

# Journal of Pakistan Association of Dermatologists

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## Editorial

# Mastocytosis: from Nettleship and Darier to Metcalfe and Valent

**Shahbaz A. Janjua**

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In 1869, Nettleship and Tay described a unique cutaneous disease that showed a symmetrical spread with pigmented maculopapular lesions and an urticaria-like response to rubbing or scratching.<sup>1</sup> The disease was termed urticaria pigmentosa (UP) by Sangster in 1878.<sup>2</sup> Soon after the discovery of the mast cell by Paul Ehrlich in 1879, the lesions were found to contain focal accumulations of mast cells.<sup>3</sup> For a long time, it was assumed that such pathological accumulation of mast cells, called mastocytosis (MC), is restricted to skin. However, in 1949, Ellis described a systemic form of mastocytosis with involvement of visceral organs.<sup>4</sup> In 1905, Darier<sup>5</sup> wrote an article about UP and its pathognomonic sign and the clinical test was associated with Darier.

Mastocytosis (MC) is a proliferation of mast cells and their subsequent accumulation in one or more organ systems. Mast cell disease can be limited to the skin, which is referred to as cutaneous mastocytosis (CM), or involve extracutaneous tissue, which is called systemic mastocytosis (SM). The diagnosis of cutaneous mastocytosis (CM) is

based on typical clinical and histological skin lesions and absence of criteria of systemic involvement. Most patients with CM are children and present with urticaria pigmentosa. Other less frequent forms of CM are diffuse cutaneous mastocytosis (DCM) and mastocytoma of skin. Systemic mastocytosis (SM) is commonly seen in adults and defined by multifocal histological lesions in the bone marrow (affected almost invariably) or other extracutaneous organs (major criteria) together with cytological and biochemical signs (minor criteria) of systemic disease (SM-criteria). SM is further divided into the following categories: indolent systemic mastocytosis (ISM), SM with an associated clonal hematologic non-mast cell lineage disease (AHNMD), aggressive systemic mastocytosis (ASM), and mast cell leukemia (MCL).<sup>6</sup>

In September, 2000, the World's leading experts in MC met to discuss and present data at the "Year 2000 Working Conference on Mastocytosis," held in Vienna, Austria. Valent *et al.*<sup>6</sup> presented a uniform classification system for MC at the conference.

Symptoms of MC occur when pharmacologic or physical stimuli cause mast cell degranulation and release of histamine, prostaglandins, leukotrienes and other chemical mediators. These episodic

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**Table 1** Classification of mastocytosis by Valent *et al.* [6]

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Cutaneous mastocytosis (criteria for systemic mastocytosis not fulfilled)		
Maculopapular cutaneous mastocytosis		
Typical urticaria pigmentosa		
Plaque form		
Nodular		
Telangiectasia	macularis	eruptiva
perstans		
Diffuse cutaneous mastocytosis		
Mastocytoma of the skin		
Indolent systemic mastocytosis		
Systemic mastocytosis with AHNMD		
Aggressive systemic mastocytosis		
Mast cell leukemia		
Mast cell sarcoma		
Extracutaneous mastocytoma		

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attacks can be manifested by flushing, urticaria or, in extreme cases, by life-threatening vascular collapse.<sup>7</sup>

Mast cells originate from bone marrow progenitor cells and are distributed throughout the connective tissues. They are concentrated in the skin around the peripheral nerves and adjacent to blood and lymphatic vessels. When activated by IgE or other stimuli, mast cells release preformed mediators of inflammation (**Table 3**). These mediators initiate a leukocyte-cytokine cascade that contributes to the acute and delayed hypersensitivity reactions and the various cutaneous and systemic manifestations of MC.

There has been a progressive evolution in the understanding of the biologic role of mast cells over the last 30 years. Key discoveries include the description of mast cell growth factors, documentation that mast cells are derived from CD 34+ pluripotential stem cells, recognition of the expression of key adhesion molecules on mast cells, description of mast cell apoptosis, discovery

**Table 2** Stimuli and substances that can cause degranulation of the mast cells [7]

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Emotional stress
Physical stimuli (e.g., heat, cold, friction, exercise, sunlight, sexual intercourse)
Bacterial toxins
Venoms (bee sting)
Biologic polypeptides (e.g., lobster, crayfish, jellyfish, Ascaris)
Polymeric eye drops (containing dextran)
Immunologic stimuli (e.g., IgE)
Complement-derived anaphylotoxins
Drugs
Acetylsalicylic acid (aspirin)
Amphotericin B (Fungizone)
d-Tubocurarine
Dextromethorphan
Ethanol
Gallium (Ganite)
Narcotics (e.g., morphine, meperidine [Demerol], codeine)
Nonsteroidal anti-inflammatory drugs
Polymyxin B (Aerosporin)
Quinine
Radiographic contrast containing iodine
Reserpine
Scopolomine (Transderm Scop)

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of the leukotrienes, and the recognition that mast cells produce cytokines.

Metcalfe is well known for his highly cited work in allergic diseases, particularly his work in the role of mast cells in allergic inflammation. In his studies of patients with mast cell disorders, Metcalfe has characterized the spectrum of the diseases associated with mastocytosis, and has developed the currently accepted treatment programs for this disease. His basic laboratory research focuses on the growth and differentiation of mast cells, employing molecular biologic techniques. His work has led to the current appreciation of the spectrum of mast cell phenotypes, the growth factors regulating mast cell

**Table 3** Mast cell products and their clinically significant activity

Mast cell product	Clinically significant activity
<i>Preformed secretory granule-associated mediators</i>	
Histamine	Vasodilatation, erythema, edema, pruritus, urticaria, bronchoconstriction, increased gastric acid, intestinal cramping, further degranulation of mast cells, leukocyte activation
<i>Proteoglycans</i>	
Heparin	Osteoporosis, inhibition of localized clotting; rarely, prolonged partial thromboplastin time
<i>Neutral proteases</i>	
Tryptase	Inhibition of coagulation locally, bronchoconstriction, osteoporosis
Chymase	Inhibition of coagulation locally, activation of mast cells, blistering (?)
Cathepsin G and carboxypeptidase	Kinin generation, hepatic fibrosis (?)
Acid hydrolases	Bone lesions, osteoporosis
<i>Lipid mediators</i>	
Leukotrienes	Bronchoconstriction, increased vascular permeability and contractility
Prostaglandin D2	Pruritus, pain, rhinorrhea, hypotension, flushing, osteoporosis

differentiation, and interactions between mast cells and tissue matrix.

Metcalf<sup>8</sup> classified mastocytosis as indolent disease confined to skin, indolent systemic disease with or without cutaneous involvement, mastocytosis with an associated hematologic disorder, aggressive lymphadenopathic mastocytosis with eosinophilia and mastocytic leukemia.

Although the exact pathogenicity of mastocytosis is still unclear but, recent studies have suggested that activating mutations of *c-kit*, a proto-oncogene encoding for the receptor (*kit*) of stem cell factor, are a possible cause of some forms of mastocytosis. The type III receptor tyrosine kinase (*kit*) is critical to the development and survival of mast cells and melanocytes. A mutation of the receptor causes it to remain in the "on" position. The ligand for *kit* can stimulate mast cell development, proliferation, and mediator release, as well as melanocyte proliferation and pigment production.<sup>9</sup> The induction of melanocytes explains the hyperpigmentation that is commonly associated with cutaneous mast cell lesions.

**Table 4** Metcalfe classification of mastocytosis (Produced with permission from Dr. Dean Metcalfe (NIH, NIAID) for JPAD)

Category IA	Indolent disease confined to skin
Category IB	Indolent systemic disease with or without cutaneous involvement
Category II	Mastocytosis with an associated hematologic disorder
Category III	Aggressive lymphadenopathic mastocytosis with eosinophilia
Category IV	Mastocytic leukemia

Systemic mastocytosis is diagnosed if one major and one minor criterion are met, or three minor criteria are fulfilled.<sup>6</sup> The major criterion is multifocal dense infiltrates of mast cells (>15 MC aggregating) detected in sections of bone marrow and/or other extracutaneous organ(s) by tryptase-immunohistochemistry or other stains. Minor criteria are:

- In mast cell infiltrates detected in sections of bone marrow or other extracutaneous organs, >25% of mast cells are spindle shaped or, in bone marrow smears, atypical mast cells compose >25% of all mast cells.
- Detection of a *c-kit* point mutation at codon 816 in bone marrow or blood or other extracutaneous organ(s).
- Kit mast cells in bone marrow or blood or other extracutaneous organ(s) co-express CD2 and/or CD25.
- Serum total tryptase concentration >20 ng/ml (in case of an AHNMD, this is not valid).<sup>6</sup>

Despite significant advances in research on mastocytosis, curative treatment is not yet available. Current management is based on avoidance of mediator-releasing triggers and symptomatic treatment.<sup>10</sup>

## References

1. Nettleship E. Rare forms of urticaria. *Br Med J* 1869; **2**: 323-4.
2. Sangster A. Urticaria pigmentosa. *Lancet* 1878; **I**: 683.
3. Ehrlich P. Beiträge zur Kenntnis der granulierten Bindegewebszellen und der eosino-philen Leukozyten. *Arch Anat Physiol* 1879; **3**: 166-9.
4. Ellis JM. Urticaria pigmentosa. A report of a case with autopsy. *AMA Arch Pathol* 1949; **48**: 426-9.
5. Darier JF. Quelques remarques sur l'urticaire pigmentaire. *Ann Dermatol Syphiligr* 1905; **6**: 339-44.
6. Valent P, Horny HP, Escribano L *et al.* Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res* 2001; **25**: 603-25.
7. Longley J, Duffy TP, Kohn S. The mast cell and mast cell disease. *J Am Acad Dermatol* 1995; **32**: 545-61 [Published erratum in *J Am Acad Dermatol* 1995; **33**:52].
8. Metcalfe DD. Classification and diagnosis of mastocytosis: current status. *J Invest Dermatol* 1991; **96**: 2S-4S.
9. Longley BJ, Tyrrell L, Lu SZ *et al.* Somatic c-kit activating mutations in urticaria pigmentosa and aggressive mastocytosis: establishment of clonality in a human mast cell neoplasm. *Nat Genet* 1996; **12**: 312-4.
10. Hartmann K, Bruns SB, Henz BM. Mastocytosis: review of clinical and experimental aspects. *J Invest Dermatol Symp Proc* 2001; **6**: 143-7.

## Original article

# Zosteriform lichen planus: a new variant of a common disorder

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**Abstract** *Background* Lichen planus (LP) is generally easily recognizable but sometimes it comes in disguise. It has been reported to occur in the scars of previous herpes zoster lesions. Zosteriform pattern in LP, without evidence of herpes zoster, is an extremely rare occurrence. We describe a series of nine patients seen with this peculiar pattern.

*Materials and methods* Nine patients of varied ages presenting during Jan, 2002 to Dec, 2003, with grouped lichenoid lesions on various regions of the body. There was no previous or concomitant history of herpes zoster on the involved site or elsewhere on the body. Lesions were clinically assessed and laboratory investigations including blood counts, blood sugar, serum liver function tests, serology for hepatitis B and C, serum urea and creatinine were carried out. Skin biopsies were also performed for histopathological studies in all cases.

*Results* Most patients were young to middle aged males. No associated systemic clinical illness was seen in any patient. Skin lesions were suggestive of LP. Laboratory investigations were within normal limits in all patients except one, who was positive for hepatitis C. Skin biopsies revealed classical changes of lichen planus in most cases.

*Discussion* Linear lesions following lines of Blaschko have not been so uncommon, but zonal or zosteriform distribution of LP lesions without koebnerization is a very rare occurrence. Exact etiology of this unusual pattern could not be ascertained. The possible cause could be an unknown drug, food or a form of blaschkitis.

*Conclusion.* Zosteriform LP is an emerging new variant, which should be looked for in clinical practice.

### *Key words*

Lichen planus, zosteriform, herpes zoster, Blaschko lines

## Introduction

Lichen planus (LP) is a pruritic, papular eruption characterized by its violaceous color, polygonal shape and sometimes fine scales. It is most commonly found on the flexor surfaces of the upper extremities, on the genitalia, and on the mucous membranes. LP is most likely a cell-

mediated immune response of unknown origin and it may be found with other diseases of altered immunity; these conditions include ulcerative colitis, alopecia areata, vitiligo, dermatomyositis, morphea, lichen sclerosis, and myasthenia gravis.<sup>1-3</sup> An association is noted between LP and hepatitis C infection, chronic active hepatitis, and primary biliary cirrhosis.<sup>4</sup> Incidence is about 1% with no significant geographical variation and no racial predispositions. Male and female ratio is almost equal. LP can occur at any age but most of the patients have the disease between 30-60 years of age. Most

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cases are insidious and the initial lesion is usually located on the flexor surface of the limbs, such as the wrists. The clinical presentation of LP has several forms: actinic, annular, atrophic, erosive, follicular, guttate, hypertrophic, linear, and vesicular. Some cases of zonal or zosteriform LP have also been described in literature. In classical cases of LP, the papules are violaceous, shiny, and polygonal; varying in size from 1 mm to greater than 1 cm in diameter. They can be discrete or arranged in groups of lines or circles. Pruritus is common but varies in severity. Hypertrophic lesions are extremely pruritic. Oral lesions may be asymptomatic or have a burning sensation. In more than 50% of patients with cutaneous disease, the lesions resolve within 6 months, and 85% of cases subside within 18 months.<sup>1-3</sup> On the other hand, oral LP had been reported to have a mean duration of 5 years. Large annular, hypertrophic lesions and mucous membrane involvement are more likely to become chronic. In addition to skin and mucous membranes, LP can involve the genitalia,<sup>5</sup> the nails, and the scalp. The histopathologic features include; irregular acanthosis, colloid bodies in the epidermis with liquefactive degeneration and linear fibrin deposition in the basal layer. The upper dermis has a bandlike infiltrate of lymphocytes and histiocytes. Direct immunofluorescence study reveals globular deposits of immunoglobulin M (IgM) and complement mixed with apoptotic keratinocytes.<sup>1-4</sup> Cutaneous LP does not have a higher risk of skin cancer, but ulcerative lesions in the mouth, particularly in men, have a higher incidence of malignant transformation. Vulvar lesions<sup>5</sup> in women may also be associated with squamous cell carcinoma. Mild cases can be treated symptomatically with antihistamines and fluorinated topical

steroids. More severe cases, especially those with scalp, nail, and mucous membrane involvement may need more intensive therapy, e.g. systemic steroids, topical and systemic cyclosporine, oral or topical retinoids.<sup>6-7</sup> Even with these effective treatments, relapses are common. The prognosis for LP is generally good, as most cases regress within 18 months. In the present study, we describe clinicopathological aspects of this uncommon disorder in a series of patients.

### **Materials and methods**

Patients of varying ages and both sexes presenting with grouped lichenoid lesions on various regions of the body with no previous or concomitant history of herpes zoster on the involved site or elsewhere on the body were included in the study. They were not taking any particular drugs, e.g. antimalarials, antihypertensive or anti tuberculosis prior to eruption. Individuals with any past or current history of herpes zoster on the involved site or elsewhere on the body or patients having grouped lichenoid lesions (suggestive of lichen planus) but developing in some existing scar (due to any disease) were excluded. During the period of two years (Jan 2002 to Dec 2003) a total of nine patients were selected, who were fulfilling the inclusion criteria. All patients were clinically examined thoroughly to see any other evidence of LP in mouth, nails and scalp. Laboratory investigations including blood counts, blood sugar, serum liver function tests, serology for hepatitis B and C, serum urea and creatinine were carried out. Skin biopsies were also performed for histopathological studies in all cases and they were treated with potent topical corticosteroids (betamethasone dipropionate) after confirmation of histological diagnosis.

## Results

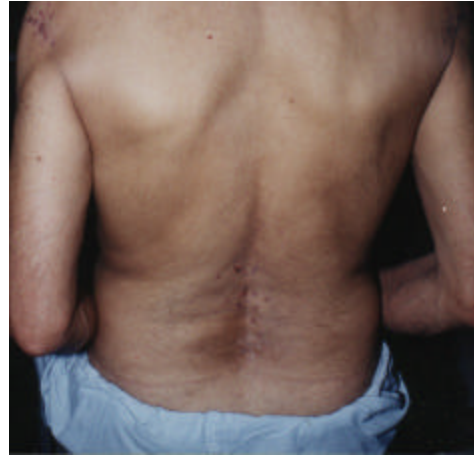
All patients were young adults to elderly (18-56 years). They were eight males and one female. There was no recordable history of any particular drug intake like antimalarials, anti hypertensive and antituberculous. Duration of eruption was 1 to 8 weeks and pruritus was not marked in all cases. No associated systemic clinical disease was seen in any patient. Skin lesions were clinically diagnostic of LP. Laboratory investigations were within normal limits. Serology for hepatitis B was negative in all patients and only one patient was positive for hepatitis C. Skin biopsies revealed classical changes of lichen planus in six cases. Histology was suggestive of lichenoid drug reaction in two cases and of lichen planus pigmentosus in another. These results are summarized in **Table 1**. Clinical photographs of four of the patients have also been shown as **Figures 1, 2, 3 and 4**.



