 1: *Fusarium solani* in lactophenol cotton blue stain

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The fungus was identified as *Fusarium solani*. All the cases were treated with oral Itraconazole 200 mg per day for 2 months and significant clinical and mycological recovery was achieved in all three cases.

Discussion

Onychomycosis is caused by dermatophytes and non dermatophyte fungi like *Acremonium*, *Altenaria*, *Aspergillus*, *Scytalidium*, *Fusarium* and *Candida* species.[5] *Fusarium* is a large genus of filamentous fungi widely distributed in soil and in association with plants. Most species are harmless saprobes, relatively abundant members of the soil microbial community.[6]

Some species may cause a range of opportunistic infections in humans. In humans with normal immune systems, fusarial infections may occur in the nails and in the cornea. Onychomycosis by *Fusarium* species usually involves the toe nails and enter the body through trauma. This was noted in two of our cases and the likely route of entry was probably due to trauma as both patients were agriculturists.[7]

Fusarial onychomycosis is seen as white superficial lesions in immunocompetent patients, with these lesions presenting as only a cosmetic effect requiring long-term treatment but in immunocompromised patients they can cause disseminated infections with poor response to antifungals. Disseminated infections are seen in patients with hematological malignancies[2,5,4] and even extensive burns.[4] In immunocompromised individuals, onychomycosis may act as a portal for life-threatening systemic infection.[3] These infections require proper identification and early treatment. Hence, severely immunocompromised patients with skin or other tissue breakdown conditions should avoid exposure to environmental sources of *Fusarium* species like tap water and soil which may be potentially contaminated with *Fusarium* species.[7]

Infections due to *Fusarium* involving skin and nails should be thoroughly investigated[8] in the laboratory down to the species level before discarding them as laboratory contaminants and reporting the same to the treating clinician keeping in mind the invasive potential[9] of this emerging pathogen so as to bring down mortality with appropriate treatment particularly among agricultural workers and laborers.[10]

What is new?
Fungal nail infection can be seen in immunocompetent individuals too.

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Announcement

67th Brazilian Congress of Dermatology

100 years celebration of the Brazilian Society of Dermatology
September 1-4, 2012 - Rio de Janeiro - Brazil
Languages: Portuguese/English

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Giant Seborrheic Keratosis of the Genitalia

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Abstract

Genital seborrheic keratosis (SK) is a rare entity, which can be easily misdiagnosed as genital warts. Dermoscopy is a useful tool to make diagnosis of SK in such cases. We report a 50-year-old woman with a large polypoidal growth on the external genitalia. Dermoscopic examination showed fissures and ridges, cerebriform appearance, and comedo-like openings consistent with SK. The histopathology confirmed the diagnosis of SK.

Key Words: *Genitalia, giant, seborrheic keratosis*

What was known?
SK involving the genital region is a rare entity, which can be easily misdiagnosed as genital warts. Histopathology helps in clinching the diagnosis in such cases.

Introduction

Seborrheic keratosis (SK) is common benign epidermal proliferation, which can occur anywhere in the skin the exception of palms, soles, and mucosa (there was only one report of mucosal SK in the conjunctiva).[1] SK involving the genital region is a rare entity, which can be easily misdiagnosed as genital warts. Histopathology helps in clinching the diagnosis in such cases. Recently, dermoscopy is available as a noninvasive diagnostic procedure which can be used to diagnose SK by its typical findings. We hereby report a rare and unusual case of large SK of the genitalia which initially caused a diagnostic confusion with condyloma acuminata. The diagnosis of SK in our case was established by dermoscopy and was confirmed by histopathology.

Case Report

A 50-year-old woman presented with a large polypoidal growth on the vulva of 2 years duration. The lesion started as a small pigmented patch on the right vulva, which slowly increased in size to become a large polypoidal mass and in extent to involve the entire external genitalia. There was no pain or discharge, but of late the lesion became foul smelling. There was no history of sexual promiscuity in either spouse. On physical examination, a large, pigmented, polypoidal mass (of size around 15 × 10 cm) was seen in the external genitalia involving both labia majora, labia minora, fourchette, and mons pubis [Figure 1]. Areas of reddish and whitish verrucous portions were seen within the mass. The mucosa of vagina was normal. We considered differential diagnosis of condyloma acuminata and giant SK. Dermoscopic examination was carried out, which showed fissures and ridges, cerebriform appearance, and comedo-like openings consistent with SK [Figure 2]. The histopathologic examination of a biopsy sample showed hyperkeratosis, acanthosis, and multiple horn cysts, which were also consistent with SK (acanthotic type) [Figure 3].

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Discussion

SKs are common benign epidermal proliferations, which present as sharply demarcated, tan to black, round or oval, elevated, "stuck on" skin lesions.[1] Classically, SK tends to increase with age.[1] The lesions are more common in the sun-exposed areas.[2] Several morphologic forms of SK are described—flat SK, pedunculated skin-tag-like, stucco keratosis, dermatosis papulosa nigra, melanoacanthoma, and inverted follicular keratosis.[1,3]

SK can manifest as macules, papules, or plaques.[4] Pediculated forms have also been observed in intertriginous areas.[1] Polypoidal mass (as was seen in our case) has been reported in the genital region in several case reports. Livaoglu *et al*.[2] and Thakur *et al*.[5] reported large, polypoidal SK in the genitalia in 42-year-old and 50-year-old male patients, respectively. Melanoacanthoma is a variant of SK characterized by epidermal proliferation of keratinocytes and melanocytes where the melanocytes are scattered throughout the tumor lobules rather than only in the basal layer as seen in SK.[6] Shenoy *et al*.[6] reported a case of melanoacathoma in the genital region. We considered the diagnosis of melanoacanthoma in our case, but ruled it was out as histopathology showed melanocytes only in the basal layer (not throughout the tumor lobule). Roth *et al*. reported a case of inverted follicular keratosis (a variant of SK) of the vulva.[7] Inverted follicular keratosis is considered a SK that involves the epithelium of hair

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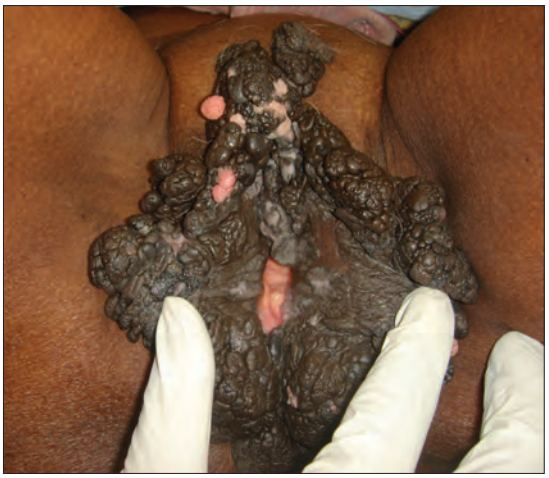

Figure 1: Large polypoidal mass over the entire external genitalia

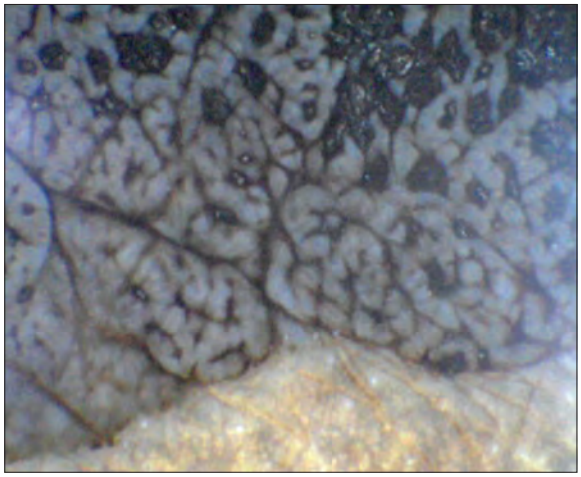

Figure 2: Dermoscopic image showing fissures and ridges and comedo-like openings

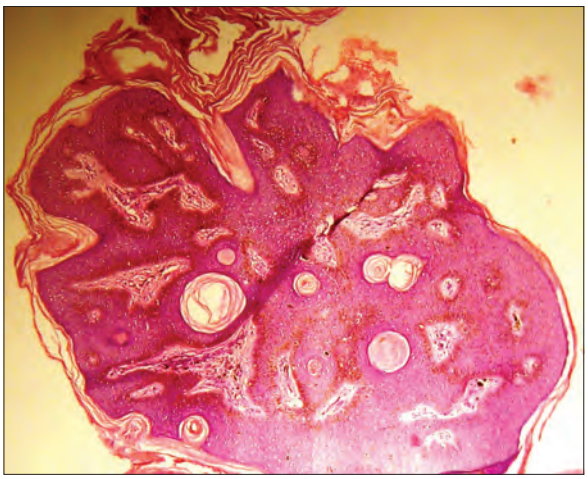

Figure 3: Histopathology showing hyperkeratosis, marked acanthosis, and multiple horn cysts (hematoxylin and eosin stain, ×100)

follicles, that proliferates in an endophytic fashion, and that exhibits squamous differentiation in association with inflammation.[7]

The clinical diagnosis of SK may be difficult at times with only 49% accuracy in a study done by Stern *et al*.[4] Diagnosis becomes more difficult in the genital region as the classical clinical features of SK (distinct keratotic and follicular plugging, stuck-on appearance, etc.) disappear because of the friction and maceration typical of this area.[5] In our case, however, distinct keratotic and follicular pluggings were well discernible.

SK may be grouped into different histological subtypes: acanthotic, hyperkeratotic (also verrucous), adenoid (reticulated), plane, clonal, Bowenoid, irritated, inverted follicular keratosis, benign squamous keratosis, and melanoacanthoma.[1,8] Of these, the acanthotic subtype appears to be the most common. The acanthotic type, like in our case, shows marked acanthosis with predominantly basaloid cells, moderate papillomatosis and hyperkeratosis, and characteristic presence of horn cysts or pseudocysts.[1] Proliferation of melanocytes and hyperpigmentation, inflammatory lichenoid or circumscribed lymphocytic are uncommon features. Squamous eddies, as seen in irritated SK, are absent.[1]

Because the lesions of SK may not be easily diagnosable in the genital region, dermoscopy could become a handy replacement to tedious and sometimes unacceptable biopsy/histopathologic examination. The most common dermoscopic features of cutaneous SK are comedo-like openings and milia-like cysts.[1,9] Other features include fissures, hairpin vessels, sharp demarcation, and moth-eaten borders.[9] Comedo-like openings, that is, keratin-filled invaginations of the epidermis, are usually not seen in the vulva, due to the friction that prevents their formation in this anatomical site. Milia-like cysts, on the other hand, are histologically included in the epidermis, and therefore not eliminated by friction and maceration.[5] In our case, comedo-like openings were plentiful, but milia-like cysts were not seen. Multiple fissures (giving a cerebriform appearance) were also prominently seen in our case.

Our case highlights a rare presentation of SK as giant, polypoidal growth in the genital region and diagnostic utility of dermoscope in establishing the diagnosis.

What is new?
This report emphasizes a rare presentation of SK as giant, polypoidal growth in the genital region and diagnostic utility of dermoscope in establishing the diagnosis.

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Announcement

Psoriasis Workshop

Organised by

IADVL - Psoriasis - Special Interest Group (SIG)

On 22nd July, 2012,
Venue: The Golden Park, 13, Ho Chi Minh Sarani, Kolkata-71, West Bengal, India.