**Figure 1** Lichenoid grouped papules on one side of the neck (histopathology revealed classical picture of lichen planus).

## Discussion

Some congenital or acquired dermatoses, either inherited or sporadic, have a linear distribution following the embryonic lines described in 1901 by Blaschko. Most of them are nevoid skin lesions presenting at



**Figure 2** Grouped lichenoid lesions over back of an elderly person (histopathology suggested a lichenoid drug rash)



**Figure 3** Lichenoid macules and patches in left axilla of a young male (histopathology was suggestive of lichen planus pigmentosus)



**Figure 4** Lichenoid zosteriform rash on the side of neck of a young girl (histological picture was of lichen planus).

birth or having a later onset: epidermal nevi (nevus unius lateris, linear porokeratosis), adnexal nevi (linear

sebaceous nevus, linear basal cell nevus), pigmented lesions (systematized linear achromic nevus) or intricated nevi of the connective tissue (angioliomatous nevus). Rarely, genodermatoses with X-chromosomal mosaicism, that occurs in females only such as incontinentia pigmenti, focal dermal hypoplasia, etc., also exhibit a linear arrangement following Blaschko's lines. This pattern is obvious in some cases of common inflammatory skin diseases like, lichen planus, lichen nitidus, scleroderma, vitiligo, fixed drug eruption and chronic lupus erythematosus.<sup>8</sup> In lichen planus, linear lesions are frequently seen but cases of zonal or zosteriform LP have rarely been described in the literature.<sup>9</sup> Zosteriform lichen planus has so far been considered, either a blaschkitis without koebnerization or a result of Wolf's isotopic response (Koebner phenomenon).<sup>8,10</sup> The cases described in literature with zosteriform distribution of LP have mostly occurred in the healed lesions of herpes zoster as an isotopic response.<sup>10-12</sup> There have also been occasional reports of lichenoid drug eruption and lichen planus pigmentosus occurring in Blaschko's lines.<sup>9,13</sup> To the best of our knowledge such cluster of cases has never been described in local or international literature. The cases previously described in literature under this heading mostly occurred as an isotopic response in connection with herpes zoster. The exact cause of this relatively new pattern could not be ascertained. The patients neither belonged to a particular geographical area, nor reported in any particular season of the year and more over, they did not have any associated symptoms, so infective cause was unlikely. Lesions did not occur on any previous site of trauma or disease and there were no specific triggering factors, so the Koebner phenomenon (Wolf's

isotopic response) can also be ruled out. We are left with two possibilities; i.e. either a new drug or food is causing this peculiar pattern or it can be some kind of blaschkitis. We hope that as we see more and more such cases in future, we will be able to explain the etiology with some certainty.

### Conclusion

Zosteriform pattern in LP, without evidence of herpes zoster, is an extremely rare occurrence. This pattern may be taken as an emerging new variant, which should be looked for in clinical practice.

### References

1. Boyd AS, Neldner KH. Lichen planus. *J Am Acad Dermatol* 1991; **25**: 593-619.
2. Black MM. Lichen planus and lichenoid disorders. In: Champion RH, Burton JL, Burns DA, Breathnach SM, eds. *Rook/Wilkinson/Ebling textbook of dermatology*. 6<sup>th</sup> edn. London; Blackwell Science; 1998. p. 1899-1916.
3. Daoud MS, Pittelkow MR. Lichen planus. In: Freedberg IM, Eisen AZ, Wolff K *et al.*, eds. *Dermatology in general medicine*. 5<sup>th</sup> edn. New York; Mc Graw-Hill; 1999. p. 463-77.
4. Korkij W, Chuang TY, Soltani K. Liver abnormalities in patients with lichen planus. A retrospective case-control study. *J Am Acad Dermatol* 1984; **11**: 609-15.
5. Lewis FM. Vulval lichen planus. *Br J Dermatol* 1998; **138**: 569-75.
6. Cribier B, Frances C, Chosidow O. Treatment of lichen planus. An evidence-based medicine analysis of efficacy. *Arch Dermatol* 1998; **134**: 1521-30.
7. Lim KK, Su WP, Schroeter A *et al.* Cyclosporine in the treatment of dermatologic disease: an update. *Mayo Clin Proc* 1996; **71**: 1182-91.
8. Grosshans E, Marot L. Blaschkitis in adults. *Ann Dermatol Venereol* 1990; **117**: 9-15.
9. Munoz MA, Perez-Bernal AM, Camacho FN. Lichenoid drug

- eruption following the Blaschko lines. *Dermatology* 1996; **193**: 66-7.
10. Shemer A, Weiss G, Trau H. Wolf's isotopic response: A case of zosteriform lichen planus on the site of healed herpes zoster. *J Eur Acad Dermatol Venereol* 2001; **15**: 445-7.
  11. Braun RP, Barua D, Masouyc I. Zosteriform lichen planus after herpes zoster. *Dermatology* 1998; **197**: 87-8.
  12. Lutz ME, Perniciaro C, Lim KK. Zosteriform lichen planus without evidence of herpes simplex virus or varicella-zoster virus by polymerase chain reaction. Report of two cases. *Acta Derm Venereol* 1997; **77**: 491-2.
  13. Cho S, Whang KK. Lichen planus pigmentosus presenting in zosteriform pattern. *J Dermatol* 1997; **24**: 193-7.

## Original article

**Melasma: a comparative trial of azelaic acid (20%) cream alone and in combination with tretinoin (0.1%) cream**

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**Abstract** *Background* Melasma is a common acquired disorder of symmetrical hypermelanosis characterized by irregular, light to gray brown macules involving exposed areas of skin. Therapy for melasma is generally difficult especially in dark skin. The open comparative trial was carried out in the outpatient department of 'BISD' to compare the effect of azelaic acid (20%) cream alone and in combination with tretinoin (0.1%) cream in the management of melasma.

*Materials and methods* The study was carried out in the outpatient department of 'BISD', from 1<sup>st</sup> May 2002, till 30<sup>th</sup> April 2003, over a period of 1 year. A total of 48 patients were included in the study. The patients were studied in two groups of 24 each. The group 'A' applied azelaic acid cream (20%) twice daily i.e. in the morning and evening. The other group labelled group 'B' applied azelaic acid cream (20%) twice-daily plus tretinoin cream (0.1%) in the nighttime. The treatment was advised for a period of 6 months. For the initial 3 months, the treatment was given daily but in the remaining 3 months every alternate day. All the patients were also advised a broad-spectrum sunscreen.

*Results* Forty eight patients belonging to both sexes were included in the study, the age range being 18-40 years. There were 12 males and 36 females. In group "A", there were 5 males and 19 females, while group "B" comprised 7 males and 17 females. Significant clinical improvement i.e. excellent and good response, was observed in both the groups by the end of 6 months therapy i.e. group 'A' 17 patients (71%,  $p < 0.05$ ) and group 'B' 19 patients (79%,  $p < 0.05$ ). In group 'A', 7 patients (29%) had moderate or no response while only 5 patients (21%) in group 'B' showed mild to moderate response.

*Conclusion* Azelaic acid when used in combination with tretinoin is more effective than azelaic acid monotherapy.

**Key words**

Melasma, azelaic acid, tretinoin

**Introduction**

The color of skin is influenced by a number of factors including various pigments, blood flow and the optical properties of skin. Melanin is the major pigment responsible for imparting skin its

normal color. Melanin pigmentation of the skin is a genetically determined multistage process accounting for intrinsic racial and individual differences in skin color. Skin pigmentation is subject to a wide variety of pathological disturbances giving rise to a reduced or enhanced melanocytic activity and proliferation resulting in cutaneous hypo- or hyperpigmentation.

Melasma is a common acquired disorder of symmetrical hypermelanosis

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characterized by irregular, light to grey brown macules involving exposed areas of skin. It affects all the races and is predominantly a disease of women,<sup>1,2</sup> although it can occur in men, as well.<sup>3</sup> Clinicohistological features are the same in both sexes. Multiple factors are implicated in the etiology and pathogenesis of melasma.<sup>4</sup> Important etiological factors include endocrinal factors, oral contraceptives,<sup>5</sup> estrogen-progesterone therapy,<sup>6</sup> pregnancy, UV radiations,<sup>4,7</sup> genetic factors, thyroid dysfunction,<sup>8</sup> cosmetics and drugs.<sup>1</sup>

Melasma can be divided into 3 types based on Wood's light examination i.e. epidermal, dermoepidermal and dermal<sup>9,10</sup> On Wood's light examination, epidermal and dermoepidermal types show accentuation, while there is no change in the dermal type. Therapy for melasma is generally difficult especially in dark skin.<sup>11</sup> Conventional therapy for melasma consists of hydroquinone, retinoic acid, azelaic acid and topical steroids used alone or in various combinations. Recent advances include chemical peeling with various agents like trichloroacetic acid, alpha hydroxy acids, salicylic acids, alpha ketoacids, Jessner's solution, phenol, resorcinol and Baker's solution.<sup>12</sup> These may be used alone or in various combinations with variable results. Azelaic acid<sup>15</sup> as well as tretinoin<sup>2,11</sup> are used in melasma as monotherapy and in combination with other therapeutic agents.

The comparative open trial was carried out to compare the effect of azelaic acid (20%) cream alone and in combination with tretinoin (0.1%) cream in the management of melasma.

### **Materials and methods**

The study was carried out in the outpatient department of 'BISD', from 1<sup>st</sup> May 2002, till 30<sup>th</sup> April 2003, over a period of 1 year. Forty eight patients were included in the study. There were 12 males and 36 females. The age range was 18-40 years. Patients with epidermal or dermoepidermal pigmentation as determined by Wood's light examination were included in the study. Lactating and pregnant women were excluded. Only those patients were included who had not been taking any treatment for the past two months. Patients on oral contraceptive therapy or any antiepileptic drugs were also excluded. Patients with some intrinsic disease like ovarian tumors were excluded as well. The patients were divided in two groups of 24 each. Group 'A' applied azelaic acid cream (20%) twice daily i.e. in the morning and evening. Group 'B' applied azelaic acid cream (20%) twice-daily plus tretinoin cream (0.1%) at night. The treatment was advised for a period of 6 months. For the initial 3 months, the treatment was given daily but for the following 3 months on every alternate day. A broad-spectrum sunscreen was also advised to all the patients. The sunscreen was advised after the daytime application of azelaic acid cream as well as 30 minutes before going into sunlight. All the patients were followed up monthly to look for any clinical improvement and side effects. The clinical assessment was made by a decrease in the intensity of pigmentation and the size of lesions. Decrease in intensity was assessed by comparison with the surrounding normal skin. The size of lesions was assessed by observing their margins. The results were labeled as excellent, good, moderate and poor. All the findings were tabulated.

## Results

In group 'A', there were 5 males and 19 females, while group 'B' comprised 7 males and 17 females. **Table 1** reveals the results at the completion of study. Significant clinical improvement i.e. excellent and good response, was observed in both the groups by the end of 6 months therapy i.e. group 'A' 17 patients (71%,  $p < 0.05$ ) and group 'B' 19 patients (79%,  $p < 0.05$ ). In group 'A', clinical improvement was observed by the end of 9<sup>th</sup> week of therapy while group 'B' subjects responded earlier i.e. by the 6<sup>th</sup> week. Maximum response was seen by the end of 3 months therapy in both groups. In group 'A', 7 patients (29%) had moderate or no response. Only 5 patients (21%) in group 'B', showed mild to moderate response. There was slight improvement thereafter in the second half, once the patients were switched to alternate day therapy. Therefore, significant treatment difference was not a feature by the end of 6 months therapy.

There was no systemic toxicity in any of the patients. Serious local adverse effects were not observed. Mild skin irritation of transient nature was observed in 10% of the patients. Clinical findings comprised of mild erythema, scaling, itching and stinging sensations. No residual hypochromia and leukoderma were observed. There was no complaint of post-inflammatory hyperpigmentation.

## Discussion

Azelaic acid is a saturated dicarboxylic acid,<sup>16</sup> a naturally occurring substance. It is an established therapeutic agent for the management of acne having comedolytic,<sup>17,18</sup> antibacterial<sup>19,20</sup> and anti-inflammatory<sup>21</sup> effects. Earlier, for its

**Table 1** Clinical response at the completion of therapy (n=48)

Response	Group A %	Group B %
Excellent	2 (8.5%)	8 (33%)
Good	15 (62.5%)	11 (46%)
Moderate	4 (16.5%)	3 (12.5%)
Poor	3 (12.5%)	2 (8.5%)

effect to induce hypopigmentation in tinea versicolor, it was assumed to have a direct competitive inhibition of tyrosinase, the key enzyme in melanin synthesis.<sup>22</sup> Hu *et al.*<sup>23</sup> indicated later on that this inhibitory influence is partial and indirect. He showed that azelaic acid inhibits the membrane enzyme thioredoxin reductase leading to an increased intracellular concentration of thioredoxin, which in turn is a potent inhibitor of tyrosinase. Moreover, azelaic acid also exerts inhibitory effect on the growth and viability of melanocytes.<sup>24</sup> This in turn is brought about by the inhibition of mitochondrial cellular respiration as well as DNA synthesis. The efficacy of azelaic acid is good in melasma but it is not considered superior to hydroquinone.<sup>25</sup>

Tretinoin on the other hand is a potent inhibitor of new melanin synthesis and is effective in the management of postinflammatory pigmentation as well as melasma.<sup>26-28</sup> In addition, tretinoin also exerts keratolytic effect, which in turn also inhibits pigmentation.<sup>29-31</sup>

Generally, azelaic acid is not considered superior to hydroquinone. Azelaic acid as a monotherapy is however, superior to hydroquinone 2% but inferior to hydroquinone 4%, when used in combination with a broad-spectrum sunscreen.<sup>32</sup> Azelaic acid used in combination with a broad-spectrum sunscreen has been reported to be well

tolerated with an efficacy of 65-70% in melasma.<sup>33,34</sup> In group 'A', 71% patients showed significant clinical improvement i.e. excellent (8.5%) and good (62.5%) response, while the other 29% responded moderately (16.5%) or poorly (12.5%) ( $p<0.05$ ) Therefore, the finding in our study as far as the group 'A' is concerned, is consistent with the literature.<sup>34,35</sup>

As the response to therapy in melasma is slow, multidrug regimens, e.g. azelaic acid in combination with tretinoin may be advised. Tretinoin promotes melanosome transfer and epidermal turnover leading to removal of melanin. Tretinoin (0.01%) cream as a monotherapy acts slowly.

Our results indicate that the combination therapy of azelaic acid and tretinoin is better than azelaic acid therapy alone. The net result in the group 'B' was a significant improvement in 79% of the patients ( $p<0.001$ ) in contrast to 71% ( $p<0.05$ ) in group 'A'. Moreover, a shorter time was required to produce the clinical result with the combination therapy. The lightening in color was seen by the end of 6<sup>th</sup> week of therapy in contrast to 9<sup>th</sup> week in group B. Thus, tretinoin augments the effect of azelaic acid by a synergistic mechanism. Verallo Rowell *et al.*<sup>35</sup> have already confirmed the clinical efficacy of azelaic acid cream (20%) used in combination with tretinoin and a broad-spectrum sunscreen. Therefore, the combination regimen of tretinoin and azelaic acid is superior to when either is used as a monotherapy. Zaumseil *et al.*<sup>36</sup> have reported the success of a similar combination therapy. Thus, the results of our open comparative trial are in accordance with previous studies.

Regarding the tolerability of these therapies, there was no systemic toxicity in any of the patients. No serious local adverse effects were observed. Mild skin irritation of transient nature was observed in 10% of the patients. Clinical findings comprised of mild erythema, scaling, itching and stinging sensations.

## Conclusion

It can be concluded from the above study that azelaic acid when used in combination with tretinoin is more effective than azelaic acid monotherapy. The combination induces lightening of skin color in a shorter time interval.

## References

1. Grimes PE. Melasma; etiological and therapeutic considerations. *Arch Dermatol* 1995; **131**: 1453-7.
2. Griffith CEM, Finkel LJ, Ditre CM *et al.* Topical tretinoin improves melasma, a vehicle controlled trial. *Br J Dermatol* 1993; **129**: 415-21.
3. Vazoquez M, Maldanalo H, Benmaman C, Sanchez JLP. Melasma in men: a clinical and histological study. *Int J Dermatol* 1998; **27**: 25-7.
4. Sanches SP, Pathek MA, Sato S *et al.* Melasma: a clinical, light microscopic, ultrastructural and immunofluorescence study. *J Am Acad Dermatol* 1981; **4**: 689-710.
5. Resnik S. Melasma induced by oral contraceptives drugs. *JAMA* 1967; **199**: 95-9.
6. Johnson GA, Sviland L, Melleland J. Melasma of the arms associated with hormone replacement therapy. *Br J Dermatol* 1998; **139**: 932.
7. Pathak A, Fitzpatrick TB, Kraus EW. Usefulness of retinoic acid in the treatment of melasma. *J Am Acad Dermatol* 1986; **14**: 894-9.
8. Lutfi RJ, Fridmanis M, Misiunas AL *et al.* Association of melasma with thyroid autoimmunity and other thyroid abnormalities and their relationship to the origin of melasma. *J Clin Endocrinol Metab* 1985; **61**: 28-31.

9. Ortonne J-P, Bahadoran P, Fitzpatrick TB *et al.* Hypomelanosis and hypermelanosis. In: Freedberg IM, Eisen AZ, Wolff K *et al.*, eds. *Dermatology in general medicine*, 6<sup>th</sup> edn. New York; McGraw-Hill, 2003: 836-80.
10. Pandya AG, Guevara IL. Disorders of pigmentation. *Dermatol Clin* 2000; **18**: 91-8.
11. Green CK, Griffith CEM, Finkel LJ *et al.* Topical tretinoin for melasma in black patients. A vehicle controlled trial. *Arch Dermatol* 1994; **130**: 727-33.
12. Cottelessa C, Peris K, Onarati MT *et al.* The use of chemical agents in the treatment of different cutaneous hyperpigmentation. *Dermatol Surg* 1999; **25**: 450-4.
13. Bari AU, Iqbal Z, Rehman SB. Melasma: an overview and therapeutic update. *J Pak Assoc Dermatol* 2003; **13**: 21-9.
14. Kang WH, Chun SC, Lee S. Intermittent therapy for melasma in patients with combined topical agents (tretinoin, hydroquinone and hydrocortisone): clinical and histological studies. *J Dermatol* 1998; **28**: 587-96.
15. Luis MB, Klaus G. The treatment of melasma; 20% azelaic acid versus 4% hydroquinone cream. *Int J Dermatol* 1991; **30**: 893-5.
16. Nazzaro- Porro M. Azelaic acid. *J Am Acad Dermatol* 1987; **17**: 1033-41.
17. Detmar M, Mayer De Silva A, Stadler R *et al.* Effects of azelaic acid on proliferation and ultrastructure of mouse keratinocytes in vivo. *J Invest Dermatol* 1989; **93**: 70-4.
18. Mayer De Silva A, Gollnick H, Detmar H. Effects of azelaic acid on sebaceous glands, sebum excretion rate and keratinization pattern in human skin. *Acta Derm Venereol* 1989; **143**: 20-30.
19. Cunliffe WJ, Holland KT. Clinical and laboratory studies on treatment with 20% azelaic acid cream for acne. *Acta Derm Venereol* 1989; **143**: 31-4.
20. Holland KT, Bojar RA. The effect of azelaic acid on cutaneous bacteria. *J Dermatol Treat* 1989; **1**: 17-9.
21. Akamatsu H, Miyaichi Y, Komura J. Effect of azelaic acid on neutrophil function: a possible cause for its efficacy in treating pathogenetically unrelated diseases. *Arch Dermatol* 1991; **23**: 162-6.
22. Nazzaro-Porro M, Passi S. Identification of tyrosinase inhibitors in culture of *Pityrosporum*. *J Invest Dermatol* 1978; **71**: 205-8.
23. Hu F, Mah K, Teramura DJ. Effects of dicarboxylic acids on normal and malignant melanocytes in culture. *Br J Dermatol* 1986; **114**: 17-26.
24. Ward BJ, Breathnach AS, Robins E *et al.* Analytical ultrastructural autoradiographic and biochemical studies on 3H dicarboxylic acid added to cultures of melanoma cells. *Br J Dermatol* 1984; **111**: 29-36.
25. Piquero Martin J, Rothe de Arocha J, Beniamani Locker D. Double blind clinical study of the treatment of melasma with azelaic acid versus hydroquinone. *Med Cutan Ibero Lat Am* 1988; **16**: 511-4.
26. Ransby SMB, Griffiths CEM, Green CKK *et al.* Topical tretinoin therapy for hyperpigmented lesions caused by inflammation of the skin in black patients. *N Engl J Med* 1993; **328**: 1438-43.
27. Weiss JS, Ellis CM, Headington JT *et al.* Topical tretinoin improves photo-damaged skin. A double blind vehicle controlled study. *JAMA* 1988; **257**: 527-32.
28. Ratal ES, Griffith CEM, Ditre CM *et al.* Topical tretinoin treatment for liver spots associated with photodamage. *N Engl J Med* 1992; **326**: 368 -74.
29. Ransby SMB, Griffiths CEM, Green CKK *et al.* Topical tretinoin therapy for hyperpigmented lesions caused by inflammation of the skin in black patients. *N Engl J Med* 1993; **328**: 1438-43.
30. Grimes PE. Melasma: etiological and therapeutic considerations. *Arch Dermatol* 1995; **131**: 1453-7.
31. Griffiths CEM, Finkel LJ, Ditre CM *et al.* Topical tretinoin improves melasma. A vehicle-controlled trial. *Br J Dermatol* 1993; **129**: 415-21.
32. Gano SE, Garcia RL. Topical tretinoin, hydroquinone and betamethasone valerate in the therapy of melasma. *Cutis* 1979; **23**: 239-41.
33. Mingrone G, Greco AV, Nazzaro-Porro M, Passi S. Toxicity of azelaic acid. *Drugs Exp Clin Res* 1983; **9**: 447-55.

34. Grammatico P, Scarpa S, Steindi K *et al.* Effect of azelaic acid on viability, ultrastructure and karyotype of melanoma cells in long-term culture. *Cancer J* 1991; **4**: 39-44.
35. Verallo Rowell V, Sioson-Delos Ryes G. South East Asian experience with azelaic in melasma. *Med Prog* 1993; **6**: 26-30.
36. Zaumseil RP, Graupe K, eds. *Melasma: new approaches to treatment*. London: Martin Dunitz; 1998.

## Original article

# Comparative efficacy of topical calcipotriol ointment with betamethasone valerate ointment in chronic plaque psoriasis

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**Abstract** *Background* Topical steroids are an established therapy for localized psoriasis. Calcipotriol (vitamin D<sub>3</sub> analogue) is a relatively newer edition to the therapeutic armamentarium of psoriasis. We compared the efficacy and safety of calcipotriol 0.005% ointment and betamethasone valerate 0.1% ointment in the treatment of chronic plaque psoriasis.

*Patients and methods* One hundred diagnosed cases of chronic plaque psoriasis, 50 patients in each group, were enrolled in the study. Age range was 20-55 years for calcipotriol group with a mean of 33.6 years and 15-52 years for betamethasone valerate group with a mean age of 32.6 years. Male to female ratio was 1.17:1 in calcipotriol and 2.13:1 in betamethasone group. Patients in both groups were advised to apply the topical agents twice daily for 6 weeks. They were followed up at 2, 4 and 6 weeks. The assessment was made on the basis of PASI. Overall response was graded as clearance (>70% reduction in PASI), marked improvement (60-70% reduction in PASI), mild improvement (50-60% reduction in PASI), no change and worsening.

*Results* The mean PASI reduction in calcipotriol group was from 6.33 at week 0 to 1.90 at week 6, whereas betamethasone valerate ointment group showed a decrease in mean PASI from 6.22 at week 0 to 2.26 at the end of treatment. The scores for erythema, infiltration and desquamation at each follow-up i.e. 2, 4 and 6 weeks were comparable in both groups. All the three parameters were effectively reduced by both the topical modalities during six weeks treatment period, but the difference was not significant statistically when compared with each other ( $p>0.05$ ). Side effects were observed with both topical agents during 6 weeks of application. Most commonly observed side effects with calcipotriol were persistent lesional erythema in 10 (20%), lesional/perilesional irritation in 7 (14%), pruritus in 4 (8%) and folliculitis in 2 (4%) of the patients. Adverse events noted with betamethasone valerate ointment were atrophy in 6 (12%), folliculitis in 5 (10%), persistent erythema in 4 (8%), pruritus in 2 (4%) and lesional irritation in 1 (2%) of the patients.

*Conclusion* Topical calcipotriol is as efficacious and safe as betamethasone valerate in the treatment of chronic plaque psoriasis.

**Key words**

Calcipotriol, betamethasone valerate, psoriasis

## Introduction

Psoriasis is a common, genetically determined, proliferative and inflammatory disease of the skin, characterized by well-defined, dull-red,

plaques with adherent scales, situated particularly over the extensor surfaces and the scalp. It is a disease of variable morphology and course, affecting 2-3% of the world population<sup>1</sup> Prevalence of psoriasis increases with age. Early onset may be associated with more severe disease. Psoriasis vulgaris typically has a

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protracted course, with frequent recurrences and resistance to treatment.

Treatment of psoriasis depends upon age, sex, occupation, general health, intelligence and resources of the patient as well as the type, extent, duration and natural history of the disease. The objective of treatment is to clear each episode of the disease. Psoriasis is still not completely curable, although a wide variety of treatment modalities, both topical (keratolytics, corticosteroids, tar, dithranol and ultraviolet A and B) and systemic agents like methotrexate, photochemotherapy, retinoids and cyclosporine etc. are available for its control. The doctor and the patient must be goal-oriented in terms of what they want to accomplish when using a topical preparation.<sup>1</sup>

Topical vitamin D<sub>3</sub> analogue (calcipotriol) undoubtedly finds its place as the first or second-line therapy along with topical steroids for mild to moderate cases of psoriasis vulgaris, covering up to 40% of the body surface area. The major improvement occurs during the first 4-6 weeks of treatment. Mild irritant dermatitis of face and anogenital area has been reported frequently but such unwanted effects generally do not lead to withdrawal of calcipotriol<sup>2</sup>

Although extensively prescribed, the use of topical corticosteroids to treat psoriasis vulgaris is controversial because the therapeutic response can be variable, short lasting or associated with side effects.<sup>3</sup> The potent forms of topical steroids, in contrast to less potent ones, offer the best opportunity for selected patients to temporarily clear or almost clear their disease in a shorter time.<sup>4</sup> Following initial daily treatment, responsive patients with

plaque-type psoriasis, may have their remission status extended with the use of intermittent applications of topical corticosteroids.<sup>5</sup>

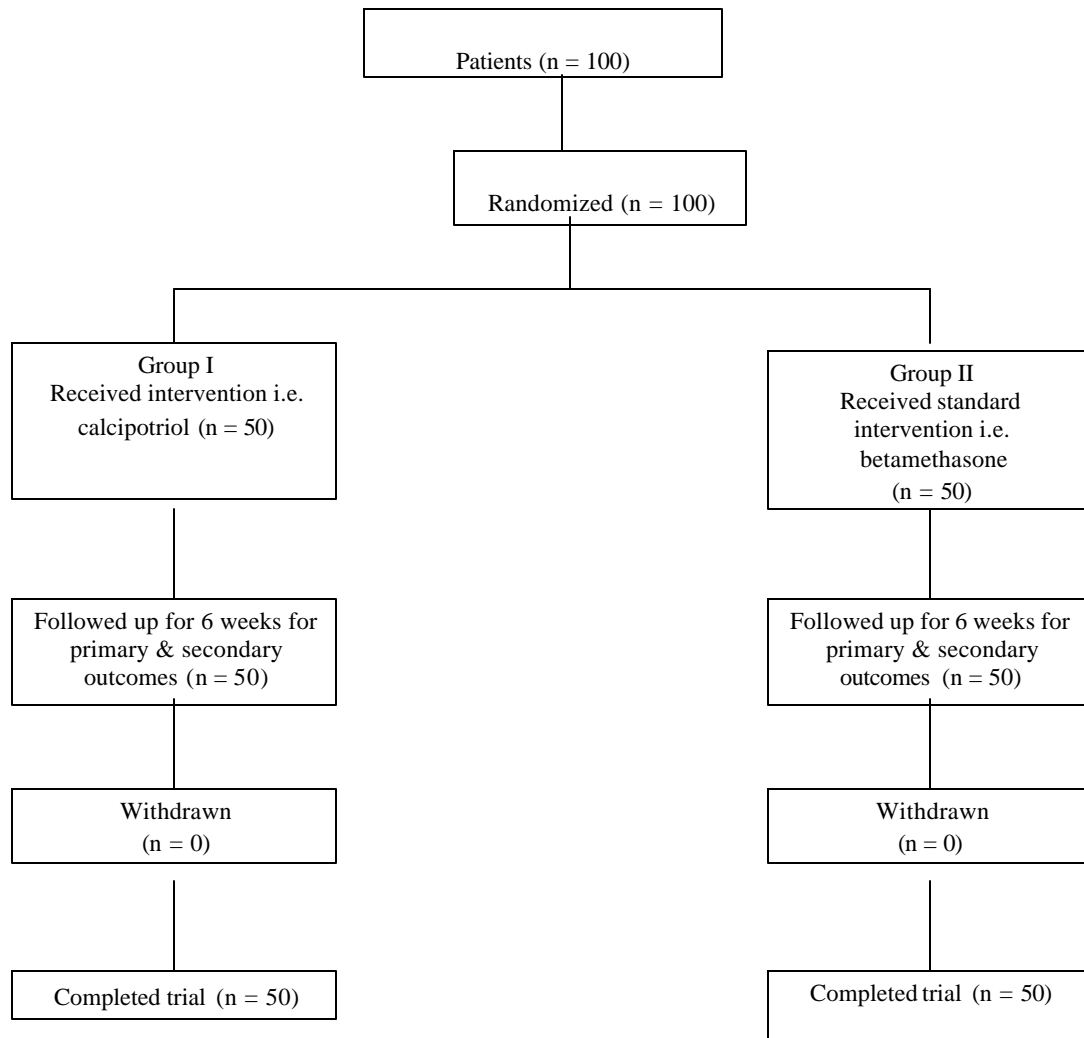
The present study was conducted to compare the efficacy and safety of topical calcipotriol and betamethasone valerate ointment in chronic plaque psoriasis.

### **Patients and methods**

One hundred diagnosed cases of chronic plaque psoriasis, aged 15 and above, of either sex, were enrolled in the trial. Fifty-six patients were enrolled at the Department of Dermatology, Jinnah Hospital, Lahore and forty-four were recruited at the Department of Dermatology, Mayo Hospital, Lahore, from February 1998 to June 2000. Patients selected in this study, were not on any systemic or topical medication for the past eight weeks and the area of involvement was less than 40% in every patient. Pregnant and breast feeding women were excluded from the study.

Eligible patients were randomized into two groups i.e., group 1 (calcipotriol group) and group 2 (betamethasone group), as shown in **Figure 1**. Both medicines, 0.005% calcipotriol ointment and 0.1% betamethasone valerate ointment, were applied twice daily for a maximum period of six weeks. The maximum allowance for calcipotriol ointment was 100 grams per week.

On the first visit, relevant history and general, cutaneous and systemic examination were conducted and recorded on a pre-designed pro forma. Laboratory investigations included hemoglobin, total and differential leukocyte counts, ESR, serum calcium and phosphate.

**Figure 1** An overview of clinical study*Evaluation of severity of psoriasis*

Severity of psoriasis was assessed on the basis of PASI (psoriasis area and severity index) score. The erythema (E), infiltration (I) and desquamation (D) were recorded according to a four point scale (0=absent; 1=mild; 2=moderate; 3=severe). For the assessment of Area (A), four main anatomical sites were examined i.e. the head (h), upper extremities (u), trunk (t) and lower extremities (l). Area was assigned a numerical value based on the extent of lesions in each anatomical site.

The PASI score was calculated according to the following formula:

$$\text{PASI} = 0.1 (E_h + I_h + D_h) A_h + 0.2 (E_u + I_u + D_u) A_u + 0.3 (E_t + I_t + D_t) A_t + 0.4 (E_l + I_l + D_l) A_l$$

Where E = erythema, I = induration, D = desquamation and A = area; and h = head, u = upper limb, t = trunk and l = lower limb.