FREE Registration
Last date of registration 15th July, 2012

Program Highlights:

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- Difficult psoriasis, Psoriatic arthropathy, Biologics
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Eccrine Angiomatous Naevus Revisited

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Abstract

Hamartomatous, circumscribed swellings of the extremities make an interesting study. Presentations are manifold and the naevi are not always present from birth. Excessive growth of hairs leads to remarkable appearance of such swellings. A young woman presented to the dermatology department, complaining of tenderness over 4th finger of her left hand. The defect was present for the last couple of years and was typified by visible hyperhidrosis on gentle tapping. Counseling of the affected lady made her agree for a skin biopsy. The histopathology revealed it to be of the nature of eccrine angiomatous hamartoma. Blood vessels were scarce. Eccrine ducts were plentiful without other associated anomalies. The deformity was removed by simple excision with good result.

Key Words: *Eccrine, hyperhidrosis, naevus sudoriferous*

What was known?
Rare tumour. Recurrences known albeit reported infrequently. Relapse usually occurred within 2 years.

Introduction

Eccrine angiomatous hamartoma (EAH) is a benign enlargement of eccrine components, accompanied by abundance of vascular channels. Increased proliferation of pilar structures, adipose tissue, and epidermis may be present.[1] The anomaly is usually asymptomatic, but pain, hypertrichosis, and hyperhidrosis have been reported in a few patients. Less than 50 cases have been described in the literature. Recurrence is rare. Differentiation from other angiomatous growths is necessary.

Case Report

A 26-year-old female presented with a 2.5 cm × 1.5 cm blue-colored, ill-defined swelling over the dorsum of her left hand near the last intertriginous space encroaching over the ring finger. The surface was irregular in texture and she could demonstrate small beads of perspiration on patting the lesion [Figure 1]. This swelling was present for the last 2 years and she had sought medical aid as it was painful to touch. The adjoining skin over the 3rd metacarpophalangeal joint and proximal interphalangeal joint of the 3rd finger showed a skin-colored swelling and it represented an area of similar tumor which had grown slowly since birth. This earlier nevoid lesion had been excised 10 years back. Operated area was asymptomatic. There was neither suggestive family history nor any history of trauma to the part. Her blood reports were normal as was her chest radiograph. A 4 mm punch biopsy was performed and the histopathology revealed lobulated, unencapsulated structure composed of mature, numerous eccrine glands enmeshed in loose connective tissue [Figure 2]. Blood vessels could not be demonstrated with the eccrine coils in the specimen [Figure 3]. The person was sent to a surgeon and the hamartoma was completely removed. Eight months have passed without reappearance of the tumor.

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Discussion

Sebaceous naevi often contain eccrine element. Pure eccrine naevi are rare and usually accompanied by capillary angiomatosis. Such angioma was first described by Lotzbeck in 1859 and termed as EAH by Hymann and colleagues in 1968.[2] A case with familial disposition has been recorded in the literature. Clinically, the lesion presents as solitary, bluish, or skin-colored nodules or plaques usually over the extremities as trauma may be an inciting factor. Other areas like the trunk and face are known to be involved. Verrucous form has been reported. EAH can be multiple.[3] Numerous lesions in the same individual can be the result of mosaicism of a gene mutation occurring in the early developmental stage. Adult onset hamartoma has been described.[3,4] The tumor is painless, but involvement of nerve fibers by the enlarging eccrine elements can result in tenderness. Sudoriparous angiomas, as they are also known as, can display increased eccrine sweat production on exercise or when lightly stroked. Involvement of pilar structures by the malformation may manifest as hypertrichosis over the naevi.

Etiology of sudoriparous angiomas is unclear. It has been suggested that as yet an unclear chemical interaction between the differentiating epithelium and the mesenchyme leads to the abnormal proliferation of eccrine structures.[5] The tumor has to be differentiated from other structures like tufted angiomas, capillary hemangiomas, smooth muscle hamartomas, and dermatofibromas. Histopathology helps in confirmation of the diagnosis. Dilatation of eccrine

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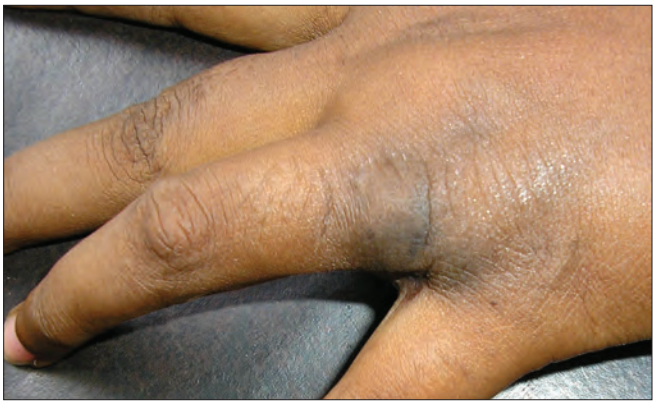

Figure 1: Beads of perspiration on eccrine angiomatous hamartoma

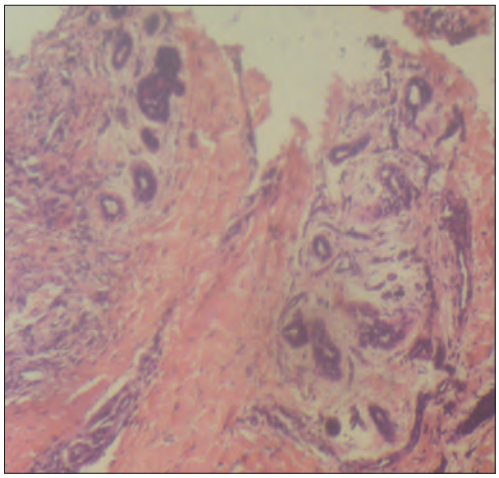

Figure 2: Lobulated structures in the dermis showing eccrine glands (H and E, ×100)

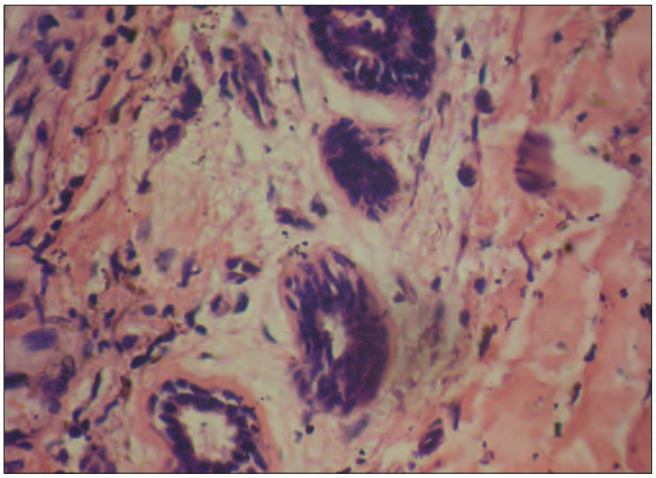

Figure 3: Plentiful eccrine coils without blood vessels (H and E, ×400)

coils is a constant feature with amplification in their numbers, but associated enlargement of vascular channels may not be present. This modification has been termed "naevus sudoriferous."[6] Apart from closely entwined pilar structures and infiltration of adipose tissue, profuse deposition of mucin in the connective tissue has been detailed in the literature.[3,7] Seraly[8] *et al.* coined the term eccrine pilar angiomatous mucinous nevus for this variant of EAH.

Immunohistochemistry can give added and more specific information regarding the malformation. Carcinoembryonic antigen (CEA) and S-100 protein, which are commonly found in the eccrine sweat apparatus, are found to be diminished.[9] This investigation could not be performed in our case.

Malignant transformation has not been reported in such hamartomas. Spontaneous regression may occur. Simple surgical procedures like excision have produced excellent results where it was sought for pain or for cosmetic reasons. Lasers have not proved to be effective. Recurrences have not been known to occur.[10] Reason for reappearance in our case could be incomplete removal of the previous tumor. Associations of such eccrine hamartomas are not common. A case with Cowden's syndrome, who had developed a thyroid adenoma,[11] and another with neurofibromatosis[12] are the only two such reports.

EAH are rare malformations presenting diverse clinical and histological deviations which need differentiation from other complex tumors. They carry a good prognosis and treatment is simple, often providing complete gratification for the sufferer.

Acknowledgment

All the medical personnel of the Department of Dermatology, IPGMER and SSKM Hospital, are acknowledged.

What is new?
Clinical relapse in this case occurred after a period of 10 years of quiescence after operation.

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High Risk Factors for Severe Hand, Foot and Mouth Disease: A Multicenter Retrospective Survey in Anhui Province China, 2008-2009

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Abstract

Objectives: This study sought to determine the high risk factors for severe hand, foot, and mouth disease (HFMD). **Materials and Methods:** Retrospective 229 severe HFMD cases from four hospitals in FuYang, HeFei, and BoZhou (Anhui Provincial Hospital, Fuyang City People's Hospital, No. 2 People's Hospital of Fuyang and Bozhou city People's Hospital) in 2008-2009 were studied, with 140 mild HFMD cases in the same area. Using univariate and multivariate logistic regression analyses, the high risk factors of HFMD were identified by comparing clinical and laboratory findings between severe cases and mild cases. **Results:** There was a significant difference in age, total duration of fever, rate of respiratory and heart, shake of limbs, white blood cell count, blood sugar, and CK-MB between the two groups. Univariate logistic regression analysis showed that severe cases were associated with age (<3 years), withdrawnness and lethargy, shake of limbs, tachycardia, total leukocyte count (≥17×10^9/l), blood sugar (≥7 mmol/l), and CK-MB (≥16 mmol/l). Furthermore, age (<3 years), withdrawnness, and lethargy, shake of limbs, WBC (≥17×10^9/l), and CK-MB (≥16 mmol/l) were found to be high risk factors for severe cases after multivariate logistic regression analysis. **Conclusions:** Clinicians should give importance to these risk factors. Early recognition of children at risk and timely intervention is the key to reduce acute mortality and morbidity.

Key Words: *Complication, hand foot and mouth disease, risk factor*

What was known?

1. Hand, foot, and mouth disease (HFMD) was a common acute infectious disease in children. EV71 was one of very few viruses that caused HFMD as well as a variety of other clinical manifestations.
2. The progression of the severe HFMD disease was very fast, The duration was about several hours, even less than 48 hours,The mortality rate was very high if it progressed to pneumonedema.

Introduction

Hand, foot, and mouth disease (HFMD) was a common acute infectious disease in children[1] caused by a group of enteroviruses, including coxsackievirus (Cox) A16, A5, A7, A9, A10, B2, B5, and enterovirus71 (EV71) [2-5] with CoxA16 being the most common etiologic agent. Its clinical manifestation was cutaneous lesions over hands, feet, and buttocks along with oral. In most instances, it was mild and self-limited over 3-5 days with no complications. However, severe complicated forms involving encephalitis, meningitis, encephalomyelitis, pulmonary edema, or circulatory failure occurred in the Fuyang HFMD outbreak in 2008.[6] In the same year, the epidemic spread to other areas of Anhui province; fatal cases were the most in Anhui province so far. Of 229 severe and fatal HFMD cases, the 19 EV71-positive children died of pulmonary edema, 10 fatal HFMD cases were selected for a closer investigation. The chief causes of death were found: severe cases being escaped from early recognition; lack of detection for important indicator; fulminant pulmonary edema being not correctly assessed and severe cases being not treated timely. This was consistent with the other.[7-9] In order to detect severe cases earlier, prevent deterioration, increase the ratio of successful rescue, and reduce acute mortality and morbidity, high risk factors for severe HFMD disease were determined in this article.