Fifty patients were treated with topical calcipotriol ointment twice daily and the other fifty patients were advised to apply betamethasone valerate ointment on psoriatic plaques. Both topical modalities were applied for six weeks. Patients were assessed at 2, 4 and 6 weeks of treatment on the basis of PASI. Overall efficacy was evaluated according to the following criteria:

*Efficacy*

The treatment was said to be effective and further subcategorized as cleared if >70% reduction in PASI score; marked improvement if 60-70% clearance; and mild improvement if there was 50-60% improvement in disease activity. The treatment was considered ineffective if there was <50% PASI reduction or even worsening of disease.

*Safety*

On each visit, patients were asked and examined about any cutaneous or extracutaneous side effects.

*Statistical analysis*

Mean PASI reduction in both groups was compared at the end of six weeks using unpaired t test. The decrease in individual parameters i.e. erythema, infiltration and desquamation in each group, was analyzed using 'paired t test'. Chi-square test was applied to the ratio of patients' overall clearance of psoriasis at the end of study. A cut-off *p* value of 5% or less was considered significant.

**Results**

Between February 1998 and June 2000, one hundred patients with chronic, plaque psoriasis were enrolled in this comparative study. There were 50 patients in each group. Group 1 i.e. calcipotriol group

**Table-1** Demographic data

	<i>Calcipotriol Group</i>	<i>Betamethasone Group</i>
No. of patients	50	50
Age range (years)	20-55	15-52
Mean age (years)	33.60	32.66
Sex: male/ female	27/23	34/16
Extent of skin involvement	10-38%	5-40%
Mean area of skin involvement	24%	23%
Mean PASI	6.33 ± 2.23	6.27 ± 3.33

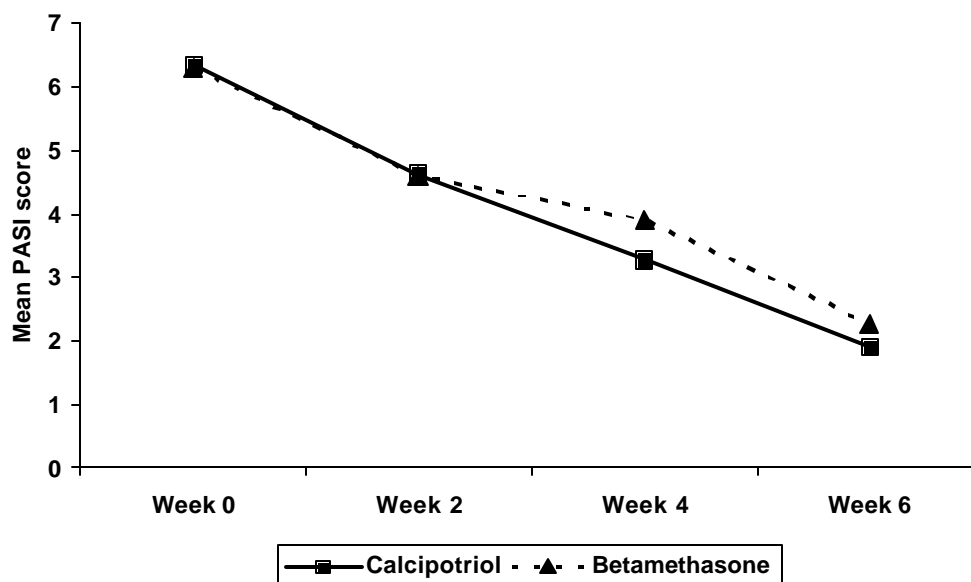
**Table 2** Overall assessment of efficacy at the end of treatment

	<i>Calcipotriol (n=50)</i>	<i>Betamethasone (n=50)</i>
<i>Effective therapy</i>	50 (100%)	44 (88%)
Cleared	23 (46%)	4 (8%)
Marked improvement	27 (54%)	40 (80%)
<i>Ineffective therapy</i>	-	6 (12%)
No change	-	6 (12%)
Worse	-	-

comprised of 27 males and 23 females while group 2 i.e. betamethasone group included 34 males and 16 females. Demographic characteristics are shown in **Table 1**.

*Overall assessment of efficacy*

All patients in these two groups showed good response to both the topically applied modalities. The treatment was 100% effective in calcipotriol and 88% in betamethasone group. Twenty three calcipotriol-treated patients showed clearance (>70% PASI reduction) [**Figure 2**], whereas betamethasone group showed clearance in 4 patients. Between 60-70% reduction in PASI (marked improvement) was seen in 27 patients of calcipotriol group and 40 patients of betamethasone group (**Table 2**).

**Figure 2** Pre- and post-treatment mean PASI score in two groups.**Table 3** Side effects of topical calcipotriol therapy

Side effects	Calcipotriol group n (%)	Betamethasone group n (%)
<i>Cutaneous</i>		
Persistent lesional erythema	10 (20%)	4 (8%)
Lesional and perilesional irritation	7 (14%)	1 (2%)
Pruritus	4 (8%)	2 (4%)
Folliculitis	2 (4%)	5 (10%)
Atrophy	-	6 (12%)
<i>Extracutaneous</i>		
Nausea/ vomiting	1 (2%)	-
Headache	1 (2%)	-
Arthralgias	1 (2%)	-

#### Adverse events

Both drugs were well-tolerated. The common side effects seen with calcipotriol, were persistent erythema, lesional/perilesional irritation, pruritus and infections. Serum calcium and phosphate levels, before and after treatment with calcipotriol, did not show any significant change in their values. Three patients (6%) had non-dermatologic side effects (**Table 3**). Adverse events recorded in the betamethasone group included atrophy, folliculitis, persistent lesional erythema, pruritus and lesional irritation. No extracutaneous side effects were noted

with betamethasone valerate ointment during six weeks study period.

#### Discussion

Psoriasis has always posed a therapeutic challenge and various modalities have proved beneficial in this regard. Vitamin D<sub>3</sub> analogues are relatively a newer therapy in psoriasis. This study clearly demonstrates that the efficacy of topical calcipotriol in the treatment of chronic plaque psoriasis is almost the same as that of betamethasone valerate. The amount of calcipotriol prescribed to each patient was

<100 gm/ week (50 µg/gm of calcipotriol) which has proved to be safe, effective and well tolerated, as shown by other studies.<sup>6,7</sup>

The clinical efficacy was measured using the PASI. The present study confirms the significant reduction in PASI score (69.6%) with calcipotriol over a period of 6 weeks. Similarly, treatment with betamethasone valerate showed a comparable decrease in PASI during the entire treatment period (63.8%). The results are comparable with the study by Kragballe *et al.*<sup>6</sup> which showed a reduction in PASI for calcipotriol and betamethasone valerate as 68.8% and 61.4%, respectively.<sup>6</sup> In a study by Molin *et al.*,<sup>7</sup> comparing calcipotriol and betamethasone valerate cream, no statistically significant reduction in PASI was noted with calcipotriol at the end of six weeks. The better response in our study is possibly due to the effective absorption of drug from its ointment form.

From second week onwards, there was a significant and constant decrease in infiltration, erythema and desquamation in both the groups. The reduction in infiltration score with topical calcipotriol was slightly greater than betamethasone valerate ointment at the end of 6 weeks, but not statistically significant ( $p>0.05$ ). The reduction in infiltration score with calcipotriol is possibly due to the effective inhibition of both cell proliferation and inflammation. The erythema and desquamation scores also showed a consistent decrease at week 2, 4 and 6.

Betamethasone valerate ointment also proved to be efficacious in reducing the scores for erythema, infiltration and desquamation. However, the difference

was not significant ( $p>0.05$ ) at the end of treatment period.

The reduction of infiltration, erythema and desquamation imply that calcipotriol is at least as effective as betamethasone in the inhibition of both cell proliferation and inflammation. Similar results were also found in earlier studies using the same ointment formulations of calcipotriol and betamethasone in psoriasis.<sup>6</sup>

Betamethasone valerate ointment reduced erythema score by a relatively higher ratio at 2, 4 and 6 weeks of treatment but at the end of treatment, it was not found to be superior to calcipotriol in this regard ( $p>0.05$ ). The possible reason for this effect may be that the topical steroids have known vasoconstrictor and anti-inflammatory effects which add to the better control of erythema in psoriasis.

Adverse events were seen with both the topical modalities. In our study, persistent lesional erythema was the most common side effect, seen with calcipotriol. Various studies have demonstrated the occurrence of this unwanted effect due to the local irritant effect of calcipotriol.<sup>6</sup> Another possibility may be allergic contact dermatitis due to topical vitamin D<sub>3</sub> analogues as reported by Bruynzeel *et al.*<sup>8</sup> Lesional/perilesional irritation was seen in a significant number of patients. It is comparable to a double-blind study conducted by Molin *et al.*<sup>7</sup> in which 16% of the patients had lesional irritation. Cunliffe *et al.*<sup>4</sup> reported this side effect in 19.5% of patients, which is higher as compared to our study. Pruritus was noticed in four patients in the present study which is possibly due to its irritant effect.

In the betamethasone group, atrophy was seen as a major side effect in 6 patients (12%). None of the patients in calcipotriol group developed this complication. In a similar comparative study by Molin *et al.*<sup>7</sup> where betamethasone cream was applied on 210 patients, only 3 patients showed skin atrophy.<sup>7</sup>

Steroids applied topically, predispose to infections. In the present study, folliculitis developed in 5 patients. Occlusive effect of ointment-base would have been an additional contributory factor in causing this problem. Only two patients in calcipotriol group suffered from folliculitis. Calcipotriol can cause such lesions by its irritant effect.<sup>6</sup>

Persistent erythema was seen in four patients. The late vasodilatation produced by topical potent steroids could be a possible explanation. A small number of patients developed the complaint of pruritus during treatment with betamethasone which could have been caused by contact sensitivity to this medication. In the present study, efficacy and tolerability of both topical agents were quite satisfactory.

Though calcipotriol did not show greater advantage over topical steroid in psoriasis, but it can provide an efficacious and safe alternative in patients of plaque psoriasis, showing side effects with topical steroid or showing no improvement.

From this study it is concluded that calcipotriol 0.005% ointment in plaque psoriasis is as effective as betamethasone valerate 0.1% ointment. Mild to moderate lesional irritation and pruritus is observed more commonly with calcipotriol topically as compared to betamethasone valerate ointment.

## References

1. Christophers E, Mrowietz U. In: Freedberg IM, Eisen AZ, Wolff K *et al.*, eds. *Fitzpatrick's dermatology in general medicine*, 6<sup>th</sup> edn. New York: McGraw-Hill; 2003. p. 407-27.
2. Katayama I, Miyazaki Y, Nishioka K. Topical vitamin D<sub>3</sub> (talcipotrol) for steroid-resistant prurigo. *Br J Dermatol* 1996; **134**: 238-40.
3. Katz HI. Topical corticosteroids. *Dermatol Clin* 1995; **13**: 807-15.
4. Cunliffe WJ, Jones JB, Claudy A, Fairiss G, Goldin D. Comparative study of calcipotriol (MC903) ointment and betamethasone-17-valerate ointment in patients with psoriasis vulgaris. *J Am Acad Dermatol* 1992; **26**: 736-43.
5. Johansen UB, Karlsmark T, Petersen LJ. Ranking of the antipsoriatic effect of various topical corticosteroids applied under a hydrocolloid dressing-skin thickness, blood-flow and color measurements compared to clinical assessment. *Clin Exp Dermatol* 1990; **15**: 343-8.
6. Kragballe K, Gjertsen BT, Hoop DD, Karlsmarkt VK. Double-blind, right/left comparison of calcipotriol and betamethasone valerate in the treatment of psoriasis vulgaris. *Lancet* 1991; **26**: 193-6.
7. Molin L, Cutler TP, Helander L. Comparative efficacy of calcipotriol (MC903) cream and betamethasone-17-valerate cream in the treatment of chronic plaque psoriasis: A randomized, double-blind, parallel group multicentre study. *Br J Dermatol* 1997; **136**: 89-93.
8. Bruynzeel DP, Hol CW, Nieboer C. Allergic contact dermatitis to calcipotriol. *Br J Dermatol* 1992; **127**: 66.

## Original article

# Leprosy in Hyderabad

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**Abstract** *Background* Leprosy is endemic in Pakistan with an uneven distribution. Hyderabad is the fifth largest city of the country with a polyethnic population.

*Objective* To document demographic and clinical characteristics of leprosy in patients of Hyderabad region.

*Patients and methods* We reviewed 1938 patients of leprosy registered during 1967 to 2002 in all the functional leprosy centres of Hyderabad.

*Results* Males and females were equally affected. Over 65% of cases were in their 2nd to 5th decade of life. Pauci- and multibacillary leprosy were seen with almost similar frequency. The commonest presentation was tuberculoid leprosy (34.5%), followed by the rest. The prevalence of leprosy was highest in Indian migrants (57.53%) as compared to local Sindhis (15.37%).

*Conclusion* Leprosy in Hyderabad more commonly occurs in Indian migrants than in other ethnic groups. It equally affects both sexes and paucibacillary disease is more common.

*Key words*  
Leprosy, Hyderabad

## Introduction

Leprosy is a chronic non-suppurative inflammatory disease caused by *Mycobacterium leprae*. Leprosy has affected humanity since time immemorial. Spectrum of this disease shows wide diversity of clinical manifestations. It depends upon patients' cell-mediated immune response.<sup>1</sup> According to Ridley-Jopling classification,<sup>2</sup> it ranges from lepromatous

leprosy pole (LL), borderline lepromatous (BL), borderline (BB), borderline tuberculoid (BT), to tuberculoid pole (TT), where patients develop high level cell-mediated immunity.

Susceptibility to the disease is probably genetically linked. A recessively inherited HLA-linked gene (HLA-DR3) has been implicated for predisposition to tuberculoid leprosy.<sup>3</sup> A dominantly HLA-linked gene (HLA-MTI, HLA-DR2) has been implicated to lepromatous end of spectrum.<sup>4,5</sup> However, primary resistance to the disease is not influenced by HLA haplotype and has been attributed to a number of factors; mode of entry of bacilli, antigenic load etc.

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Even the best efforts by WHO have not been successful in complete eradication of leprosy from the globe. In Pakistan, leprosy is found in a focal pattern. Karachi and Hyderabad have 70-75% of the total leprosy patients.<sup>6</sup> According to the 1998 consensus, Hyderabad was the fifth largest city of Pakistan with a population of about 2.9 million,<sup>7</sup> whereas the Hyderabad division had a population of around 6.9 million, comprising of different ethnic groups. The study presented, herein, highlights the prevalence of leprosy according to age, sex, type of leprosy in various groups.

### Patients and methods

All leprosy patients (n=1938) registered in Hyderabad and Latifabad leprosy centres, and leprosy section of department of dermatology, Liaquat University of Medical and Health Sciences, Hyderabad during 1967 to 2002 were analyzed in this study. The centre in Hyderabad City covers the Hyderabad City up to Halla, Bossri, Tando Allahyar, Tando Jam, Jamshoro, Sun, Khanot, Ranikot and Thano Bulla Khan whereas Latifabad centre covers Latifabad, Hussainabad and Qasimabad. The diagnosis of disease was based on the clinical features, smear for acid-fast bacilli and histopathology. According to the number of lesions, the disease was classified as pauci- (if the number =5) or multibacillary (if the number =5).<sup>8</sup> The patients were analyzed according to age, sex, type of leprosy and deformity and ethnic origin. The ethnic origin was broadly grouped as Indian migrants, Sindhi, Pathan, Punjabi, Balochi and others.

### Results

The results of this study showed that the prevalence of leprosy was markedly low in the first decade i.e. 3.8% as compared to majority of

**Table 1** Distribution of leprosy patients according to age groups

Age group (yrs)	N (%)
<10	73 (3.8)
10-19	262 (13.5)
20-29	309 (15.9)
30-39	331 (17.1)
40-49	336 (17.3)
50-59	320 (16.5)
60-69	189 (9.7)
>70	118 (6.1)

**Table 2** Different types of leprosy in patients (n=1938)

Type of leprosy	%
Tuberculoid	34.6
Borderline tuberculoid	23.3
Midborderline	13.8
Borderline lepromatous	11.8
Lepromatous	16.5

**Table 3** Frequency of leprosy in different ethnic groups.

Ethnic origin	%
Indian immigrants	57.7
Sindhi	18.5
Pathan	10.9
Punjabi	6.8
Balochi	2.5
Others	3.6

cases presenting in 2<sup>nd</sup> to 6<sup>th</sup> decade i.e. 80% (**Table 1**). Out of 1938 patients, 1058 (54.6%) were male and 880 (45.4%) were females. Over 85% were new cases while 14.4% were contact cases. The commonest type of leprosy was TT in 34.5% followed by LL (16.5%) [**Table 2**]. The majority (57.9%) had paucibacillary disease. The highest percentage of patients in different ethnic groups was seen in migrants (57.7%) and the lowest distribution in Balochis (3%) [**Table 3**]. 241 (12.4%) patients showed some degree of deformity.

In this survey leprosy was found in focal pattern in Hyderabad i.e. a large number of patients was registered from small local areas of city i.e.

Paretabad, Phulleli, Liaquat Colony, Hoosri Camp, Hussainabad, and Hali Road, Indian migrants being the major residents in these areas.

## Discussion

Our data suggest that leprosy was predominantly seen in Indian migrants. This is in accordance with a previous study from Karachi.<sup>9</sup> The different frequencies in different ethnic groups may be due to variation in immunologic responses, genetic differences, undiagnosed reservoir of leprosy patients in the community and the ample opportunity for contacts to get infected. Leprosy is a disease with a strong genetic predisposition of polygenic nature, evidenced by familial clustering, twin studies, complex segregation analyses and HLA association studies.<sup>3-5</sup> However, different non-HLA-linked loci may exist in different populations contributing to disease susceptibility. Leprosy susceptibility locus has been mapped to chromosome 10p13 (South Indian patients families)<sup>10</sup> and chromosome 6q25-26 (Vietnamese patients families).<sup>11</sup> Similarly, variants in Parkinson's syndrome gene PAARK2 and coregulated gene PACRG may also act as common risk factors for leprosy.<sup>11</sup> It will be interesting to explore the susceptible genes in our study population.

The male to female ratio was almost equal in our study whereas females outnumbered males in other studies.<sup>9,12</sup> Patients below 10 year were less frequent indicating the long incubation period of the disease. Majority of our patients had paucibacillary (TT or BT) disease. Different studies report different types of the disease to be frequent. In a Canadian study,<sup>13</sup> the majority of patients had PB leprosy. However, data from other centres e.g. Karachi<sup>9</sup> and Lahore<sup>12</sup> reported MB leprosy as the dominant type. The deformity

rate was quite high (12.4%) in our patients, though this figure is comparable to previous local reports.<sup>6,9,12</sup> This reflects the delay in the diagnosis of disease. Although other variables like clinical form, age group, sex and mode of detection are considered to be independent variables for the presence of disease.<sup>14</sup> To obviate the late diagnosis, there is strong need to create awareness among patients, community, medical and paramedical personnel.

## Conclusion

Leprosy in Hyderabad is usually of paucibacillary type and it predominantly affects persons of Indian ancestral background.

## References

1. Rea TH, Modlin RL. Leprosy. In: Freedberg IM, Eisen AZ, Wolff K *et al.*, eds. *Fitzpatrick's dermatology in general medicine*, 6<sup>th</sup> edn. New York: McGraw-Hill; 2003. p. 1962-71.
2. Ridley DS, Jopling WH. Classification of leprosy. *Int J Lepr* 1966; **34**: 255.
3. De Vries RRP, Mehra NK, Vaidya MC *et al.* HLA linked control of susceptibility to tuberculoid leprosy; confirmation of the DR marker. *J Inf Dis* 1980; **141**: 693-701.
4. Van Eden W, De Vries RRP, D' Amero I *et al.* HLA-DR associated genetic control of the type of leprosy in a population from Surinam. *Human Immunol* 1982, **4**: 343-50.
5. Van Eden W, Gonzalez NV, De Vries RRP, Convit J, Van Rood JI. HLA-linked control of predisposition to lepromatous leprosy. *J Inf Dis* 1985; **151**: 9-15.
6. National leprosy control programme 1989-1998. An overview. Karachi: Marie Adelaide Leprosy Centre; 1999.
7. Khalid NZ, ed. *Kitabistan World atlas*. Lahore: Kitabistan Publishing; 2002.
8. <http://www.WHO/leprosy.htm> (accessed on 22.10.2003).
9. Arain GM. Leprosy in Karachi. *J Pak Med Assoc* 1992; **42**: 160-3.
10. Siddiqui MR, Meisner S, Tosh K *et al.* A major susceptibility locus for leprosy in India maps to chromosome 10p13. *Nat Genet* 2001; **27**: 439-41.

11. Mira MT, Alcais A, Nguyen VT *et al.* Susceptibility to leprosy is associated with PARK2 and PACRG. *Nature* 2004; **427**: 636-40.
12. Ahmad TJ. *Types, complications and treatment of leprosy* (dissertation). Karachi: College of Physicians and Surgeons Pakistan; 1993.
13. Boggild AK, Correia JD, Keystone JS, Kain KC. Leprosy in Toronto. *CMAJ* 2004; **170**: 63-4.
14. Ferreira J, Mengue SS, Wagner MB, Duncan BB. Estimating hidden prevalence in Hansen's disease through diagnosis delay and grade of disability at time of diagnosis. *Int J Lepr Other Mycobact Dis* 2000; **68**: 464-73.

## Review article

# Papillon-Lefèvre Syndrome. All about palms, soles and gums: a brief review

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### Abstract

Papillon-Lefèvre syndrome (PLS) is an autosomal recessive disorder of keratinization characterized by palmoplantar keratoderma and periodontitis with subsequent loss of teeth. The exact etiology of the diseases remains to be unraveled. Nonetheless cathepsin C gene mutations may be involved. The present review focuses on the recent advances about role of cathepsin C gene in the causation of PLS and other disorders.

### Introduction

Papillon-Lefèvre syndrome (PLS) is a rare autosomal recessive disorder affecting children between the ages of 1-4 years.<sup>1,2</sup> It was first described by two French physicians, Papillon and Lefèvre in 1924. With a prevalence of 1-4 cases/million, it equally affects both sexes without any racial predominance. PLS presents as diffuse palmoplantar keratoderma (PPK) and a rapidly progressive juvenile periodontitis with subsequent loss of both primary and secondary dentitions. The PPK usually appears between the ages of 1-4 years, is characterized by well-demarcated erythematous, keratotic plaques that usually involve the entire surface of the palms (**Figure 1**) and soles (**Figure 2**) and may transgress onto the dorsa of the hands and feet.<sup>3</sup> In advanced cases, achilles tendons may also be involved. Well-circumscribed psoriasiform plaques may occur on the elbows and knees.<sup>4</sup> A foul smelling odor may result from the hyperhidrosis of the palms and soles.<sup>2</sup> The

aggressive periodontitis which affects both the primary and secondary dentitions, usually starts between the ages of 3-4 years.<sup>4</sup> The eruption of primary dentition is associated with gingivitis and subsequent periodontitis that leads to premature exfoliation of the dentition. Apparently, after exfoliation the gingiva appears healthy; but with the eruption of secondary dentition the whole process of inflammation and periodontitis is repeated with subsequent loss of the dentition (**Figure 3**). The patient is usually edentulous by the age of 15 years, but third molars may be spared.<sup>5</sup> The degree of skin involvement is not related to the level of periodontitis. Associated nail changes consist of dystrophy and transverse grooving.<sup>6</sup> An increased susceptibility to infections resulting in subsequent recurrent pyogenic infections of the skin is attributed to decreased neutrophil and lymphocyte functions.<sup>7</sup> The impairment of the immune function may also lead to recurrent pyogenic liver abscesses in PLS patients.<sup>7</sup> A radiographic evidence of intracranial calcification may also be noted in some patients.<sup>8</sup> Histopathology of the affected skin usually reveals hyperkeratosis, parakeratosis, acanthosis and perivascular infiltration of

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**Figure 1** Diffuse palmar keratoderma in PLS.



**Figure 1** Diffuse plantar keratoderma with fissuring in PLS. The keratoderma is encroaching on the dorsum, as well.



**Figure 3** Loss of permanent teeth following periodontitis in PLS.

inflammatory cells.<sup>9</sup> A few cases of late onset variation of PLS without any underlying CTSC gene mutations have also been described in the literature.<sup>10</sup>

### **Cathepsin C gene mutations associated with PLS**

The cathepsin C gene (CTSC) which is located on chromosome 11q14 encodes a cysteine lysosomal protease that functions by removing dipeptides from the amino terminal of the protein substrate. Its main functions are thought to be protein degradation and pro-enzyme activation in addition to its immunological role.<sup>11</sup> It also has endopeptidase activity. The CTSC gene is over 46 kb long and consists of 7 exons and 6 introns.<sup>12</sup> The gene is expressed in epithelial regions that are usually affected by PLS including palms, soles, knees and keratinized oral gingiva. It is also expressed in polymorphonuclear leukocytes, macrophages and their precursors. Several mutations have been reported in the CTSC gene in individuals from diverse ethnic groups. The total number of mutations in the CTSC gene described to date is 41 with 17 mutations being located in exon 7. Although the etiology of PLS is not well-established, recently two research groups reported an association of PLS with loss of function mutations affecting both the alleles of the CTSC gene.<sup>5,12</sup> Interestingly, CTSC gene mutations have also been reported in Haim-Munk syndrome and prepubertal periodontitis. Severe early onset periodontitis is a common manifestation of all three disorders and they seem to be allelic variants. Approximately one-third of the families show consanguinity.<sup>2</sup> Moreover, all PLS patients are homozygous for the same CTSC gene mutations which are inherited from a common ancestor. Heterozygous carriers either do not show the

PPK or early onset periodontitis. The periodontitis and increased susceptibility to various infections has also been attributed to impaired immunity resulting from dysfunction in neutrophil motility and bactericidal function.

### Other disorders associated with CTSC gene mutations

As mentioned earlier, two other rare disorders namely Haim-Munk syndrome and prepubertal periodontitis have also been found to be associated with CTSC gene mutations. Haim-Munk syndrome is an autosomal recessive genodermatosis that was first reported in 1965.<sup>13</sup> It is characterized by congenital PPK and progressive early onset periodontitis. Other features associated with Haim-Munk syndrome include arachnodactyly, acro-osteolysis, atrophic changes of the nails, and a radiographic deformity of the fingers. The cutaneous findings in this syndrome are reported to be more severe in contrast to PLS. A mutation of CTSC gene affecting a highly conserved amino acid residue has also been identified in Haim-Munk syndrome.<sup>14</sup> CTSC gene mutation has also been found to be associated with prepubertal periodontitis which is characterized by rapidly progressive form of early onset periodontitis resulting in the destruction of the periodontium of the primary and secondary dentitions. It may be localized or generalized and may present as an isolated disorder or as part of a recognized syndrome. Both the patterns of familial transmission have been described for prepubertal periodontitis.<sup>14</sup>

### Treatment

Topical emollients with or without salicylic acid and/or urea are usually prescribed to treat the keratoderma of PLS symptomatically<sup>7</sup> but the mainstay of the treatment of both keratoderma and periodontitis are oral retinoids. If instituted

early in the course of the disease, especially during the eruption of the secondary dentition, oral retinoids including acitretin, etretinate and isotretinoin could result in normal dentition.<sup>15</sup> It is no doubt a challenging task to treat the periodontitis but extraction of the primary dentition combined with oral antibiotics could help.<sup>7,16</sup>

### References

1. Hart TC, Shapira L. Papillon-Lefèvre syndrome. *Periodontol* 1994; **6**: 88-100.
2. Gorlin RJ, Sedano H, Anderson VE. The syndrome of palmar-plantar hyperkeratosis and premature periodontal destruction of the teeth. *J Pediatr* 1964; **65**: 895-908.
3. Bach JN, Levan NE. Papillon-Lefèvre syndrome. *Arch Dermatol* 1968; **97**: 154-8.
4. Siragusa M, Romano C, Batticane N *et al*. A new family with Papillon-Lefèvre syndrome: effectiveness of etretinate treatment. *Cutis* 2000; **65**: 151-5.
5. Hart TC, Hart PS, Bowden DW *et al*. Mutations of the cathepsin C gene are responsible for Papillon-Lefèvre syndrome. *J Med Genet* 1999; **36**: 881-7.
6. Giansanti JS, Hrabak RP, Waldron CA. Palmar-plantar hyperkeratosis and concomitant periodontal destruction (Papillon-Lefèvre syndrome). *Oral Surg Oral Med Oral Pathol* 1973; **36**: 40-8.
7. Almuneef M, Al Khenazian S, Al Ajaji S, Al-Anazi A. Pyogenic liver abscess and Papillon-Lefèvre syndrome: not a rare association. *Pediatrics* 2003; **111**: e85-8.
8. Reyes VO, King-Ismael D, Abad-Venida L. Papillon-Lefèvre syndrome. *Int J Dermatol* 1998; **37**: 268-70.
9. Angel TA, Hsu S, Kornbleuth SI *et al*. Papillon-Lefèvre syndrome: a case report of four affected siblings. *J Am Acad Dermatol* 2002; **46** (2 Suppl.): S8-10.
10. Pilger U, Hennies HC, Truschnegg A, Aberer E. Late-onset Papillon-Lefèvre syndrome without alteration of the cathepsin C gene. *J Am Acad Dermatol* 2003; **49** (5 Suppl.): S240-3.
11. Rao, NV, Rao, GV, Hoidal, JR. Human dipeptidyl-peptidase I. Gene characterization, localization, and expression. *J Biol Chem* 1997; **272**: 10260-5.
12. Toomes C, James J, Wood AJ *et al*. Loss-of-function mutations in the cathepsin C gene

- result in periodontal disease and palmoplantar keratosis. *Nat Genet* 1999; **23**: 421-4.
13. Haim S, Munk J. Keratosis palmo-plantaris congenita, with periodontosis, arachnodactyly, and peculiar deformity of the terminal phalanges. *Br J Dermatol* 1965; **77**: 42-54.
  14. Hart TC, Hart PS, Michalec MD *et al.* Haim-Munk syndrome and Papillon-Lefèvre syndrome are allelic mutations in cathepsin C. *J Med Genet* 2000; **37**: 88-94. Erratum in: *J Med Genet* 2001; **38**:79.
  15. Al-Khenaizan S. Papillon-Lefèvre syndrome: the response to acitretin. *Int J Dermatol* 2002; **41**: 938-41.
  16. Ishikawa I, Umeda M, Laosrisin N. Clinical, bacteriological, and immunological examinations and the treatment process of two Papillon-Lefèvre syndrome patients. *J Periodontol* 1994; **65**: 364-71.

Pakistan Association of Dermatologists is holding its Silver Jubilee Conference at Karachi from 9th to 12th December, 2004. JPAD will publish a special issue on this historic occasion. Readers are requested to fully contribute about the achievements/challenges to dermatology in Pakistan, and history of and achievements by their departments. Manuscripts should reach the Editorial Office by 30th June, 2004.

## Review article

# Mastocytoses

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### Abstract

Mastocytoses are an important group of dermatoses characterized by histological infiltrates predominantly rich in mast cells. The present review focuses on the salient clinical, diagnostic and therapeutic features of different entities included in this group.

### Introduction

Mastocytoses are benign or very rarely malignant proliferative disorders of the reticuloendothelial system. Mastocytosis is frequently self-limited especially in childhood, and represents an exaggerated accumulation of essentially normal looking mast cells in their regular distribution. The mast cell is the repository of a number of pharmacological substances, resulting in protean clinical manifestations. The skin is frequently involved with or without internal organ involvement. The present article presents an overview of the clinicopathological correlation and treatment options in mastocytoses in a simplified and tabulated version.