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Materials and Methods

Diagnostic criteria

HFMD cases in 2008-2009 were divided into two groups according to Guidelines on the Diagnosis and Treatment of HFMD.[10]

Mild cases

The clinical features of the patients included acute onset, lesions over buccal, and labial mucosae, and erythematous vesicles with a red areola over palms, soles, and buttocks. They may develop cough, nasal discharge, anorexia, etc. Part of them only showed cutaneous lesions or herpangina. Most subjects recovered within a week. Some of them had atypically manifestations of cutaneous lesions.

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Severe cases

The subjects had the same clinical manifestation with the mild cases, but progressed rapidly. On 1-5 days of illness, neurologic complications including lethargy, drowsiness, irritability, delirium; headache, vomiting; shake of limbs, myoclonus, ocular flutter, ataxia; asthenia, seizures. Some patients presented with meningeal irritation, diminished, or disappeared tendon reflexes. Fatal cases: Children with HFMD were considered to have more serious illness if they had at least one of the following features: (1) seizures, coma or cerebral hernia; (2) respiratory distress, cyanosis, bloody frothy sputum, lung rales, etc; (3) poor peripheral perfusion such as shock.

Case definitions

The study protocol has been approved by the Ethics Committee, Anhui Medical University, Hefei, China. Written consent was obtained from each child's accompanying parent. A total of 369 HFMD cases from four hospitals in FuYang and HeFei (Anhui Provincial Hospital, Fuyang City People's Hospital, No. 2 People's Hospital of Fuyang and Bozhou city People's Hospital) in 2008-2009 were divided into two groups according to Guidelines on the Diagnosis and Treatment of HFMD. A total of 229 children were labeled as severe HFMD cases because their clinical findings were in accordance with diagnostic criteria of severe and fatal HFMD cases. A total of 140 children were classified as mild HFMD cases because their clinical findings were in accordance with diagnostic criteria of mild HFMD cases.

Risk factor analysis

Many factors such as gender, age, clinical manifestation, laboratory findings, electroencephalogram, and imaging finding were analyzed by univariate logistic regression analyses. The high risk factors of HFMD were identified by comparing clinical and laboratory findings between severe cases and mild cases using multivariate logistic regression analyses.

Statistical analysis

All analyses were conducted by SPSS for Windows 11.5 software package. Measurement data were presented in mean values with standard deviations ($x \pm s$) and compared by a chi-square test. In case, count data were presented, they were compared by Student's *t*-test. Factors were analyzed by univariate logistic regression analyses. Statistically significant variables were then analyzed by multivariate logistic regression analyses with a significant ($P<0.05$).

Results

General data

A total of 369 HFMD cases were recruited according to guidelines on the diagnosis and treatment of HFMD (published by Chinese Ministry of Health in 2010). Of 229 severe children, 147(64.19%) children were male, 82(35.81%) children were female; their mean age was (1.94±1.31) years, and 193(84.28%) cases were at age of 0-3 years old. Of 140 mild cases, 94(67.14%) cases were male, 46(32.86%) cases were female; the mean age was (4.17±2.50) years, and 60(42.8%) cases were at age of 0-3 years old. There was no significant difference in the male:female ratio between the two groups ($P>0.05$). There was a significant difference in the age between the two groups, especially at age of 0-3 years ($P<0.01$).

Clinical features

Fever

Of 229 severe cases, 222(96.9%) had fever, and 7(3.1%) had no fever. The peak range of fever was 36.7-41.0°C (mean, 38.68±0.66). A total of 34(14.8%) children had continuous high fever, and the mean duration of fever was (3.15±1.81) days. Of 140 mild cases in the control group, 135(96.4%) had fever, and 5(3.6%) had no fever. The mean peak temperature was 38.62±0.63°C. A total of 10(7.1%) children had continuous high fever, and the mean duration of fever was 1.90±0.74 days. There was no significant difference in the mean peak temperature and fever between the two groups ($P>0.05$). However, the mean duration of fever and continuous high fever between the two groups was significant ($P<0.05$) [Table 1].

Cutaneous lesions

A total of 212(92.6%) severe cases had cutaneous lesions on palms, 212(92.6%) on soles, 188(82.8%) on buttocks, and 126(55%) on oral. A total of 128(91.4%) children in the control group had cutaneous lesions on palms, 129(92.1%) on soles, 109(78.4%) on buttocks, and 70(50%) on oral. There was no significant difference in the distribution of cutaneous lesions between the two groups ($P>0.05$) [Table 1].

Symptom of the respiratory system

The mean respiratory rates in the severe group were 32.44±11.48 times per minute. A total of 71(31.0%) had breathlessness, 32(14.0%) respiratory distress, 19(8.3%) changes of respiratory rhythm, 40(17.5%) cyanosis, 40(17.5%) spit white, pink or bloody frothy sputum, and 54(23.6%) crackles in the lungs. The mean respiratory rates in the control group were 25.41±3.30 times per minute. A total of 25(17.9%) had breathlessness. None of mild cases had respiratory distress, respiratory rhythm change, cyanosis, bloody frothy sputum, or crackles in the lung. The mean respiratory rates and breathlessness were significantly different between the two groups ($P<0.01$) [Table 1].

Symptom of the gastrointestinal system

In the severe group, 45(19.7%) children felt nausea, 80(34.9%) had nonprojectile vomiting, 2(0.9%) stomach ache, 4(1.7%) diarrhea. In the control group, 32(22.9%)

Table 1: Compared symptom and sign of HFMD between the severe and mild groups

Symptom and sign	Severe group (*n*=229)	Mild group (*n*=140)	*t*	X	*P* value
Fever	222	135		0.073	0.787
The mean peak temperatures (°C)	38.68±0. 66	38.62±0. 63	0.92		0.358
Continuous high fever	34	10		4.91	0.027*
The mean duration of fever (days)	3. 15±1. 81	1.90±0.74	2.12		0.040*
Cutaneous lesion					
Palms	212	128		0.158	0.691
Soles	212	129		0.023	0.879
Buttocks	188	109		1.092	0.296
Oral	126	70		0.880	0.348
Respiratory system					
The mean respiratory rate (times/min)	32.44±11.48	25.41±3.30	8.68		0.000*
Breathlessness	71	25		7.802	0.005*
Gastrointestinal system					
Nausea	45	32		0.541	0.462
Nonprojectile vomiting	80	44		0.479	0.489
Diarrhea	2	1			
Stomach ache	4	2			
Nervous system					
Withdrawnness and lethargy	212	31		191.6	0.000*
Irritability	162	25		97.21	0.000*
Lethargy	28	11		1.755	0.185
Headache	26	6		5.48	0.019*
Shake of limbs	86	9		44.03	0.000*
Circulatory system					
Pallor complexion	22	11		0.327	0.568
Tachycardia	84	27		12.50	0.000*

**P*-value<0.05 was considered significant. HFMD: hand, foot and mouth disease

children felt nausea, 44(31.4%) had nonprojectile vomiting, 1(0.7%) stomachache, 2(1.4%) diarrhea. There was no significant difference in the symptom of the gastrointestinal system between the two groups ($P>0.05$) [Table 1].

Symptom of the nervous system

In the severe group, 212(92.6%) withdrawnness and lethargy, 162(70.7%) irritability, 28(12.2%) lethargy, 24(10.5%) coma, 26(11.4%) headaches, 39(17.0%) seizures, 10(4.4%) myoclonus, 40(17.5%) paralysis, 86(37.6%) shake of limbs, 3(1.3%) encephaledema, 60(26.2%) stiff neck, 38(16.6%) positive Babinski sign, 11(4.8%) positive Kernig sign, 15(6.6%) positive Brudzinski sign. A total of 222(96.9%) normal tendon reflexes, 6(2.6%) tendon reflexes hyperfunction, 1(0.4%) diminished tendon reflexes. A total of 213(93.0%) normal muscular tone, 4(1.7%) hypermyotonia, 12(5.2%) hypomyotonia. In the control group, 31(22.1%) withdrawnness and lethargy, 25(17.9%) irritability, 11(7.9%) lethargy, 6(4.3%) headaches, 9(6.4%) shake of limbs. None of mild cases had the symptom of coma, seizures, myoclonus, paralysis, and encephaledema, meningeal irritation, positive Babinski sign, tendon reflexes hyperfunction, or hypofunction, hypermyotonia or hypomyotonia. There was a significant difference in withdrawnness and lethargy, irritability, headache, shake of limbs between the two groups ($P<0.01$) [Table 1].

Symptom of the circulatory system

In the severe group, 22(9.6%) had pallor complexion, 84(36.7%) tachycardia, 12(5.2%) bradycardia, 71(31.0%) poor peripheral perfusion, 27(11.8%) cyanosis, 37.1% hypertention, and 1.3% hypotention. None of severe cases had myocarditis or arrhythmia. In the control group, 11(7.9%) had pallor complexion, 27(19.3%) tachycardia. None of mild cases had bradycardia, poor peripheral perfusion, cyanosis, myocarditis, or arrhythmia. There was a significant difference in tachycardia between the two groups ($P<0.01$) [Table 1].

Auxiliary examination

Blood tests

The mean white blood cell (WBC) count in the severe group and the control group was $(13.132\pm5.38)\times10^9$/l and $(7.85\pm4.11)\times10^9$/l, respectively. There was a significant difference in WBC count between the two groups ($P<0.01$). A total of 54(23.58%) severe cases and 9(6.43%) mild cases showed that the total leukocyte counts were both more than 17×10^9/l. The total leukocyte count ($\geq17\times10^9$/l) was significantly different between the two groups ($P<0.01$) [Table 2].

Table 2: The data of laboratory between severe and mild cases

Data laboratory	Severe group (*n*=229)	Mild group (*n*=140)	*t*	X	*P* value
The mean of WBC ($\times10^9$/l)	13.132±5.38	7.85±4.11	10.62		0.000
WBC ($\geq17\times10^9$/l)	54	9		18.05	0.000*
The mean of blood sugar (mmol/l)	8.02 ±5.11	5.06±1.41	8.27		0.000
Blood sugar (≥7 mmol/l)	102	16		43.79	0.000*
The mean of CK-MB (mmol/l)	41.37±4.29	11.11±1.36	10.10		
CK-MB (≥16 mmol/l)	199	32		152.2	0.000*

**P*-value<0.05 was considered significant. WBC: white blood cell count; CK-MB: MB isoenzyme of creatine phosphokinase

Biochemical examination

Blood

The mean blood sugar levels in the severe group and the control group were 8.22±5.08 mmol/l and 4.69±0.97 mmol/l, respectively. There was a significant difference in blood sugar between the two groups (P<0.01). A total of 102(44.54%) severe cases and 16(11.43%) mild cases showed that blood sugar levels were both higher than 7 mmol/l. Blood sugar (≥7 mmol/l) was significantly different between the two groups (P<0.01).

CK-MB

The mean CK-MB levels in the severe group and the control group were 41.37±4.29 mmol/l and 11.11±1.36 mmol/l, respectively. There was a significant difference in the CK-MB level between the two groups (P<0.01). A total of 199(66.56%) severe cases and 32(22.86%) mild cases showed that CK-MB levels were both higher than 16 mmol/l. CK-MB (≥16 mmol/l) was significantly different between the two groups (P<0.01) [Table 2].