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**Table 1**  
**Mastocytoses**

Tumor	Clinical Features	Histopathology	Prognosis	Work up
<b>Benign mastocytosis [1-23]</b>				
<i>Cutaneous</i>				
<b>Urticaria pigmentosa</b>	<ul style="list-style-type: none"> <li>• Children, adults</li> <li>• Macules, papules</li> <li>• Nodules, plaques</li> <li>• Monomorphic</li> <li>• Pigmented</li> <li>• Symmetrical</li> <li>• Trunk</li> <li>• Darier's sign elicitable</li> <li>• Systemic manifestations</li> </ul> <p><i>Variants:</i></p> <ul style="list-style-type: none"> <li>• Bullous, ecchymotic</li> <li>• Anetoderma-like</li> <li>• Sjogren's syndrome-like</li> <li>• Xanthomatous</li> </ul>	<ul style="list-style-type: none"> <li>• Mast cells</li> <li>• Oval, spindle shaped</li> <li>• Metachromatic granules</li> </ul>	<ul style="list-style-type: none"> <li>• Depends on the extent of disease</li> <li>• Usually self-limiting</li> </ul>	<p><i>For diagnosis:</i></p> <ul style="list-style-type: none"> <li>• Clinical evaluation</li> <li>• Skin biopsy</li> <li>• Increased plasma histamine and tryptase</li> <li>• Increased urinary histamine and PGD2</li> </ul> <p><i>For extent:</i></p> <ul style="list-style-type: none"> <li>• Based on symptoms</li> </ul> <p><i>Follow up:</i></p> <ul style="list-style-type: none"> <li>• For disease state and opted therapy</li> </ul> <p><i>Therapeutic options:</i></p> <ul style="list-style-type: none"> <li>• Antihistamines</li> <li>• Antihistamine + aspirin (for GI symptoms)</li> <li>• Sodium chromoglycate</li> <li>• PUVA therapy</li> <li>• Topical and systemic steroids</li> <li>• Cytokines</li> <li>• Excision of solitary lesions</li> </ul>
<b>Solitary mastocytoma</b>	<ul style="list-style-type: none"> <li>• Children</li> <li>• Solitary nodules</li> <li>• Pink red, yellow</li> <li>• Systemic manifestations</li> </ul>	<ul style="list-style-type: none"> <li>• Mast cells</li> <li>• Oval, spindle shaped</li> <li>• Metachromatic granules</li> </ul>	<ul style="list-style-type: none"> <li>• Resolve in 2-3 years</li> </ul>	<ul style="list-style-type: none"> <li>• As for urticaria pigmentosa</li> </ul>

**Table 2**  
**Mastocytoses (contd....)**

<b>Tumor</b>	<b>Clinical features</b>	<b>Histopathology</b>	<b>Prognosis</b>	<b>Work up</b>
<b>Telangiectasia macularis eruptiva perstans</b>	<ul style="list-style-type: none"> <li>• Adults</li> <li>• Telangiectatic macules</li> <li>• Persistent</li> <li>• Treatment resistant</li> </ul>	<ul style="list-style-type: none"> <li>• Mast cells</li> <li>• Oval, spindle shaped</li> <li>• Metachromatic granules</li> </ul>	<ul style="list-style-type: none"> <li>• Persistent</li> </ul>	<ul style="list-style-type: none"> <li>• As for urticaria pigmentosa</li> </ul>
<b>Diffuse cutaneous mastocytosis</b>	<ul style="list-style-type: none"> <li>• Infants, adults</li> </ul> <p><b>Variants:</b></p> <ul style="list-style-type: none"> <li>• Pseudoxanthomatous</li> <li>• Pachydermatous</li> <li>• Nodular, bullous</li> <li>• Systemic manifestation</li> <li>• Flexural involvement</li> </ul>	<ul style="list-style-type: none"> <li>• Mast cells</li> <li>• Oval, spindle shaped</li> <li>• Metachromatic granules</li> </ul>	<ul style="list-style-type: none"> <li>• Depends on the extent of disease</li> </ul>	<ul style="list-style-type: none"> <li>• As for urticaria pigmentosa</li> </ul>
<b>Systemic mastocytosis</b>	<ul style="list-style-type: none"> <li>• Adults</li> </ul> <p><b>Systemic symptoms:</b></p> <ul style="list-style-type: none"> <li>• Flushing, headache</li> <li>• Diarrhea, weight loss</li> </ul> <p><b>Systemic signs:</b></p> <ul style="list-style-type: none"> <li>• <i>Gastrointestinal tract:</i> <ul style="list-style-type: none"> <li>• Hepatosplenomegaly</li> <li>• Peptic ulcer, malabsorption</li> </ul> </li> </ul> <p><b>Hematological system:</b></p> <ul style="list-style-type: none"> <li>• Anemia, leucocytosis</li> <li>• Eosinophilia</li> <li>• Marrow infiltration</li> </ul> <p><b>Skeletal system:</b></p> <ul style="list-style-type: none"> <li>• Osteoporosis, osteosclerosis</li> </ul>	<ul style="list-style-type: none"> <li>• Mast cells</li> <li>• Oval, spindle shaped</li> <li>• Metachromatic granules</li> </ul>	<ul style="list-style-type: none"> <li>• Depends on the extent of disease</li> </ul>	<ul style="list-style-type: none"> <li>• As for urticaria pigmentosa</li> </ul>

**Table 3**  
**Mastocytoses (contd...)**

<b>Tumor</b>	<b>Clinical features</b>	<b>Histopathology</b>	<b>Prognosis</b>	<b>Work up</b>
<b>Malignant mastocytosis [24-26]</b>				
<b>Lymphadenopathic with eosinophilia</b>	<ul style="list-style-type: none"> <li>Extremely rare</li> <li>Depend on the system/extent of involvement</li> </ul>	<ul style="list-style-type: none"> <li>Cytological atypia</li> <li>Architectural atypia</li> </ul>	<ul style="list-style-type: none"> <li>Depends on the extent of disease</li> </ul>	<ul style="list-style-type: none"> <li>As for urticaria pigmentosa</li> <li>Chemotherapy</li> </ul>
<b>Mast cell leukemia</b>				
<b>Childhood mastocytosis</b>				
<b>Childhood mastocytosis</b>	<ul style="list-style-type: none"> <li>Half of all cases of mastocytosis</li> <li>Urticaria pigmentosa is the commonest presentation</li> <li>Frequent bullous lesions</li> <li>Resolution by puberty</li> <li>Aggressive disease and malignancy is rare</li> </ul>	<ul style="list-style-type: none"> <li>Mast cells</li> <li>Oval, spindle shaped</li> <li>Metachromatic granules</li> </ul>	<ul style="list-style-type: none"> <li>Good</li> </ul>	<ul style="list-style-type: none"> <li>As for urticaria pigmentosa</li> </ul>

## References

1. Clark DP, Buescher L, Havey A. Familial urticaria pigmentosa. *Arch Intern Med* 1990; **150**: 1742-4.
2. Hass N, Hamann K, Grabbe J. Phenotypic characterization of skin lesions of urticaria pigmentosa and mastocytomas. *Arch Dermatol Res* 1995; **287**: 247-8.
3. Longley J, Duffy TP, Kohn S. The mast cell and mast cell disease. *J Am Acad Dermatol* 1995; **32**: 545-61.
4. Niordson AM. Urticaria pigmentosa: age of onset and prognosis. *Acta Derm Venereol* (Stockh) 1962; **42**: 433-9.
5. Greaves MW, Sondergaard J. Urticaria pigmentosa and factitious urticaria: direct evidence for release of histamine and other smooth muscle-contracting agents in dermographic skin. *Arch Dermatol* 1970; **101**: 418-25.
6. Sanchez R, Oblender M, Raimer S. Leukemia cutis: Darier's sign in neonate with acute lymphoblastic leukemia. *J Am Acad Dermatol* 1996; **34**: 375-8.
7. Nagayo K, Sakai M, Mizuno N. Juvenile xanthogranuloma with Darier's sign. *J Dermatol* 1983; **10**: 283-5.
8. Caplan RM. The natural course of urticaria pigmentosa. Analysis and follow up of 112 cases. *Arch Dermatol* 1963; **87**: 146-57.
9. Aubin F, Gutknecht J, Faivre B. Unusual ecchymotic presentation of systemic mastocytosis. *Eur J Dermatol* 1995; **5**: 237-9.
10. Gebauer KA, Navaratnam TE, Holgate C. Pruritic pigmented papules posing permanent problems. Urticaria pigmentosa (UP) with secondary anetoderma. *Arch Dermatol* 1992; **128**: 105-10.
11. Bac DJ, Van Marwijk Kooy M. Mastocytosis and Sjogren's syndrome. *Ann Rheum Dis* 1992; **128**: 105-10.
12. Christopher SE, Honigsman MH, Wolff K. PUVA treatment of urticaria pigmentosa. *Br J Dermatol* 1978; **98**: 701-2.
13. Vella Briffa D, Eady RAJ, James MP. Photochemotherapy (PUVA) in the treatment of urticaria pigmentosa. *Br J Dermatol* 1983; **109**: 67-75.
14. Barton J, Lavker RM, Schecter NM, Lazarus GS. Treatment of urticaria pigmentosa with corticosteroids. *Arch Dermatol* 1985; **121**: 1516-23.
15. Kolde G, Sunderkotter C, Luger TA. Treatment of urticaria pigmentosa using interferon alpha. *Br J Dermatol* 1995; **133**: 91-4.
16. Guzzo C, Lavker R, Roberts LJ. Urticaria pigmentosa: system evaluation and successful treatment with topical steroids. *Arch Dermatol* 1994; **127**: 191-6.
17. Moynahan EJ. Urticaria pigmentosa (telangiectasia macularis eruptiva perstans). *Proc R Soc Med* 1949; **42**: 346-7.
18. Warin RP, Hughes RCW. Diffuse cutaneous mastocytosis. *Br J Dermatol* 1963; **65**: 296-7.
19. Griffiths WAD, Daneshbod K. Pseudoxanthomatous mastocytosis. *Br J Dermatol* 1975; **93**: 91-5.
20. Johnson EC, Helwig EB. Solitary mastocytosis (urticaria pigmentosa). *Arch Dermatol* 1961; **84**: 806-15.
21. Birt AR, Nickerson M. Generalized flushing of the skin with urticaria pigmentosa. *Arch Dermatol* 1959; **80**: 311-17.
22. Ferguson J, Thompson RPH, Greaves MW. Intestinal mucosal mast cells: enumeration in urticaria pigmentosa and systemic mastocytosis. *Br J Dermatol* 1988; **119**: 573-8.
23. Bank S, Marks JN. Malabsorption in systemic mast cell disease. *Gastroenterology* 1963; **45**: 535-49.
24. Kettelhu BV, Metcalfe DD. Pediatric Mastocytosis. *J Invest Dermatol* 1991; **96**: 15S-18S.
25. Travis WD, Li C-Y, Hoagland HC. Mast cell leukemia: report of a case and review of the literature. *Mayo Clin Proc* 1986; **61**: 957-66.
26. Kors JW, Van Doormaal JJ, Breukelman H. Long term follow up of indolent mastocytosis in adults. *J Intern Med* 1996; **239**: 157-64.

## Case report

# Vogt-Koyanagi-Harada Syndrome: A case report and review of literature.

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**Abstract** Vogt-Koyanagi-Harada (VKH) syndrome is a rare multisystem disorder in which cell-mediated autoimmunity against melanocytes affects the eyes, inner ears, central nervous system and skin. Alopecia, poliosis and vitiligo are the cutaneous manifestations. Visual and hearing loss is the important complications which can be prevented by early diagnosis and aggressive systemic therapy. We report a case of VKH syndrome in which alopecia was the only cutaneous manifestation and early diagnosis and prompt systemic corticosteroid therapy prevented the visual loss and reduced the morbidity.

**Key word**

Vogt-Koyanagi-Harada syndrome

### Introduction

Vogt-Koyanagi-Harada (VKH) syndrome is a rare systemic disease characterized by bilateral uveitis associated with poliosis, vitiligo, alopecia, and central nervous system and auditory signs. The syndrome was first described by Ali-ibn-Isa (940-1010 AD), an Ophthalmologist, and reported independently by Vogt, Harada, and Koyanagi in 1906, 1926 and 1929 respectively. In 1932, Babel classified the disease as Vogt-Koyanagi-Harada syndrome.<sup>1</sup>

VKH is currently considered to be a cell-mediated autoimmune disease with genetic predisposition. The autoimmunity appears to be directed against melanocytes. It occurs more commonly in darkly pigmented individuals including Asians, Native Americans, and Latin Americans. Clinical manifestations are variable and

race-dependent. Typical cases are uncommon. Because of the wide spectrum of the disease, the American Uveitis Society adopted a diagnostic criteria (table I) in 1978 for the diagnosis of VKH syndrome.<sup>2</sup> Visual loss is the major complication, which is due to cataract, glaucoma and choroidal neovascularization. The key to successful therapy of VKH syndrome is early and aggressive treatment with systemic corticosteroids.

We describe a patient of VKH syndrome in which alopecia is the only cutaneous manifestation in addition to the ophthalmic and auditory involvement. This is the first case report in Pakistan in which early diagnosis and prompt systemic therapy improved the prognosis.

### Case history

A 20-year-old young man presented in the dermatology OPD with a 3-month history of gradually increasing alopecia of scalp, which started with the feeling of pain in the hair roots. Since then he also had

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bilateral progressive hearing loss and tinnitus. For the last 5 months, he had 4 - 5 episodes of increasing severity of pain, photophobia and redness in both eyes with progressive decrease in the visual acuity. He was not evaluated for alopecia and the ear complaints before, but he did receive topical treatment from various ophthalmologists with waxing and waning of the eye symptoms. Two years ago, he had recurrent episodes of headache, which were usually relieved by analgesics. These lasted for one year. Attacks of headache were not accompanied by nausea, vomiting or neck stiffness and were never investigated. There was no history of any motor or sensory loss, seizures, unconsciousness or any impairment in the memory. The patient also denied of photosensitivity, or any other skin eruption, joint pains, fever, intraocular surgery or penetrating trauma to the eyes. History of any other systemic symptom could not be elicited.

On examination he had patchy diffuse alopecia of scalp without any signs of active inflammation, scaling or scarring. There were neither poliosis, vitiligo, halo naevi, nor any other cutaneous eruption. Ophthalmological examination revealed bilateral anterior and posterior uveitis, without any retinal detachment. The visual acuity of right eye was to projected light only and of the left eye was 4/60. Optic discs were edematous. There was bilateral complicated cataract (right > left) and the intraocular pressure was 17.3 mm Hg in both eyes (by Schiotz's tonometry). ENT examination and audiometry showed moderate sensorineural deafness. Higher mental

**Table 1** Diagnostic criteria of VHK syndrome

*In the absence of prior trauma or surgery, at least three of the following four criteria must be present:*

1. Bilateral chronic iridocyclitis.
2. Posterior uveitis, including multifocal exudative retinal detachments, retinal pigment epithelial changes, and disc hyperemia or edema.
3. Neurological signs of tinnitus, neck stiffness, cranial nerve or central nervous system dysfunction, or cerebrospinal fluid pleocytosis.
4. Cutaneous findings of alopecia, poliosis, or vitiligo.

functions were normal and there was no neurological deficit. Examination of other systems was unremarkable. There was no abnormality in routine blood and urine examination. Blood sugar, blood urea, serum creatinine, Liver function tests and serum complements (3 & 4) were within normal range. ANA, Anti-DNA and VDRL test were negative. Scraping for fungus from the scalp was also negative. X-ray chest and CT scan of brain were normal.

The diagnosis of Vogt-Koyanagi-Harada syndrome was made based on the criteria of American Uveitis Society for the diagnosis of VKH syndrome (**Table 1**) and by exclusion of other possible etiologies on the basis of clinical and laboratory findings. The patient was managed in collaboration with the ophthalmology department. Oral steroids (prednisolone 60 mg/day) were started. Within a week his visual acuity started improving and after 4 weeks it became 6/60 in the right and 6/12 in the left eye. The intraocular pressure decreased from 17.3 to 8.5 mm Hg bilaterally and the ocular inflammation had settled. Up till that time the alopecia also moderately improved and the deafness became less

subjectively as well as on audiometry. On further improvement, after another four weeks, he was discharged on the same dose of oral steroids to be tapered very slowly according to the clinical status. The ophthalmology department has also planned cataract surgery with IOL after complete resolution.

## Discussion

Vogt-Koyanagi-Harada (VKH) syndrome is a rare systemic disease involving various organs containing melanocytes. Granulomatous panuveitis with exudative retinal detachments in association with cutaneous, neurologic, and auditory abnormalities characterize this syndrome. VKH is more common in darkly pigmented races, including Asians particularly Japanese, Latin Americans, Native Americans, and African Americans. It is rarely seen in Northern European individuals. The incidence of VKH in USA is 1-4% and in Japan 7-8% of all uveitis cases.<sup>3</sup> Females are slightly more affected than males. The age of onset is usually between the second and fifth decades, with a mean age of 30 to 40 years, however, children as young as 4 years have been reported with VKH syndrome.<sup>4</sup>

The strong association between VKH and certain racial and ethnic groups and the statistically significant frequency of HLA-DR4 (an antigen commonly associated with other autoimmune diseases) suggests the immunogenetic predisposition in the development of this disease.<sup>5</sup> Granulomatous inflammation and loss of melanocytes has been described in a number of tissues, including the skin, inner ear, meninges, and uveal tract.<sup>1,6</sup> The histopathologic changes, clinical and experimental data suggest an infectious or

autoimmune basis for the disease. Though a viral aetiology has been suggested<sup>7</sup> but majority of the evidences are in favour of autoimmune process.<sup>8,9,10,11</sup> In view of these findings, the pathogenesis of VKH syndrome is considered to be a cell-mediated autoimmune process against the melanocytes, with strong genetic predisposition. Despite its diverse manifestations, the clinical course of VKH syndrome has been categorized into four phases; prodromal, uveitic, chronic and recurrent (**Table 2**).<sup>1</sup> Except for the sensitivity to touch of the hair and skin in the prodromal phase, the major dermatological manifestations, i.e., alopecia, poliosis and vitiligo, develop in the third phase. In general the cutaneous signs occur several weeks to months after the onset of ocular inflammation, but in some patients skin changes were observed many years before uveitis appeared. According to a Japanese study,<sup>12</sup> alopecia may be patchy or diffuse and affects 50% of the patients. Poliosis usually appears after the onset of alopecia. It occurs in 90% of the patients and involves the eyebrows and eyelashes, and occasionally the scalp and body hair extensively. Vitiligo presents in 63% of the patients and is often symmetrical. It usually occurs over the head, face and trunk. The sacral region is the common site on the trunk. Atypical variants of vitiligo with inflammatory raised borders and plaque-type inflammatory erythema also have been reported. Halo naevi and perilimbal vitiligo in the eye (The Sugiura's Sign) may also occur.<sup>13</sup>

The differential diagnosis of VKH syndrome includes diseases of eye, CNS and skin, and systemic inflammatory or

**Table 2** Phases of VKH syndrome

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*1. Prodromal phase*

- Lasts for few days
- Headache, fever, meningismus, confusion
- Photophobia, orbital pain
- Auditory symptoms (at any stage): nausea, vertigo, tinnitus, dysacusis
- Skin and hair sensitive to touch
- Lymphocytic pleocytosis in CSF
- Uncommon: cranial nerve palsies and optic neuritis.
- These prodromal symptoms may not develop or pass unnoticed by some patients.

*2. Uveitic phase:*

- Lasts for several weeks
- Pain & redness in eyes, blurring of vision
- Photodysphoria, decreased visual acuity
- Posterior uveitis with retinal edema
- Optic disc hyperemia or edema
- Exudative retinal detachments
- Anterior uveitis often accompanies
- Intraocular pressure may be elevated

*3. Chronic Phase*

- Lasts for several months to years
- Dermatologic changes: alopecia, poliosis, vitiligo, halo naevi
- Uveal depigmentation

*4. Recurrent Phase*

- Chronic panuveitis
- Recurrent granulomatous anterior uveitis
- Rarely, recurrent posterior uveitis with retinal detachment
- Complications of VKH: cataract, glaucoma, choroidal neovascularization, subretinal fibrosis

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**Table 3** Differential diagnosis of VKH syndrome

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*Inflammatory diseases*

- Systemic lupus erythematosus
- Sarcoidosis
- Ocular Lyme borreliosis
- Multiple sclerosis
- Behcet's disease
- Inflammatory bowel disease

*Infectious diseases*

- Syphilis
- Tuberculosis
- Herpes Simplex encephalitis
- Whipple disease
- Cryptococcal meningitis
- HIV meningitis
- CMV infection
- Toxoplasmosis

*Eye/CNS diseases*

- Sympathetic ophthalmia
- Acute posterior multifocal placoid pigment epitheliopathy (APMPPE)
- Multifocal secondary retinal and pigment epithelial detachment in:
  - Grade IV systemic hypertension
  - and pregnancy-induced hypertension

*Dermatological diseases*

- Vitiligo
- Piebaldism
- Alezzandrini syndrome
- Alopecia areata
- Tinea capitis

infectious diseases (**Table 3**). The diagnosis is made clinically based upon a constellation of clinical signs and symptoms with no confirmatory tests. However, several diagnostic tests and procedures may be useful to substantiate the diagnosis. Depending upon the clinical features and stage of the disease at the time of presentation, fluorescein

angiography, ultrasonography, CSF examination, MRI, electrophysiological studies and specific tests for inflammatory or infectious diseases may be helpful. Due to its varied clinical manifestations and absence of any confirmatory laboratory test, a diagnostic criteria (**Table 1**) was adopted by the American Uveitis Society for the diagnosis of VKH syndrome.<sup>2</sup>

The goal of therapy in VKH syndrome is to reduce morbidity and to prevent complications. Topical therapy only is not associated with complete recovery without complications. The key to

successful therapy is early and aggressive use of systemic corticosteroids. Treatment with corticosteroids may shorten the duration of the disease, prevent complications, and decrease the occurrence of extraocular signs.<sup>3</sup> The usual treatment includes systemic steroids with average initial dose of 1-2 mg/kg of oral prednisone per day. For most severe cases, some authors recommend pulse therapy with methyl prednisolone (up to 1 g/day) for several days before beginning oral prednisone. If patients are resistant to steroids, addition of intravenous immunoglobulins (IV IgG) may be helpful.<sup>14</sup> The length of treatment and subsequent tapering must be individualized for each patient. Most patients require therapy for 6 months and occasionally up to 1 year before successful tapering of systemic corticosteroids. In general, systemic therapy should not be discontinued during the 3 months following the onset of the disease because of the risk of recurrence. Alternatively, immunosuppressive therapy, such as cyclosporin, tacrolimus, azathioprine, cyclophosphamide or methotrexate, may be required in patients who fail to respond to high-dose systemic corticosteroids or develop significant adverse effects.<sup>15</sup> Topical therapy for eyes includes corticosteroids and cycloplegic-mydratic eye drops. For pigmentary changes, treatment options are the same as for vitiligo.<sup>13</sup>

Most signs and symptoms resolve with corticosteroid therapy. Final visual

outcome depends on rapid and appropriate treatment. Hearing is restored completely in most of the patients. Pigmentary changes are usually permanent. Long term complications include reversible and irreversible vision loss, glaucoma and cataract. Ocular complications are more severe in children than in adults, leading to rapid deterioration in vision.<sup>16</sup>

Our patient did not report any prodromal symptom of 1<sup>st</sup> phase, which is possible as these symptoms may not develop or pass unnoticed by the patient.<sup>3</sup> The clinical features and time frame of episodic headache (two years before) did not fit in the prodromal phase. In the 2<sup>nd</sup> phase he received topical treatment for recurrent uveitis from various sources. It was the start of 3<sup>rd</sup> phase when he presented in the dermatology OPD with alopecia of scalp. Development of alopecia after the uveitis is in accordance with the usual course of the disease. All the cutaneous manifestations are not present in every case. The poliosis usually appears after the alopecia and the frequencies of alopecia, poliosis and vitiligo are reported as 50%, 90% and 63%, respectively.<sup>12</sup> These findings can explain the absence of poliosis and vitiligo, and alopecia as the sole cutaneous sign in the reported case. Consistent clinical features, exclusion of other possible causes by clinical/laboratory findings, and the fulfillment of diagnostic criteria by American Uveitis Society were the basis for the diagnosis of VKH

syndrome in our patient. Treatment with systemic corticosteroids not only prevented the visual loss but also resulted in the marked improvement of all the ophthalmic parameters as well as deafness and alopecia. A local case of VKH syndrome was also reported previously in which visual and auditory loss could not be prevented due to late diagnosis and treatment.<sup>17</sup> To our knowledge, this is the first case report in Pakistan in which alopecia is the sole cutaneous manifestation and early diagnosis and prompt systemic corticosteroid therapy reduced the morbidity.

## References

1. Moorthy RS, Inomata H, Rao NA. Vogt-Koyanagi-Harada syndrome. *Surv Ophthalmol* 1995; **39**: 265-92.
2. Snyder DA, Tessler HH. Vogt-Koyanagi-Harada syndrome. *Am J Ophthalmol* 1980; **90**: 69-75.
3. Walton RC. Vogt-Koyanagi-Harada Syndrome. *eMedicine Journal* 2001; **2**.
4. Cunningham ET Jr, Demetrius R, Frieden IJ *et al*. Vogt-Koyanagi-Harada syndrome in a 4 year old child. *Am J Ophthalmol* 1995; **120**: 675-7.
5. Islam SM, Numaga J, Fujino Y *et al*. HLA class genes in Vogt-Koyanagi-Harada disease. *Invest Ophthalmol Vis Sci* 1994; **35**: 3890-6.
6. Rao NA. Vogt-Koyanagi-Harada syndrome. *Int Ophthalmol Clin* 1995; **35**: 69-86.
7. Morris WR, Schlaegel TF Jr. Viruslike inclusion bodies in subretinal fluid in uveo-encephalitis. *Am J Ophthalmol* 1964; **58**: 940-5.
8. Jovic NS, Nesovic M, Vranjesevic DN *et al*. The Vogt-Koyanagi-Harada syndrome: association with autoimmune polyglandular syndrome type 1. *Postgrad Med J* 1996; **72**: 495-97.
9. Kogiso M, Tanouchi Y, Miki S, Mimura Y. Characterization of T-cell subsets, soluble interleukin-2 receptors and interleukin-6 in Vogt-Koyanagi-Harada disease. *Jap J Ophthalmol* 1992; **36**: 37-43.
10. Yokoyama MM, Matsui Y, Yamashiroya HM *et al*. Humoral and cellular immunity studies in patients with Vogt-Koyanagi-Harada syndrome and pars planitis. *Invest Ophthalmol Vis Sci* 1981; **20**: 364-70.
11. Maezawa N, Yano A, Taniguchi M, Kojima S. The role of cytotoxic T lymphocytes in the pathogenesis of Vogt-Koyanagi-Harada disease. *Ophthalmologica* 1982; **185**: 179-86.
12. Mondkar SV, Biswas J, Ganesh SK. Analysis of 87 cases with Vogt-Koyanagi-Harada disease. *Jpn J Ophthalmol* 2000; **44**: 296-301.
13. Choczaj-Kukula A, Janniger CK. Vogt-Koyanagi-Harada Syndrome. *eMedicine Journal* 2001; **2**.
14. Helveston WR. Treatment of Vogt-Koyanagi-Harada syndrome with intravenous immunoglobulin. *Neurology* 1996; **46**: 584-5.
15. Nussenblatt RB, Palestine AG, Chan CC. Cyclosporin A therapy in the treatment of intraocular inflammatory disease resistant to systemic corticosteroids and cytotoxic agents. *Am J Ophthalmol* 1983; **96**: 275-82.
16. Rubsamen PE, Gass JD. Vogt-Koyanagi-Harada syndrome. Clinical course, therapy, and long-term visual outcome. *Arch Ophthalmol* 1991; **109**: 682-7.
17. Javed MA, Jahangir M, Sial MSH. Vogt-Koyanagi-Harada syndrome. *Pak J Neurol* 1998; **4**: 59-61.

## Case report

# Acquired hemangioma: An uncommon vascular cutaneous tumour in elderly persons

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**Abstract** Among recently characterized vascular tumors, tufted angioma or angioblastoma is a benign acquired slowly progressive cutaneous tumor, which most commonly arises in the neck and upper trunk in children and young adults. We describe such a case occurring in an elderly person. Clinically this tumour may closely mimic Kaposi's sarcoma and should be biopsied for histological confirmation of the diagnosis.

**Key words**

Acquired hemangioma

### Introduction

Acquired cutaneous angiomatous proliferation is characterized by slowly spreading erythematous macules and plaques, sometimes surmounted by nodule formation. Synonyms are progressive capillary hemangioma and Nakagawa's angioblastoma.<sup>1</sup> Acquired hemangioma is a benign cutaneous angioma that must be distinguished from other vascular tumors, especially from Kaposi's sarcoma and if it appears in an older patient, angiosarcoma should be excluded. It is a slowly progressive cutaneous tumor, which normally occurs in the neck and upper trunk in children and young adults.<sup>1,2</sup> Little is known about the etiology of hemangiomas, but these lesions are found to contain proliferating cell nuclear antigen, vascular endothelium derived growth factor (VEGF), vitronectin deposition in the subendothelial interstitial space, and higher levels of basic fibroblast

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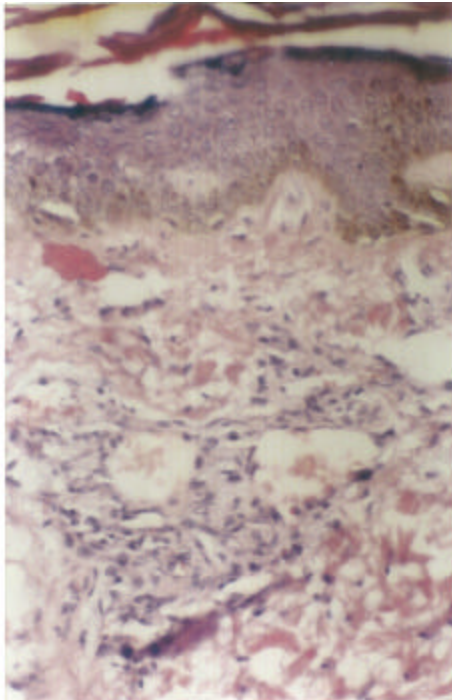
growth factor (bFGF) and basement membrane molecules (collagenase type 4, laminin) and these factors in some ways have a role in growth of hemangiomas.<sup>3,4</sup> Hemangiomas may arise de novo or after certain infections including herpes and HIV.<sup>5</sup> There is an interdependent relationship of tumor growth and angiogenesis.<sup>6</sup> It was found that tumors needed to induce the formation of new blood vessels to grow beyond a few millimeters.<sup>7</sup> Light microscopic examination reveals lobules of closely packed capillaries scattered throughout the dermis. Vascular lumina are difficult to define and there are no atypical cells. Immunohistochemistry by using markers like VEGF, bFGF is another useful tool for making a diagnosis. Treatment in most of the cases is local surgical excision of the tumour, when indicated.

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### Case history

A 55-year-old male patient presented with six months history of sudden appearance of mildly painful and occasionally



**Figure 1** Multiple thin walled closely packed capillaries in the dermis with mild perivascular lymphocytic infiltrate

discharging three small skin lesions over right wrist region. The lesions started abruptly and gradually increased in size. At the time of presentation, there were three isolated but closely placed, grayish blue soft nodular lesions, measuring in size (5mm to 1cm) individually in diameter on the extensor aspect of right wrist area. Surface was intact. Epitrochlear and axillary lymph nodes were not palpable on the right side. There was no history of any similar lesions elsewhere over the body. He neither visited abroad, nor did he receive any transfusion in the past. There was no history of any preceding illness. His general health was good and systemic examination proved unremarkable. Skin biopsy of the lesion was done and histopathology revealed

multiple thin walled closely packed capillaries in the dermis with mild perivascular lymphocytic infiltrate (**Figure 1**). There was no evidence of Kaposi sarcoma. The patient was reassured about the benign nature of the tumour and was advised to consult the surgeon for excision of the tumour.

## Discussion

Hemangiomas are quite prevalent in infancy and childhood and are infrequently seen in young adults and elderly people. In normal adult tissues, the angiogenic process is quiescent by virtue of a well balanced harmony between pro- and anti-angiogenic factors. In normal adults, only 0.01% of vascular endothelial cells divide.<sup>7</sup> During reproduction, development, and wound repair, angiogenesis is highly regulated; it “switches on” for short periods and then is completely inhibited. When this tightly regulated, biochemical balance of pro- and anti-angiogenic factors is upset, angiogenesis “switches on” to supply pathologic tissues and disease starts. Several triggers are known to flip this pathologic switch, including metabolic factors, mechanical stress, immune or inflammatory responses, and genetic mutation.<sup>7,8</sup> Hemangioma in our case, most likely arose de novo as there was no history of any preceding viral infection or any underlying immunosuppression. Familiarity with such acquired tufted angioma should prevent this lesion from being misdiagnosed as malignant vascular tumor arising in middle aged or elderly persons, especially Kaposi's sarcoma.

## References

1. Vanhootehem O, Andre J, Bruderer P *et al.* Tufted angioma, a particular form of angioma. *Dermatology* 1997; **194**: 402-4.