In the severe group, normal findings were shown in the liver function, kidney functions, and electrolyte. There was no significant difference between the severe and control groups (P>0.05).

Cerebrospinal fluid examination

Of 138 severe cases, 114(82.6%) cases showed that cerebrospinal fluid (CSF) pleocytosis was more than 10×10^6/l, and in the mild HFMD patients lumbar puncture was not performed.

Physical examination in the severe group:

1. Chest radiograph: Of 126 severe cases, 82(65%) had increased lung markings or infectious bronchus, 34(27%) bronchopneumonia, 10(8%) exudative lesion.
2. ECG: Of 36 severe cases, 1(2.8%) had change of T wave, 10(27.8%) sinus tachycardia.
3. Brain magnetic resonance: Of 62 severe cases, 40(64.5%) showed normal findings, 22(35.5%) abnormal signal in the brainstem or medulla oblongata.

Treatment and clinical outcome

In the mild group, patients were treated with virazole under home quarantine. They would see the doctor timely whenever needed. In the severe group, patients were treated with sedative, oxygen, fluid restriction, 20% mannitol in time to keep them in mild dehydration. Large dose of r-globulin (2 g/kg) was intravenous dripped in two days. High-dose intravenous methylprednisolone (15-30 mg/kg/d) was used for 3 days. Trachea cannula and positive pressure mechanical ventilation were used in 28 fatal cases with respiratory failure. The mean hospitalization of 229 severe children was (9.0±7.3) days. A total of 199(86.9%) were cured or improved, 3(1.3%) gave up treatment and left voluntarily, 27(11.8%) died.

By using the one-factor logistic regression analysis method, many factors such as age, withdrawnness, and lethargy, shake of limbs, tachycardia, total leukocyte count, blood sugar, and CK-MB were significantly associated with incidence of severe HFMD. Univariate logistic regression analysis showed that severe cases were associated with age (<3 years), withdrawnness, and lethargy, shake of limbs, tachycardia, total leukocyte count ($\geq17\times10^9$/l), blood sugar (≥7 mmol/l), and CK-MB (≥16 mmol/l). Moreover, age (<3 years), withdrawnness, and lethargy, shake of limbs, WBC ($\geq17\times10^9$/l), and CK-MB (≥16 mmol/l) were found to be high risk factors for severe cases after multivariate logistic regression analysis [Table 3].

Discussion

HFMD was a common acute infectious disease in children. EV71 was one of very few viruses that caused HFMD as well as a variety of other clinical manifestations. The most important of these was serious complications including encephalitis, parencephalitis, brainstem encephalitis, myelitis, which caused significant morbidity.[5,11-13] HFMD had outbroken in many countries and regions such as Japan, Switzerland, Australia, America, Malaysia, Singapore, Indian, China Taiwan, etc.[2,5,14-17] HFMD cases confirmed that they were mainly caused by EV71, recruited from four hospitals in FuYang, HeFei, and BoZhou during the period 2008-2009.

Almost all the severe cases had CNS involvement; some then had circulatory failure, pulmonary edema, and pneumorrhagia. The progression of the HFMD disease was very fast. The duration was about several hours, even less than 48 hours. The mortality rate was very high if it progressed to pulmonary edema. Fortunately, severe HFMD could be stopped by effective treatment without

Table 3: The result of high risk factors of HFMD under logistic regression analysis

Variables	B	S.E.	Wald	OR	95% CI	*P* value
Ages (<3 years)	2.240	0.562	15.897	9.397	3.124-28.268	0.000*
Continuous high fever	0.522	0.848	0.379	1.685	0.320-8.879	0.538
Breathlessness	-0.136	0.574	0.056	0.873	0.283-2.687	0.812
Withdrawnness and lethargy	-4.020	0.765	27.62	0.018	0.004-0.08	0.000*
Irritability	-4.78	0.639	0.559	0.620	0.177-2.170	0.455
Headache	-1.282	1.344	0.909	0.278	0.020-3.869	0.340
Shake of limbs	-2.648	0.655	16.325	0.071	0.02-0.256	0.000*
Tachycardia	-1.247	0.584	4.562	0.287	0.092-0.902	0.033*
WBC ($\geq 17\times10^9$/l)	-3.383	0.950	12.671	0.034	0.005-0.219	0.000*
Blood sugar (≥7 mmol/l)	-1.092	0.585	3.484	0.335	0.107-1.056	0.062
CK-MB (≥16 mmol/l)	-3.334	0.536	38.624	0.036	0.012-0.102	0.000*

**P*-value<0.05 was considered significant. HFMD: hand, foot, and mouth disease. WBC: white blood cell count; CK-MB: MB isoenzyme of creatine phosphokinase; B: Unstandardized coefficients; S.E: Standard error; OR: Odds ratio; CI: Confidence interval

delay because the early pathological change was reversible. Early recognition of severe cases and timely intervention is key to prevent cardiorespiratory failure, increase the ratio of successful rescue, and reduce the acute mortality.

Through comparative analysis between two groups, the study showed that there were mainly patients of severe cases younger than 3 years, with continuous hyperpyrexia, withdrawnness, and lethargy, irritability, shake of limbs, breathlessness and tachycardia, total leukocyte count ($\geq 17\times10^9$/l), and blood sugar (≥7 mmol/l). It was consistent with the other reports.[18,19]

The primary cause of aggravation was involved in the central nervous system. The study of the deaths caused by EV71 showed that the virus could injure all the central nervous system, especially cerebellum, brainstem, and spinal.[15,20] EV71 invades the central nervous system through bloodstream or cranial nerves (facial nerve or glossopharyngeal nerve) on days 2-5.[21] Rhombencephalitis was the primary fatal cause of many death. It showed that the patients would have rhombencephalitis when they occurred salivation, cough when drinking, myoclonus, nystagmus, and palpitate, etc. Rhombencephalitis was divided into three levels according to the clinical manifestation.[22] Level 1 had myoclonus, tremor, and ataxia. Level 2 had myoclonus together with vegetative nerve functional disturbance. Level 3 had vegetative nerve functional disturbance, pulmonary edema, and hemorrhage. The clinical manifestation was rapid onset of respiratory distress, cyanosis, circulatory failure, shock, coma, absence of the pupillary light reflex, apnea, etc.

Neurogenic pulmonary edema (NPE) was the major and direct reason to give rise to death of HFMD patients.[23] Autopsy and histopathology showed that pulmonary edema caused by EV71 was neurogenic.[24] EV71 destroyed the very regions of the brainstem with regulatory function which stimulated the sympathetic nervous system, caused the blood vessel to contract intensely, and the bloodstream flow from systemic circulation to pulmonary circulation with little resistance. Pulmonary edema was the result of all the points mentioned together with increased pulmonary capillary.[25] Almost all the deaths showed vasoconstriction, ochrodermia, cold sweat, and weak pulse besides anoxia and bloody frothy sputum. The mortality of NPE was high. Its prognosis was closely related to early treatment, mainly supporting treatment, including mechanical ventilation, oxygen supply, antisympathetic drugs, etc. Therefore, early recognition and rigorous monitoring is critical to rescue the severe HFMD patients with rhombencephalitis successfully.

According to the analysis of these data and the experience of clinical treatment, high risk factors were significantly associated with incidence of severe HFMD, including age (<3 years), withdrawnness and lethargy, shake of limbs, WBC ($\geq 17\times10^9$/l), and CK-MB (≥16 mmol/l).

What is new?

1. Early recognition of children at risk and timely intervention is the key to reduce acute mortality and morbidity.
2. High risk factors were significantly associated with incidence of severe HFMD, including age (<3 years), withdrawness and lethargy; shake of limbs, WBC ($\geq 17\times10^9$/l), and CK-MB (≥16 mmol/l)

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Announcement

International Society of Dermatology

The International Society of Dermatology (ISD) and the Dermatology Society of South Africa (DSSA) are proud to announce that the 3rd Continental Congress of the ISD and the 65th National Congress of the DSSA will take place in Durban, South Africa, from 24 - 27 October 2012.

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Clinicomycological Study of 150 Cases of Dermatophytosis in a Tertiary Care Hospital in South India

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Indian J Dermatol 2012:57(4):322-3

Sir,

Cutaneous fungal infections have been reported worldwide as being one of the most common human infectious diseases in clinical practice. In spite of therapeutic advances in the last decades, the prevalence of cutaneous mycoses is still increasing.[1] The skin constitutes the main site of recognizable fungal infections in humans.[2]

The present study is undertaken with a view to identify and isolate the species of the fungi from the clinical specimens. One hundred and fifty patients, clinically suspected for dermatophytosis, attending the outpatient department of our hospital, who consented to the investigations, were studied for a period of 18 months after approval from the Institution Ethical Committee.

A detailed clinical history, general physical, and systemic examination were conducted in all cases and investigations were carried out whenever necessary. All new cases of dermatophytosis, who gave consent for required investigations, were included in the study after excluding patients on antifungal treatment and non-dermatophytic fungal infections.

The specimen collected was subjected to potassium-hydroxide (KOH) wet preparation of various concentrations depending on the type of clinical specimen for the presence of fungal elements. Following this, the specimen was inoculated into three sets of test tubes — Sabouraud dextrose agar with 0.05%, chloramphenicol with and without 0.5% cycloheximide, and the third to a dermatophyte test medium. If no growth was found after four weeks, it was taken as negative for growth of fungi.

Fungal isolates were identified based on the colony morphology, pigmentation, growth rate, microscopy, slide culture, urease test, hair perforation test, and rice grain test.

Incidence of dermatophytosis in the present study constitutes 6.09% among the patients attending the outpatient department of skin and STD. Dermatophytosis was common among the age group of 21-30 years (24%) with a male to female ratio of 1.94 : 1, which was similar to other studies by Singh S *et al*.[2] A majority of the patients were manual laborers (30.6%) from a rural background (54.6%) and belonged to the lower socioeconomic status (65.4%). Tinea corporis was the most common clinical type with 33.3%, and Tinea capitis was more common in the age group of less than 10 years (94.1%).

The results of KOH and fungal culture were as per Table 1. The clinicomycological correlation was seen in only 48.6% as in Table 2.

Trichophyton rubrum was the most common isolate (58.9%) followed by *Trichophyton mentagrophytes* (24.6%), which was comparable to a study by Venkatesan *et al*.[3] The highest culture isolate was seen in Tinea corporis, in 43.8% of the cases. These culture results were almost comparable with the studies by Bindu.[4] In the present study, however, the percentage of *M. gypseum* was higher, which could be due to the patients' interaction with soil and domestic animals.