2. Croue A, Habersetzer M, Leclech C *et al.* "Tufted angioma". A benign vascular tumor to differentiate with Kaposi sarcoma. *Arch Anat Cytol Pathol* 1993; **41**: 159-63.
3. Takahashi K, Mulliken JB, Kozakewich HPW *et al.* Cellular markers that distinguish the phases of hemangioma during infancy and childhood. *J Clin Invest* 1994; **93**: 2357-64.
4. Jang Y-C, Arumugam S, Ferguson M *et al.* Changes in matrix composition during the growth and regression of human hemangiomas. *J Surg Res* 1998; **80**: 9-15.
5. Prieto VG, Shea CR. Selected cutaneous vascular neoplasms. A review. *Dermatol Clin* 1999; **17**: 507-20.
6. Goldman E. The growth of malignant disease in man and the lower animals with special reference to the vascular system. *Lancet* 1907; **2**: 1236-40.
7. Folkman J, Shing Y. Angiogenesis. *J Biol Chem* 1992; **267**: 10931-4.
8. Pettersson A, Nagy JA, Brown LF *et al.* Heterogeneity of the angiogenic response induced in different normal adult tissues by vascular permeability factor/vascular endothelial growth factor. *Lab Invest* 2000; **80**: 99-115.

# Quiz

## Annular erythematous plaque on the dorsum of hand

**Faria Asad, Sabrina Suhail Pal**

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### Report of a case

A fifty-five year old woman presented with two years history of a slowly enlarging, erythematous, annular plaque on the dorsal surface of right hand. It was completely asymptomatic. The patient had no significant medical history.

Physical examination showed erythematous papules arranged in a well-defined annular pattern on the dorsum of right hand (**Figure 1**). A biopsy was taken (**Figure 2**).

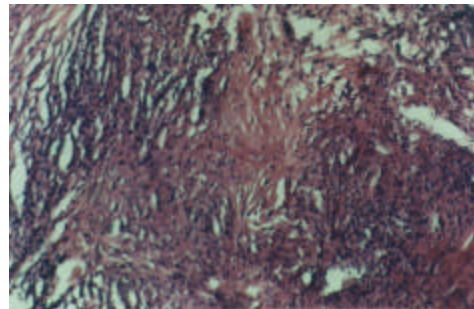
### Microscopic findings

Histologic examination of the skin specimen showed a central core of degenerated collagen surrounded by an infiltrate of lymphocytes and histiocytes. The collagen was granular and intensely eosinophilic. Few giant cells were seen in the periphery of the infiltrate.

What is your diagnosis?



**Figure 1**



**Figure 2**

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### Address for Correspondence

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Lahore.

**Diagnosis**

Granuloma annulare

**Discussion**

Granuloma annulare is a benign, inflammatory, usually self-limiting dermatosis of unknown cause. It is characterized by necrobiotic dermal papules that are commonly arranged in an annular configuration. It is predominantly a disease of children and young adults but it can start at any age.

The cause of the disease is not known but it is generally believed that the reaction is an immunologically-mediated one in which inflammation surrounds blood vessels and the collagen and elastic tissues are altered. The role of inciting agents such as tuberculin testing, herpes zoster, viral warts, HIV and trauma suggests that the antigen from these infections or immunologic agents or an altered dermal antigen may be responsible for the inflammatory reaction.<sup>1</sup>

Our patient suffered from localized type of granuloma annulare which is the most common type. It is characterized by a group of firm, erythematous to skin-

colored papules arranged in a ring or semicircle fashion. The centre of the lesion is usually depressed. It commonly appears on the dorsum of hands and feet, but rarely other parts can be involved. The lesion spontaneously clears in three months to two years without scarring.<sup>2</sup> The chief laboratory aid to the diagnosis is biopsy.

Although the disease is usually self-limiting, but a wide variety of treatment modalities are reported to be effective including topical or intralesional glucocorticoids, X-rays, laser and cryotherapy. Systemic treatments employed are dapsone, PUVA, cyclosporin, chloroquine and chlorambucil with variable results.<sup>3</sup>

**References**

1. Hogan DJ. Localised Granuloma annulare. *J Am Acad Dermatol* 1984; **10**: 1068-9.
2. Mullan E, Helmck F. Granuloma annulare: An immunohistochemical study. *J Cutan Pathol* 1994; **21**: 135-7.
3. Mark VD. Granuloma annulare. In: Freedberg IM, Eisen AZ, Wolff K *et al.*, eds. *Dermatology in General Medicine*, 5<sup>th</sup> edn. New York: McGraw-Hill; 1999. p. 1152-6.

## News

### National events

2004

*December 9-12, 2004*

**Silver Jubilee Conference of Pakistan Association of Dermatologists, Karachi.**  
Organizing Chairman: Dr. Khurshid H. Alvi, Suite No. 11, 3<sup>rd</sup> Floor, Taj Medical Complex, M.A. Jinnah Road, Karachi, 74400 Pakistan  
Tel: +92 21 7789666  
Fax: +92 21 7789677  
E-mail: [silver@pad.org.pk](mailto:silver@pad.org.pk)  
[info@pad.org.pk](mailto:info@pad.org.pk)  
Website: [www.pad.org.pk](http://www.pad.org.pk)

#### **288th Free Skin Camp, Kot Ghulam Muhammaad City, District Mirpur Khas: 28<sup>th</sup> December, 2003.**

In collaboration with Sindh Graduates Association, district Mirpur Khas, Welfare Association for Dermatological Patients (WADeP) arranged its 288th Free Skin Camp at Government Main Primary School, Kot Ghulam Muhammad, on 28<sup>th</sup> December, 2003. A total of 1031 patients from different areas of Mirpur Khas and Thar districts visited the camp. Patients were provided free consultation and medicaments.

#### **290th Free Skin Camp, Badin City, District Badin 4<sup>th</sup> January, 2004**

In collaboration with Roshan Memorial trust, Mehrabpur, Welfare Association for Dermatological Patients (WADeP) arranged its 290th Free Skin Camp at Dada Adam Government School, Mehrabpur, district Naushahro Feroze on 4<sup>th</sup> January, 2004. A total of 2281 patients from different areas of Nawabshah, Khairpur and Nausharo Feroze districts visited the camp. Patients were provided free consultation and medicaments.

### International events

2004

*May 15-18*

**ISD Regional Meeting**  
Dermatology and Dermato-Cosmetology Congress  
Secretariat Office  
c/o Skin and Allergy Centre  
540 3<sup>rd</sup> Floor Mercury Tower  
Ploenchit Road  
Patumwan, Bangkok 10330  
Thailand  
Tel: 662 658 5885  
Fax: 662 658 5884 or 662 433 7923  
E-mail: [thadapiam@thaicosderm.org](mailto:thadapiam@thaicosderm.org)

*May 19-22*

**IX ISD International Congress on Dermatology, Beijing, China**  
Contact: International Congress Secretariat  
Tel: +86 10 6524 9989 ext 1606  
Fax: + 86 10 6512 3754  
E-mail: [icd2004@chinamed.com.cn](mailto:icd2004@chinamed.com.cn)

*November 17-21*

**13<sup>th</sup> Congress of the European Academy of Dermatology and Venereology**  
Contact: Torello M. Lotti, Florence, Italy  
E-mail: [president@eadv2004.org](mailto:president@eadv2004.org) or  
[info@eadv2004.org](mailto:info@eadv2004.org)

2005

*October 12-15*

**European Academy of Dermatology and Venereology Congress (EADV)**  
London, UK  
Contact: Marilyn Benham  
Tel: 020 7383 0266  
E-mail: [eadv@bad.org.uk](mailto:eadv@bad.org.uk)  
[www.eadv.org](http://www.eadv.org)

# Measures taken by health authorities for eradication of leishmaniasis in Larkana region

## **Farooq Rahman Soomro**

Focal Person for Leishmaniasis, AIDS/ HIV Office of the Executive District Officer (Health), In charge, Leprosy-cum-Health Education Cell, Chandka Medical College Hospital, Larkana

### **About Larkana Region**

Larkana district comprises of seven talukas namely Larkana, Ratiodaro, Miro Khan, Shahdad Kot, Kamber, Warah and Dorkri. It covers an area of 7432 km<sup>2</sup>. The population of the district is 2.1 millions. Main crops are rice, sugarcane, and wheat. The climate of the region is hot in summer (33-48°C) and moderate in winter (11-21°C). Geographically, the district is divided into three tracts i.e. Kohistan, Central Canal and Eastern Tract.

### **About Leishmaniasis**

Leishmaniasis is an infectious skin disease, which occurs due to the bite of sand fly. The bite produces a hard boil on the skin which turns into a wound. The parasite of the leishmaniasis is found in rats, squirrels, mongooses, dogs and cats. When a rodent dies, sand flies consume its blood harboring the parasites of leishmaniasis and transmit it to the human being through subsequent bites. The sand fly emerges from its habitat in summer, particularly in August and goes into hibernation in the winter to lay eggs and breed, to reappear in February. These flies only appear after sunset from their inhabitation/holes and crevices of the

muddy houses. In the wake of the war in Afghanistan (which is part of the leishmaniasis belt in Asia), the migration of Afghan refugees into Pakistan led to introduction of this skin disease. The hilly areas of Larkana district i.e. Warah, Kamber and Shahdad Kot talukas, bordering with Baluchistan and Kheirthir mountains range fell a victim to the disease from February, 2001 onwards.

### **Measures taken by Health Department**

The disease was brought to the notice of Local Health Authorities in the month of February, 2001 when cases of infected wounds were reported from village Sono Khan Chandio, about 75 kilometer from Larkana city. A team of doctors comprising of Dr. Farooq Rahman Soomro (dermatologist) and Dr. Guhlam Murtaza Pathan (Assistant Professor Pathology and expert in parasitology) was sent to the affected area to diagnose a mysterious disease characterized by nonhealing wound refractory to various ointments and antibiotics. 350 patients were tested, out of which 130 cases were confirmed to have leishmaniasis and request was made to the government to arrange 3000 ampoules of injection meglumine antimonate in order to combat this infectious disease. In

addition, a “Leishmaniasis Treatment Cell” was also established in the Leprosy Cell of Chandka Medical College, Larkana.

In the month of April 2001, 3000 ampoules of injection meglumine antimonate were provided by the National Institute of Health, Islamabad, which were administered to patients along with medicated soaps, ointments and antibiotics. After these efforts leishmaniasis was brought under control.

With the cooperation of various NGOs, media and prominent figures of the area, lectures on all aspects of the disease as well as preventive steps that needed to be taken to eradicate the disease were delivered. The main focus was to create awareness amongst people as to how sand flies transmit leishmaniasis from rats, squirrels, mongooses and other rodents, which must be killed to get rid of the disease.

In the month of January, 2002 outbreak of leishmaniasis was reported again. One-day workshop was conducted by WHO at Executive District Officer (EDO), Health Department, Larkana to evaluate the strategy. Afterwards following activities took place:

1. Seven-days detailed survey was carried out in order to collect data base in affected areas of Dadu and Larkana districts from 4<sup>th</sup> to 9<sup>th</sup> February, 2002.
2. 2500 cases of active disease were detected and treated.
3. In March, 2002, WHO conducted a training programme on the treatment of leishmaniasis treatment at EDO (Health) Office, Larkana and a WHO team visited the affected area.
4. 2340 ampoules of injection meglumine antimonate were provided by Health Department of Government of Sindh in the month of March, 2002.
5. 2000 vials of injection meglumine antimonate were provided by WHO in the month of March, 2002.
6. 1000 vials of injection sodium stibogluconate were provided by WHO.
7. The doctors along with field staff reached the affected area and accorded treatment. Some areas were provided with special medicated soaps, ointments and antibiotics in case they developed symptoms. Besides these, arrangements were made to spray the area to eradicate the flies.
8. In the month of April, 2002, one day workshop was held by WHO to share the experience.
9. WHO team arrived to analyze the disease, (Dr. P. Dsjus, Focal Person WHO Headquarter, Dr. Riadh Bin Ismail, WHO EMRO, Dr. Abraham Manzava, WHO EMRO).
10. 2000 vials of injection sodium stibogluconate provided by WHO were utilized on patients.
11. In the month of October, 2002, National Agriculture Research Council and National Agriculture Research Institute were approached to pesticide the rodents. In addition, WHO representatives in Islamabad were also approached to provide specific drugs for leishmaniasis.
12. In the month of January, 2003, a three-member Japanese team of Medical experts completed its initial study regarding spread of leishmaniasis in Larkana district and promised to launch a four year project for research and control of disease, which had severely affected the rural areas of the district. Again from 13<sup>th</sup> to 25<sup>th</sup> December research was conducted on various aspects of disease. Karachi

University (H.E.J. Institute of Chemistry) and Gomal University (Pharmacy Department, Dera Ismail Khan) are also contributing towards the leishmaniasis control research.

## CONCLUSION

To combat leishmaniasis epidemic in the Larkana region, a multidisciplinary approach was launched. The role played by different agencies is shown in **Table 1**. In order to keep the treatment programme manageable Health outlets in each talukas of affected area and Leprosy Cell of CMCH, Larkana are functioning. Currently 10 to 15 cases of leishmaniasis are diagnosed at Leprosy Cell and 5-10 cases at Leprosy Cell and 5-10 cases are diagnosed at Taluka Hospitals by Dr. Farooq Rahman Soomro on daily basis.

**Table 1** Role played by different agencies.

<i>Control measures</i>	<i>Action to be taken by</i>
Insecticidal focal spray	Health department Government of Sindh
Bed nets (Insecticidal)	Health Department, Federal Government
Killing of Rodents	Agriculture Department
Arrangements of specific medicine	Health Department Government of Sindh
Initiation of preventive phase	WHO

# Information for Authors

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The JPAD agrees to accept manuscripts prepared in accordance with the "Uniform Requirements for Manuscript Submission to the Biomedical Journals" approved by the International Committee of Medical Journals Editors. Three copies of all material for publication should be sent to Dr. Ijaz Hussain, Editor, JPAD, Department of Dermatology, Mayo Hospital, Lahore, e-mail:

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In addition to the hard copy, an exact copy of the manuscript, containing all parts of the paper, must be submitted on high-density disk. The editor reserves the right to make corrections, both literary and technical, to the papers. Papers received are supposed to have been submitted exclusively to the *Journal of Pakistan Association of Dermatologists* and all authors must give a signed consent to publication in a letter sent with the manuscript. Authorship implies a significant contribution. In case of clinical trials, the names of pharmaceutical sponsors should be mentioned.

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JPAD welcomes original and review articles, case reports, quizzes, items of correspondence etc. addressing any aspect of dermatology.

The original article should be of about 2000 words, with no more than 6 tables or illustrations. Letters should not normally exceed 400 words and have more than 10 references.

## Parts of the paper

The manuscript should be prepared as below.

**Title:** In addition to the full title of the paper, a short version not more than 50 characters, for a running head, be provided.

**Author(s) details:** Name(s) of the author(s) should be given as initial(s) followed by surnames, and should be clearly linked to the respective addresses by the use of symbols e.g. \*, †, ‡ etc.

**Abstract:** All articles other than correspondence should have an abstract. The original articles should have a structured abstract comprising of 4 subheadings: background, methods, results and conclusions. Keywords ≤ 5 should be provided to aid indexing.

**Main text:** The main text should appear in the following sequence: introduction, methods, results, discussion, acknowledgments, references, tables and

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## References

Only papers closely relevant to the author's work should be referred to. References should be in the Vancouver style i.e. references should be written as unbracketed superscript numbers in the order in which they appear in the text e.g. 'our previous reports<sup>1</sup> and that of Cohen *et al.*<sup>2</sup>....'. At the end of the article, references should give the name(s) and initials of author(s). If there are more than four authors, include the first three authors followed by *et al.*, title of paper, title of the journal abbreviated in the standard manner (as published in the *Index Medicus*), year of publication, volume number, and first and final numbers of the article, e.g. Grattan C, Powell S, Humphreys F. Management and diagnostic guidelines for urticaria and angio-oedema. *Br J Dermatol* 2001; 144: 708-14. References to books should give the name(s) followed by initials of author(s) or editor(s), chapter (if relevant), book title, edition, place, publisher, year, and pages referred to e.g. Friedman WF, Child JS. Congenital heart disease in the adult. In: Fauci AS, Braunwald E, Isselbacher KJ *et al.*, editors. *Harrison's principles of internal medicine*. 14<sup>th</sup> edn. New York: McGraw-Hill; 1998. p. 1300-9.

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## Illustrations

Three sets of illustrations should be sent with each manuscript. Illustrations should be referred to in the text as 'Figures' and be given Arabic numbers. Each figure should be marked on the back with the name of the author(s), the title of the paper and the reference number used in the text. Orientation of the illustration should be indicated by marking the top with arrow. Photographs should be unmarked glossy prints. Diagrams should be on separate sheets and a legend should be provided for each illustration.

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Page proofs will be sent, without the original manuscript, to the corresponding author for proof correction and should be returned to the editor within three days. Major alterations from the text cannot be accepted. Any alterations should be marked, preferably in red