The Wood's lamp examination was performed in eight out of seventeen cases of tinea capitis. All the eight cases were negative for fluorescence. The common isolate of

Table 1: KOH and culture findings

Findings	Number of patients	Percentage
KOH +ve, culture +ve	54	36
KOH +ve, culture -ve	46	30.6
KOH -ve, culture +ve	19	12.6
KOH -ve, culture -ve	31	20.6
Total KOH and/or culture positive	119	79

KOH: Potassium hydroxide

Table 2: Dermatophytes isolated in relation to clinical types

Clinical types	Total	Total isolated	*T. rubrum*	*T. mentagrophytes*	*T. tonsurans*	*M. gypseum*	*E. flocossum*
Tinea corporis	50	32	20 (62.5)	6 (18.75)	-	6 (18.75)	-
Tinea cruris	35	17	12 (70.5)	4 (23.52)	-	-	1 (5.88)
Tinea capitis	17	5	-	1 (20)	4 (80)	-	-
Tinea pedis	3	2	1 (50)	1 (50)	-	-	-
Tinea manuum	2	1	1 (100)	_	-	-	-
Tinea barbae	3	1	-	1 (100)	-	-	-
Tinea faciale	4	2	1 (50)	1 (50)	-	-	-
Mixed	24	9	6 (66.66)	2 (22.22)	-	-	-
Total	150	73	43 (58.9)	18 (24.6)	4 (5.4)	6 (8.2)	2 (0.7)

Figures in parenthesis are in percentage

Tinea capitis in the present study was *T. tonsurans* (80%). The diagnosis of Tinea capitis caused by the *Trichophyton* species with Wood's lamp was difficult, as the infected hair did not exhibit the characteristic fluorescence.

To conclude, the present study shows that tinea corporis is the most common clinical type of dermatophytosis and *Trichophyton rubrum* is the most common isolate in this part of South Karnataka.

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Dramatic Response to Oral Zinc in a Case of Subacute form of Generalized Pustular Psoriasis

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Indian J Dermatol 2012:57(4):323-4

Sir,

Pustular psoriasis is the most severe form of psoriasis with two main types: localized and generalized. In the generalized form, whole body may be involved and the course is subacute, acute or even life threatening. We report here a case of subacute generalized pustular psoriasis successfully treated with oral zinc. A 67-year-old female was admitted to our hospital for uncontrolled diabetic status and multiple erythematous and pustular lesions over anterior trunk and extremities for three weeks. The initial skin lesion started as erythema and pustules over lower abdomen and medial thigh, which gradually spread to involve anterior trunk, groins and lower extremities including soles. There were no systemic symptoms. The general and systemic examination revealed no abnormality. The cutaneous examination showed multiple, irregularly shaped, discrete and confluent erythematous plaques topped with pustules predominantly involving

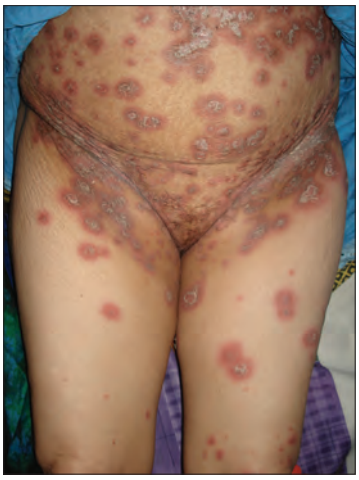

Figure 1: Multiple erythematous plaques studded with pustules and showing exfoliation

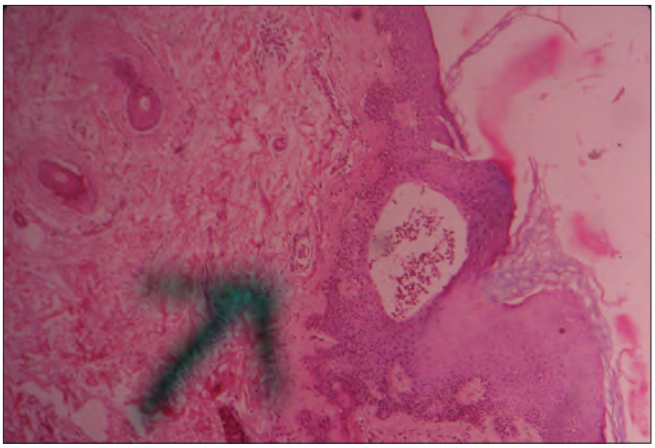

Figure 2: Histopathological examination from right thigh lesion showing parakeratosis, hypogranulosis and unilocular spongiform pustule (H&E, ×450)

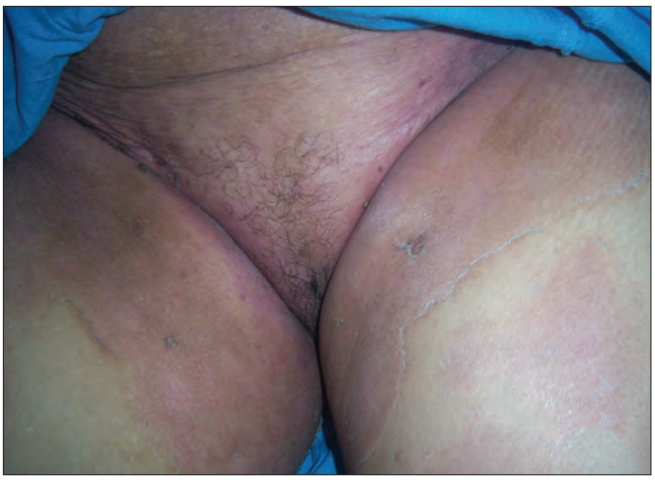

Figure 3: Clearance of lesions following treatment with oral zinc

abdomen, flexural areas and extremities including soles [Figure 1]. The plaques showed exfoliation at the centre and pustulation at the periphery. Lakes of pus were seen at places. Examination of scalp showed confluent erythematous plaques with silvery scaling. A histopathological examination of the lesional skin taken from right thigh showed parakeratosis, focal loss of granular layer, unilocular spongiform pustule in spinous layer and superficial perivascular lymphocytic infiltration [Figure 2]. Gram staining and KOH mount from pus revealed no microbes. The routine blood investigations showed leukocytosis. The fasting and postprandial sugar was raised. The culture from blood, urine, and throat swab was negative. Hepatic and renal function tests were within normal limit. Serum calcium was within normal range. The patient was diagnosed as subacute generalized pustular psoriasis. Oral zinc acetate equivalent to elemental Zinc 50 mg twice daily was started along with topical antibiotic. On the fifth day of Zinc therapy, new pustulation stopped and old lesions started healing. Marked improvement of lesions was noticed after 10 days and there was complete clearance of lesions in another 15 days [Figure 3]. There was no relapse at six month of follow-up.

Generalized pustular psoriasis is a variant of psoriasis characterized by sterile pustules on erythematous base with or without systemic features and showing spongiform pustules of kogoj histopathologically. The annular or circinate pattern without systemic toxicities is characteristic of subacute form.[1] The subacute form is characterized by sterile pustules with erythema which dessicate with exfoliation and show centrifugal spread mimicking erythema annulare centrifugum.[2] Flares are usually associated with precipitating factors like stress, irritating topical therapy (Von-Zumbusch), infection, hypocalcaemia associated with hypothyroidism. The review of literature reveals that there is an important role of zinc in pathogenesis of psoriasis.[3] It is observed that oral zinc modifies neutrophil inflammatory potential by restoring the random migration and directed chemotaxis to normal values in psoriasis vulgaris patient.[4] Keratinocytes from psoriatic plaques express high level of toll like receptors (TLR) 1, 2, 4, 5, and 9.[5] Exacerbation of psoriasis is documented following activation of TLR.[6] Zinc has anti-inflammatory effect exerted through modulation of TLR 2 surface expression.[7] The other possible mechanisms of action of zinc are immunomodulatory action, controlling bioavailability of neuropeptide mediators like substance P, neurokinin A by zinc-dependent enzyme zinc metalloproteases.[8]

Our patient developed subacute form of generalized pustular psoriasis at 67 years of age where potentially toxic drugs could not be given. She responded well with oral zinc, which could be a better substitute in elderly with systemic diseases. This is probably the first case report of subacute generalized psoriasis successfully treated with oral zinc. However, further clinical trials are required to show the efficacy of oral zinc in pustular psoriasis.

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Mometasone Menace in Melasma

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Indian J Dermatol 2012:57(4):324-6

Sir,

Melasma (from the Greek word, "*melas*" meaning black) is a common, acquired, circumscribed hypermelanosis of sun-exposed skin. It presents as symmetric, hyperpigmented macules having irregular, serrated, and geographic borders. The most common locations are the cheeks, upper lips, the chin, and the forehead, but other sun-exposed areas may also occasionally be involved.[1] Melasma occurs in all skin types and in people of all racial and ethnic groups, but is more common in those with darker complexions living in areas of intense UV radiation, such as Latin Americans, Asians, and Blacks.[2] It is the most common pigmentary disorder among Indians.[3]

Based on Wood's light findings, Sanchez *et al*.[4] classified

melasma into four subtypes: epidermal, dermal, mixed, and Wood's light inapparent. Wood's light may also serve as a prognostic guide in the treatment of melasma, as the epidermal type of melasma is more likely to respond favorably to depigmenting agents than other types. Wood's lamp can be used to determine the depth of melanin in the skin. The variations in epidermal pigmentation become more apparent under Wood's light. For dermal pigmentation, this contrast is less pronounced. However, this applies only for the fair skin types and not for type V or VI skin.[5] Three clinical patterns of distribution of the pigmentation may be recognized: Centro facial, malar, and mandibular.

In India, over-the-counter medications are often tried by patients before approaching a dermatologist. In 2004, a triple combination of hydroquinone (2%) with tretinoin (0.025%) and mometasone furoate (0.1%) was launched in India. This combination has a potent steroid mometasone furoate (0.1%) which induces local side effects like thinning of skin, persistent erythema, and telangiectasia within few weeks of application. Patient keeps on applying this combination as it can be purchased without prescription in India.

We studied the various agents used by patients before approaching a dermatologist. Fifty consecutive patients of melasma in the age group of 18–45 years with a mean age of 25.5 years were included in this study. There were 38 females and 12 males. The duration of melasma ranged from 1 to 6 years with a mean of 1.1 years.

We found the following medications were used by patients before approaching a doctor. Most were advised these medications by friends, parents, and beauticians [Table 1].

Most patients who used mometasone-based triple creams found clearing of melasma followed by relapse. Red skin after use of triple creams was noted by 15 out of 23 patients. We found only two patients who used sunscreens with triple creams.

Clinical examination revealed telangiectasia (8 out of 23) and skin thinning (4 out of 23) as side effects of mometasone-based creams [Figure 1].

Majid found that majority of patients (51.7%) had used the mometasone-based triple combination treatment well beyond the recommended duration. Steroid side effects were seen in 26 patients (43.3%).[6] The recommendation that the combination be stopped after about 4–8 weeks is followed rarely at all by the patients. Easy availability of these creams over-the-counter at a pocket-friendly price makes the patients to use this combination for a long duration. Prolonged use makes facial skin sun sensitive. Patients cannot use routine cosmetics on sensitive skin. Rubbing triple creams on hyperpigmented area vigorously worsens the situation in most patients. We found 2 patients out of 10 (20%) who used triple combination with mometasone and glycolic acid peels, with side effects of persistent erythema, irritation, and hyperpigmentation.[7]

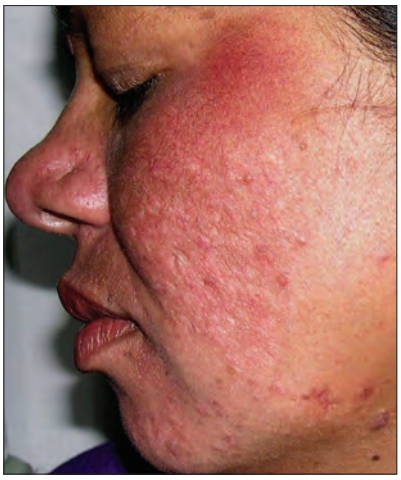

Figure 1: Persistent erythema after use of mometasone-based triple cream

Table 1: Use of medications by patients

Medications	Number of patients
Triple combination with mometasone	23
Herbal creams	10
Fair and lovely	10
Beauty parlor treatments	7
No treatment	12
Sunscreens	2

Now, triple combination cream with fluocinolone acetonide (0.01%) as steroid is available in India. Fluocinolone-based triple creams are safe for long-term use up to 24 weeks. Risk of skin atrophy with 24-week use of triple combination cream with fluocinolone for the treatment of melasma is very low.[8] We found this fluocinolone-based triple combination along with glycolic acid peels as a safe and effective option in Indian patients.[9]

We suggest triple combination creams with mometasone should be prescribed after thorough counseling with the patient. Long-term side effects of this cream should be explained to the patient.

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Extensive Discoid Lupus Erythematosus in a HIV Patient Responding to Hydroxychloroquine Monotherapy

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Indian J Dermatol 2012:57(4):326-7

Sir,

Association of systemic lupus erythematosus (SLE) or discoid lupus erythematosus (DLE) with human immunodeficiency virus (HIV) infection in the same patient is rare. Both conditions have similar clinical and serologic features, making their coexistence a diagnostic and therapeutic challenge. Moreover, HIV infection appears to have a favorable impact in the clinical course of SLE. On the other hand, immunosuppressive therapy given for SLE activity has been associated with worsening of HIV infection.[1] We report a case of a HIV-infected patient, who developed extensive DLE and responded quickly to systemic hydroxychloroquine therapy.

A 55-year-old lady, house wife by occupation, detected to be HIV positive 6 months back with CD_4 count 340 cells/mm^3, not on antiretroviral therapy (ART), presented to our OPD with history of depigmented, asymptomatic skin lesions over the face and both the forearms of 2 months duration. They started as small papules and gradually evolved into larger, depigmented plaques with dry scaly surface. She complained of burning sensation in the lesions on exposure to sunlight. Her husband died 4 years back due to some HIV-related illness, details of which are not available.

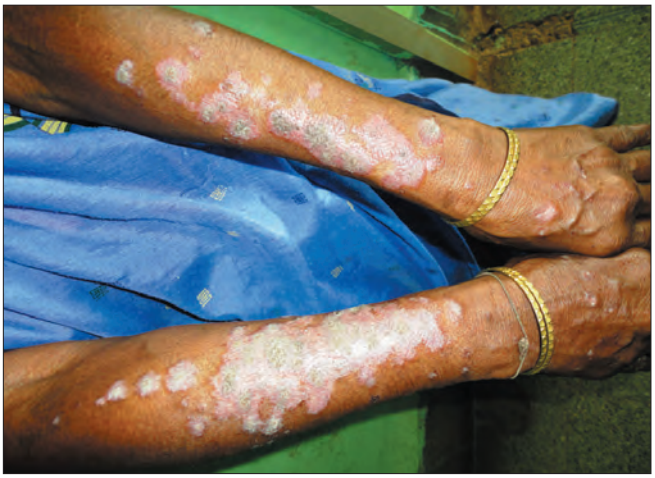

Figure 1: Extensive discoid lupus erythematosus lesions over both the forearms

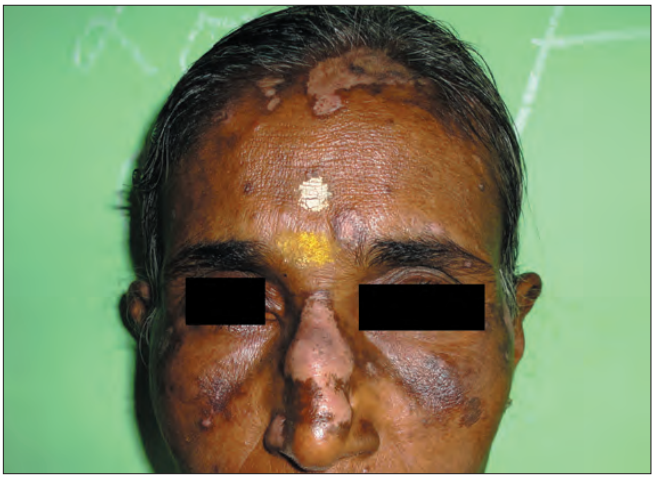

Figure 2: Discoid lupus erythematosus lesions over the face

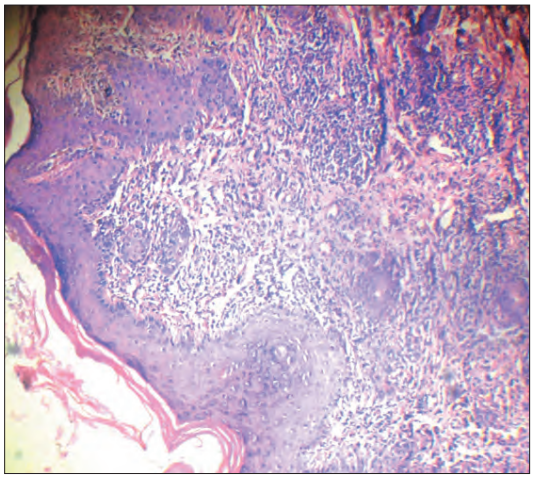

Figure 3: Histopathology showing follicular plugging and perivascular cuffing with lymphocytes

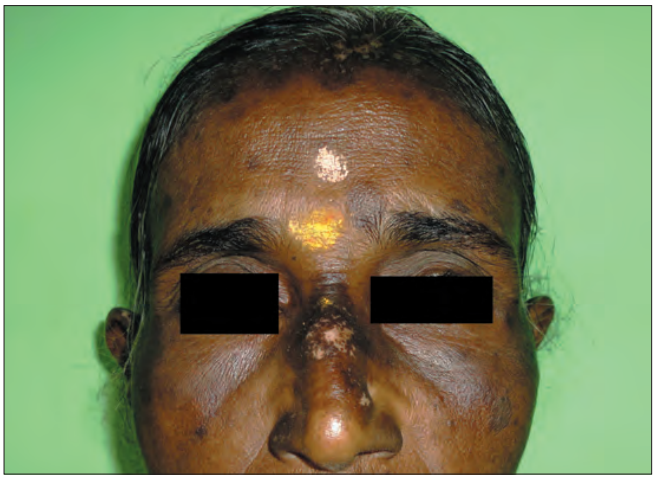

Figure 4: DLE lesions over the face subsiding within 3 weeks after hydroxychloroquine monotherapy

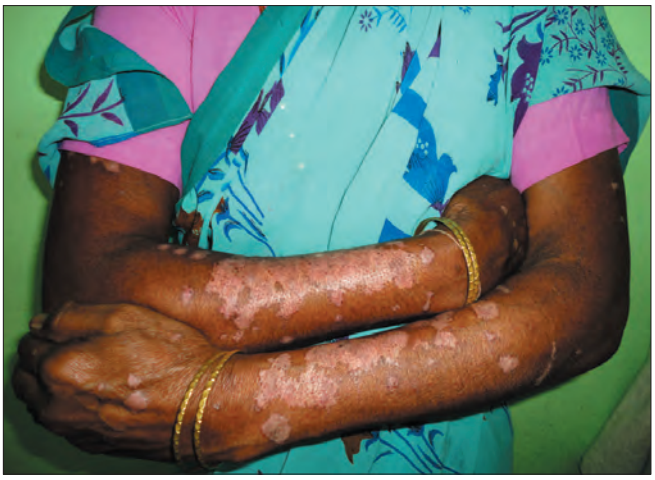

Figure 5: DLE lesions over the forearms subsiding within 3 weeks after hydroxychloroquine monotherapy leaving behind postinflammatory depigmentation

Her general physical examination and systemic examinations were normal. Cutaneous examination revealed multiple, depigmented plaques measuring 2 cm × 1 cm to 5 cm × 4 cm, with dry surface covered with thick, grayish adherent scales, distributed over both the forearms [Figure 1], forehead, nose, and cheeks [Figure 2]. The carpet tag sign was positive. On investigation, routine blood and urine investigations were within normal limits. The ANA profile was negative. A biopsy taken from the lesion was subjected to histopathological examination which confirmed the diagnosis of DLF [Figure 3]. After complete ophthalmological examination, she was started on tablet hydroxychloroquine 200 mg twice daily. Within 3 weeks, all the lesions healed with postinflammatory depigmentation [Figures 4 and 5]. She was followed up for 4 months. There was no recurrence. Later on, her CD_4 count dropped to below 200 and she was started on ART.

Although HIV infection is often associated with several rheumatic diseases, the coexistence of this retroviral infection and SLE is extremely uncommon. Generally, HIV-related immunosuppression improves SLE symptoms and ART may lead to an autoimmune disease flare subsequent to the increase of circulating CD4+ cell number. There are reports of SLE and DLE with HIV infection improving after initiation of ART.[2] Whereas, in our case, the lesions of DLE improved with hydroxychloroquine monotherapy and the patient was not on ART during the treatment with hydroxychloroquine. Many studies on cutaneous manifestations of HIV infection revealed that occurrence of DLF in HIV patients is rare.[3] There are reports of SLE and chronic cutaneous lupus erythematosus,[2,4,5] but occurrence of DLE with HIV infection appears to be extremely rare. We report this case for its rarity and peculiarity.

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Zosteriform Fixed Drug Eruption to Levofloxacin

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Indian J Dermatol 2012:57(4):327-8

Sir,

A 38 year old man presented with multiple fluid filled

lesions on the left side of the chest and dark colored lesions on the right hand of 3 days duration, associated with itching and burning. He also complained of erosions over the lips and the genitalia. He had been treated with levofloxacin and paracetamol for fever and sorethroat seven days ago. The hyperpigmented lesions on the hand had also occurred 3 months ago following intake of levofloxacin for upper respiratory tract infection. There was no history of chest trauma, herpes zoster or application of topical medications. On examination there were multiple, sharply demarcated hyperpigmented macules, a few of them surmounted by flaccid bullae, extending from the nipple to the midback in a zosteriform configuration, corresponding to the left T4, T5 dermatome [Figure 1]. Two smaller hyperpigmented macules were also seen over the dorsum of the right hand. No other similar lesion was seen over the trunk or limbs. Erosions and crusting were noted over the lips while the glans showed erosions with preputial edema. Histopathology from the hyperpigmented macule showed perivascular mononuclear cell infiltration, pigment incontinence and scattered melanophages consistent with fixed drug eruption (FDE). Hemogram was normal, while culture from throat swab grew streptococci sensitive to erythromycin. He was treated with tablet paracetamol, azithromycin, topical mupirocin with fluticasone and a short course of systemic steroids.

FDE is characterized by a sudden onset of edematous, dusky-red macules/plaques on the skin and mucous membranes, accompanied by burning and/or itching with the characteristic hallmark being reappearance of the lesions precisely over the previously affected sites on re-use of the offending drug.[1] Our patient developed FDE to levofloxacin at multiple new sites in addition to the lesions noticed on the right hand during the first exposure. Although paracetamol is known to produce bullous FDE, our patient gave history of taking the drug over-the-counter and was even continued on paracetamol during this episode. A rechallenge with levofloxacin could not be done as the patient refused it.

Site predilection of the offending drug to induce FDE is well known and has been documented as with tetracycline commonly causing lesions on the genital mucosa, naproxen on the lips, co-trimoxazole on the lips and genitalia, and metamizole on the trunk and extremities.[2,3] Site predilection of FDE occurrence have been reported with lesions preferentially occurring over previous herpes zoster, BCG vaccination, burn scar, venipuncture site, insect bite, herpes simplex or cellulitis and have been attributed to a Koebner-like phenomenon or recall phenomenon or an isotopic response.[2] Preferential localization of FDE at viscerocutaneous reflex zones has been documented and is attributed to reflex alteration in blood flow and vascular permeability.[2,4] Our patient had a history of upper respiratory tract infection with a positive throat swab culture but no specific features of internal organ pathology that could possibly explain the occurrence in a viscerocutaneous reflex zone.

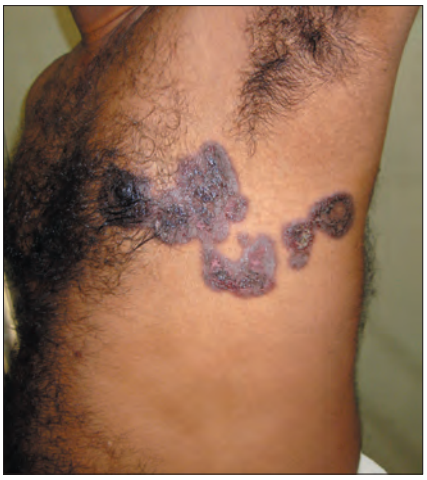

Figure 1: Sharply demarcated hyperpigmented macules exhibiting a zosteriform pattern

Genetic susceptibility for the occurrence of FDE is known,[3] and the co-occurrence of linear and disseminated drug eruption have been explained on the basis of clonal population of cells being either homozygous or hemizygous for a gene predisposing to the disease.[5] Dermatomal distribution of FDE, as in our patient, has been contemplated with FDE to cephazolin occurring along S1 nerve root and FDE to trimethoprim occurring along C8 dermatome.[6] Though the cause for the distribution of multiple lesions of FDE occurring in a peculiar, unilateral, dermatomal pattern is inexplicable, the zosteriform appearance was nevertheless quite characteristic and unique in our patient.

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Twenty Nail Dystrophy in Association with Zosteriform Lichen Planus

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Indian J Dermatol 2012:57(4):329

Sir,

A 30-year-old male presented with roughness, ridging, flattening, and opacity of all the fingernails and six of the toenails since the last two years [Figure 1]. In the beginning, these changes appeared only in two fingernails; then other nails became involved and the degree of involvement increased in severity. On detailed examination of the patient, multiple violaceous flat papules and plaques were found on the left side of his trunk in a dermatomal distribution [Figure 2]. Similar lesions were not found anywhere else in the body. Oral and genital mucosa were normal. According to him, these lesions appeared around 3 months back. Routine hematological and biochemical examinations were within normal limits. A skin biopsy done from one of the skin lesions showed basal cell degeneration, interface lymphocytic infiltrate, and melanin incontinence. Therefore a diagnosis of segmental or zosteriform lichen planus in association with 20-nail dystrophy was made [Figure 3]. The patient was started on systemic corticosteroids and antihistamines.

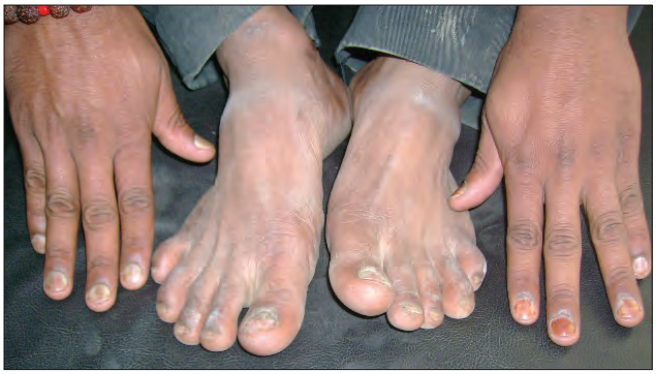

Figure 1: Finger and toe nail involvement

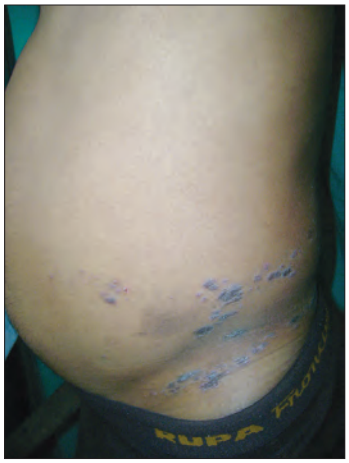

Figure 2: Multiple violaceous papules and plaques in a dermatomal distribution

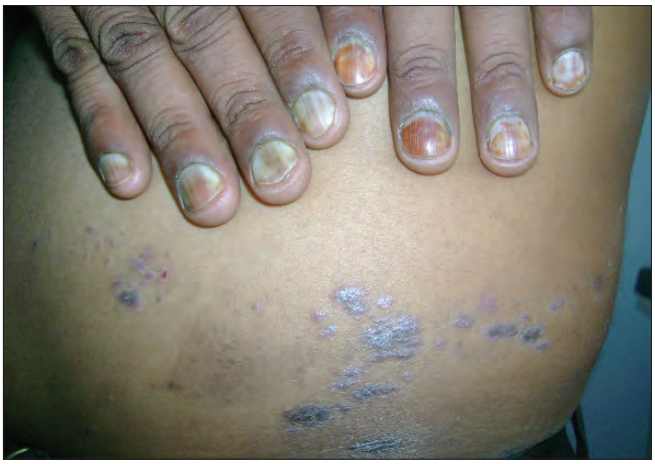

Figure 3: Skin lesions with thin, rough, longitudinally ridged opaque nails

Twenty-nail dystrophy is characterized by a spectrum of nail plate abnormalities that leads to nail roughness or trachyonychia. It can be idiopathic or may be associated with lichen planus, psoriasis, alopecia areata, ichthyosis vulgaris, eczema, vitiligo, primary biliary cirrhosis, IgA deficiency, and graft-versus-host disease.[1,2] Twenty-nail dystrophy has congenital, familial, and acquired forms. All nails may or may not be involved. The nails show excessive longitudinal ridging and become rough, thin, and opaque, giving the appearance of sandpaper nails. Lichen planus can be linear as a result of Koebner's phenomenon or can appear as a band of lesions in a dermatomal or Blaschkoid distribution.[3] Lichen planus is a common cause of 20-nail dystrophy, but 20-nail dystrophy has not been described in association with zosteriform lichen planus, making this a rare case. Also, in this case lichen planus developed long after development of 20-nail dystrophy. So, prolonged follow-up of apparently idiopathic 20-nail dystrophy cases can reveal one of the proven etiologies.

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Granular Cell Tumor of Skin Diagnosed on Fine Needle Aspiration Cytology

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Indian J Dermatol 2012:57(4):330-1

Sir,

Granular cell tumor (GCT) is an uncommon benign neoplasm of uncertain histogenesis. Although they can occur at any site, tongue, breast, upper respiratory tract, and soft tissue of upper extremities are their common locations. As the lesions presenting on skin are located deep in the subcutis, they are not aspirated very often and so the reports of their cytological diagnosis at this site are sparse in literature. We report to the best of our knowledge the third case of cutaneous GCT diagnosed by fine-needle aspiration cytology (FNAC).

A 40-year-old man presented to the dermatology outpatient clinic with a well-defined erythematous lesion on his right forearm of 2 years' duration that had been gradually increasing in size. Physical examination showed a 3.2 × 2.1 × 1.0 cm erythematous, firm, nontender plaque with smooth surface and subcutaneous firm mass [Figure 1]. The patient was referred for FNAC with provisional clinical diagnosis of dermatofibroma.

FNAC was done using a 22-gauge needle and a 20 cc syringe. The smear stained with Giemsa stain showed moderate cellularity and was composed of loosely dispersed groups of cells and stripped bare nuclei. The cells were large, polygonal, without appreciable cell borders containing abundant granular and fragile cytoplasm [Figure 2]. These cells showed PAS-positive diastase resistant cytoplasmic granules representing the phagolysosomes. The nuclear

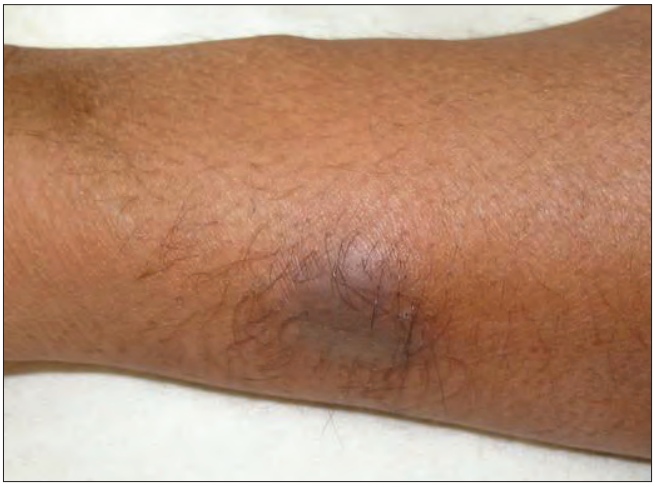

Figure 1: Subcutaneous firm mass on the right forearm

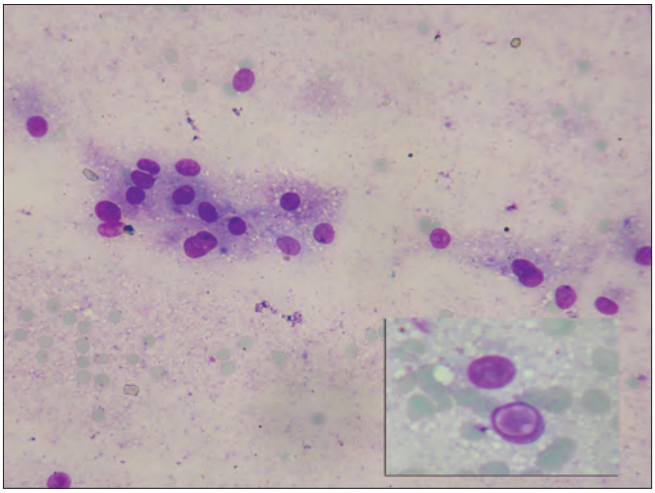

Figure 2: Polygonal cells with ill-defined borders, fragile granular cytoplasm, central nuclei with fine chromatin (Giemsa ×200) and intranuclear inclusion (Giemsa ×400, inset)

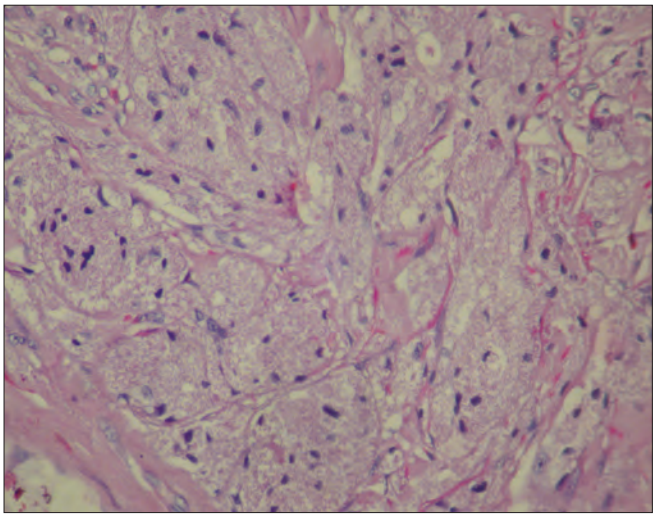

Figure 3: Photomicrograph showing polygonal cells with granular cytoplasm

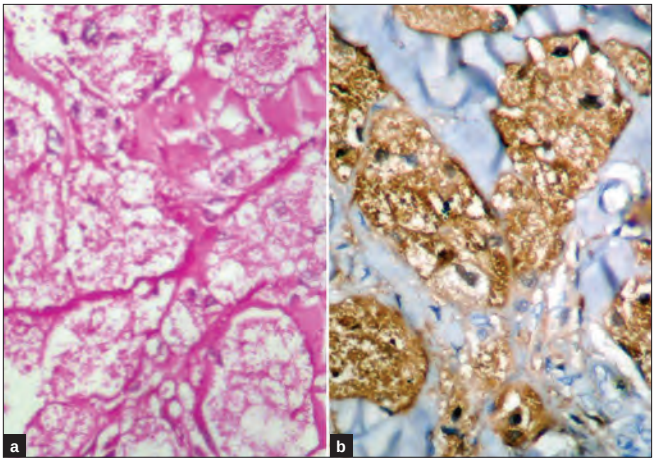

Figure 4: Biopsy showing (a) PAS positive-diastase resistant granular cytoplasm (PAS with diastase, ×200) and (b) cells showing S100 positivity

cytoplasmic ratio was low with round to oval central nucleus, small nucleoli, and fine chromatin pattern with occasional intranuclear inclusions [Figure 2, inset]. Some cells showed anisonucleosis; however no mitoses or pleomorphic spindle cells were noticed. The lesion was suggested to be a cutaneous GCT and excision biopsy was advised. Histopathological examination of the excised specimen showed a tumor consisting of polygonal cells with abundant granular cytoplasm [Figure 3]. They were arranged in lobules and extended deep into the subcutis. The cytoplasmic granules were PAS positive and diastase resistant [Figure 4a] and immunohistochemistry for S-100 was positive [Figure 4b]. A diagnosis of benign cutaneous GCT was confirmed.

GCT are uncommon tumors of putative neural origin and may occur at any site though they seldom involve the skin. They usually present between fourth to sixth decades of life and show a slight preponderance toward adult females. The cytological findings of cutaneous GCT seen in our case were in accordance with the previously described reports[1,2] and the presence of intranuclear inclusion in a few cells appears to be a useful cytomorphologic feature as described by Liu *et al*.[3] in soft tissue and later by Mallik *et al*.[2] on the skin of a forearm of a child. In most cases the cytological features are distinctive enough but differentiation from other lesions that resemble the cytological features of GCT is necessary. The foremost lesion that needs to be excluded is the alveolar soft part sarcoma that shows prominent nucleoli, multinucleated cells, and the characteristic rhomboid crystals. The absence of cross-striations and glycogen distinguishes GCT from rhabdomyoma while, the absence of lipid droplets excludes hibernoma.

To conclude, GCT may rarely present as a cutaneous lesion and both the dermatologist and the pathologist should be aware of this entity which can be diagnosed easily by FNAC.

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Clinicopathological Evaluation of Non-melanoma Skin Cancer

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Indian J Dermatol 2012:57(4):331-2

We read with great interest the recent study by Adinarayan and Krishnamurthy,[1] and although we agree with most of the article's aspects, there are some considerations, which we believe are necessary to make:

1. According to several studies,[2,3] the authors'[1] assertion that "skin cancers are relatively uncommon malignancies worldwide" seems misplaced. In fact, skin cancer is the most common cancer in humans, being a growing worldwide problem, especially in fair-skinned populations. Therefore, it is considered a global epidemic, leading to a huge demand and increased expenses with health services.[2,3]
2. Knowledge about the relationship between exposure to ultraviolet radiation and the development of non-melanoma skin cancer (NMSC) has been modified in recent years.[2,3] Chronic sun exposure seems to be the main cause of squamous cell carcinoma (SCC).[2,3] In contrast, basal cell carcinoma (BCC) occurs due to intermittent sunlight exposure and history of sunburns, especially during childhood and adolescence.[2,3] Unlike, therefore, the aspects discussed by the authors.[1]
3. Adinarayan and Krishnamurthy[1] evaluated the distribution of NMSC in different anatomical sites. Related to this, our group[4] and others[5] demonstrated recently that diagnostic accuracy varied according to the affected anatomical area of the body. In both the studies,[4,5] diagnostic accuracy, when stratified by tumor site, was highest in places where more frequently lesions occur. It is feasible to assume that the behavior learned by doctors causes an excess of malignant lesions' diagnoses (BCC and SCC) at the respective locations of the body where they most commonly occur, and an underestimation of lesions in body sites where they are less frequent.[5] The domain of this diagnostic aspect is important, considering that the diagnosis of NMSC is predominantly clinical, and it is confirmed by histopathologic evaluation that errors can delay appropriate treatment,[2,4] it is expected that doctors are able to accurately diagnose these skin lesions.[4] In this context, efforts should be taken to improve medical education regarding these lesions;[5] the diagnostic hypotheses should be based on a set of information (clinical appearance, location, and evolution of lesions) and not just on the anatomical site involved.[4,5]

Finally, we congratulate and thank the authors for their

contribution to the clinicopathological understanding and characterization of the NMSC.

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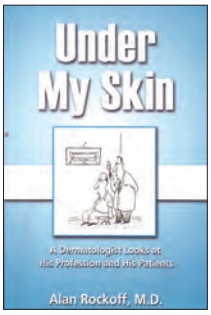
Under My Skin



Author: Dr. Alan Rockoff, M.D.
Publisher: Mill City Press Inc, 212, 3rd Avenue, Suite 290, Minneapolis, MN 55401, USA.
Year: 2011
Price: US $15
Paperback: Pages 204
Web: www.millcitypublishing.com

Dermatology as a specialty has traversed a long distance since the early days when it was considered not only a subspecialty but also a distant cousin of Medicine. Till the eighth decade of the 20th century it seemed to have no right to be placed on the same pedestal as its more prestigious cousins, pediatrics, cardiology and neurology. With the gradual entrance of dermatosurgery and cosmetology and with increasing importance being given to the relationship clinical dermatology has with other specialties, the tide has turned and more than three decades down the line dermatology has entered the hallowed portals of the leading professional fields in the medical world.

Dr. Alan Rockoff, M.D., became "a dermatologist by accident" at a time when dermatology was considered to be "tangential to internal medicine." Thirty two years on, he looks back with characteristic wit and compassion at a profession that has provided him with a lot of insight into the vagaries of human behavior. His book "Under My Skin" has the subtitle "A dermatologist looks at his profession and his patients," and is divided into two sections "Practice" and "Patients" though there is a distinct but unavoidable overlap between the two.

The first section titled "Practice" deals with his profession. Starting from the very first moments of his practice, the initial tottering, the relationship with other doctors and the finer skills needed to build up a good practice, he moves on to the rapidly changing face of modern-day practice where the Internet and modern gadgets dominate over humans, where history-taking and other mundane matters are delegated to medical assistants and counseling is offered by other personnel. Dr. Rockoff recognizes the pulls and pressures of modern-day commercialism, consumerism, bureaucracy and medico-legal issues but rightly rues the fact that the ultimate victim of this change in the pattern of practice is the basic one-to-one human relationship between the doctor and his patient.

It is this relationship he explores in the second section. The variety of patients he has encountered during his sojourn in the practicing world of dermatology presents an interesting mix. The first narrative about Letitia's brave fight to rehabilitate Stacey and the latter's miraculous recovery is captivating and sets the tone for the later chapters. Each of these chapters, written with dollops of humor, reveals Dr. Rockoff's not so inconsiderable observational powers and deep insight into the patients' psyche. In his "Remarks to the Medical Youth Forum" appended at the end of the book, he rightly comments "Though technology advances and systems change, people don't."

Dr. Alan Rockoff started his practice in Boston in 1979, the same year that this reviewer in Kolkata (or Calcutta as it was then known) started his sojourn in the fascinating world of dermatology as a young postgraduate. The two practicing fields were set thousands of miles apart in two completely different milieus. Yet one finds a lot of similarity in the experiences regarding the patients and their relatives, doctors and their gadgets, the high and low points of practice, and the distinct change in the attitude of our colleagues in other specialties toward us. It is obvious that the experiences of any dermatologist shall be the same anywhere in this globe, and one can empathize with the attitude of Dr. Rockoff toward his patients and vice versa, whatever be one's geographical location.

The essays are written in a style that is laid-back at times, racy at others, but extremely witty all the way. He looks at his patients with sympathy, at his colleagues with respect and at his profession with a lot of candor. His deep insight into the world of dermatology is reflected in almost all the pages of the book, yet he avoids the trap of sermonizing to his readers.

In his preface, Dr. Rockoff writes "Somehow, becoming a dermatologist still feels like an accident. A pleasant one." Among all the tales of joy and sorrow, of success and disappointment there is one common thread – Dr. Rockoff has immensely enjoyed the experience of his sometimes

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smooth, sometimes roller-coaster ride in the practice of dermatology during all of 32 years. With this background in mind, one wishes that the book could have a more pleasant and interesting title other than the rather creepy "Under My Skin".

Overall, the book is a must-read not only for all dermatologists, young and old but also for laymen who may be surprised at the detailed, analytical and sympathetic manner in which a dermatologist beholds them.

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IADVL - AAD Reciprocal Scholarship - 2013

Registration for nominations invited

American Academy of Dermatology (AAD) International Affairs Committee, with the understanding with IADVL, gives two young Dermatologists from India an opportunity to attend the AAD in its 71st Annual Meeting of the American Academy of Dermatology to be held the 1-5th of March, 2013 in Miami Beach, Florida, USA. The Academy will waive the non-member registration fee for this program. The selected individuals will also be provided with complimentary tuition to a one or two-day postgraduate course of their choice (subject to availability of space in the course). These scholarships are available only to those individuals who have not received a previous registration scholarship from this program. Selected candidates need to make their own travel, lodging and incidental arrangements (procurement of passport/visa etc) for the AAD meet and IADVL would not be sponsoring them. This year's AAD website did not mention anything about the possible financial grant to the reciprocal scholarship recipients.

Kindly send your complete CV and a letter addressed to the president IADVL stating the reason why you must be selected for this scholarship along with their willingness to undertake journey to go to USA to attend AAD meet if selected, before 15th August 2012 to Hon. General Secretary of IADVL. They would be scrutinized and the panel 3 presidents, past, and present and president elect. Nominations of those two selected candidates would be submitted by IADVL before 1st September 2012, along with a letter of endorsement, to AAD for consideration. Registration materials and information will be provided to the successful applicants in October 2012 by AAD.

Send details mentioning the scholarship you are applying for on the form on the next page by e-mail or by post to:

Dr. P. Narasimha Rao
Honorary General Secretary (IADVL)
B-48, Income Tax Colony, Mehdipatnam,
Hyderabad, A.P. 500 028
Mobile: 09849044898
E-mail: secretaryiadvl@gmail.com

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*Data on file

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