

# Systemic skin whitening/lightening agents: What is the evidence?

*Munisamy Malathi, Devinder M. Thappa*

## INTRODUCTION

The human skin color is one of the most perceptible phenotypic variations among humans and is determined primarily by the type and amount of melanin synthesized within melanosomes and the pattern of melanosome distribution within the melanocytes. Getting a lighter skin tone always draws a lot of interest, as for centuries, fair or light skin color has been a symbol of prominence, superiority and higher social ranking. In India, attitudes towards skin color have developed over more than 2000 years and reflect considerations of class and caste. Women especially Asian women are obsessed with fair skin and they would go to the ends of the earth to lighten their skin color as in most cases their marriage prospects or career opportunities are dominated by the hue of their skin. Hence, skin whitening products are a half a billion dollar industry today capitalizing on the insecurity of these individuals and currently, skin lightening is one of the most common forms of potentially harmful body modification practices in the world.

A host of skin lightening agents are available in dermatology and cosmetic market and newer agents

are continuing to be introduced. A lot is known about topical skin whitening agents, but systemic skin whitening agents which are slowly gaining popularity do not have much evidence to their credit in the scientific literature. In this article, we have addressed the issues related to the use of these systemic skin whitening agents.

An overview of the pathway of melanin synthesis and the site of action of the most commonly used systemic skin whitening agent (glutathione [GSH]) is depicted in Figure 1. The mechanisms governing pheomelanin to eumelanin balance are dependent on L-cysteine, GSH and tyrosinase related protein expression. Thus, as observed in the figure, the switching from eumelanogenesis to pheomelanogenesis can be influenced by modifying the ratio between cysteine and GSH levels. Pheomelanogenesis preferentially proceeds under conditions of high cysteine concentrations and low tyrosinase activity.<sup>[1]</sup>

## SYSTEMIC SKIN WHITENING AGENTS AVAILABLE IN THE MARKET

### GSH

The most commonly used systemic skin whitening agent is GSH used alone or in various combinations, both as oral and intravenous formulations. GSH is an antioxidant synthesized in all mammalian cells from three amino acids-glutamate, cysteine, and glycine. It is also available naturally in watermelon, avocado, broccoli, spinach and tomatoes. GSH exists in cells mostly in the reduced form (GSH) which is constantly oxidized forming oxidized GSH and its supply is replenished by the action of GSH reductase. GSH is involved in various biochemical processes especially those involving scavenging of free radicals and detoxification of toxic compounds, it acts as coenzyme and helps in the transport of amino acids across the cell membranes.<sup>[1]</sup> Lower GSH levels are implicated in many diseases and GSH

Department of Dermatology and STD, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India

**Address for correspondence:** Dr. Devinder M. Thappa, Department of Dermatology and STD, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry - 605 006, India. E-mail: dmthappa@gmail.com

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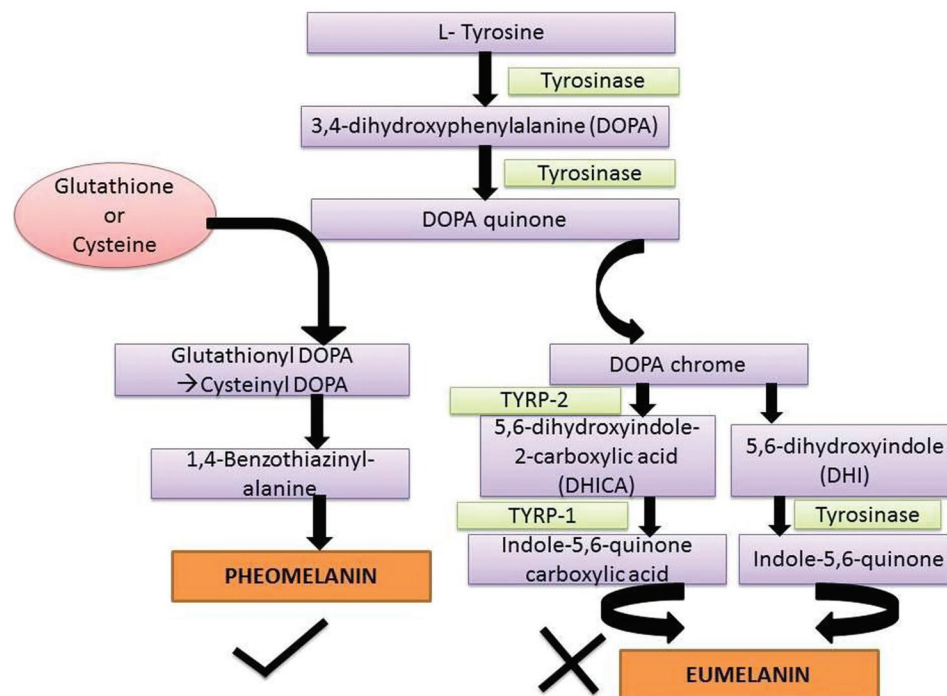
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**Figure 1: The pathway of melanin synthesis and the site of action of glutathione and cysteine, shifting the balance towards pheomelanin synthesis**

has been tried in the management of Alzheimer's disease, Parkinson's disease, multiple sclerosis, alcoholic hepatitis, atherosclerosis, acquired immunodeficiency syndrome, and chronic fatigue syndrome. It has been commonly used to combat the neuro- and nephrotoxicity associated with cisplatin chemotherapy<sup>[2]</sup> and this is the only Food and Drug Administration (FDA) approved indication for the intravenous form of GSH. The role of GSH as a skin whitening agent was an accidental discovery when skin whitening was noticed as a side effect of large doses of GSH. This led to extensive studies establishing its role in melanogenesis and the recent use of GSH as systemic skin whitening agent.

GSH exerts its action as skin whitening agent at various levels of melanogenesis which include the following:<sup>[1,3]</sup>

- Interference with cellular transport of tyrosinase
- Direct inactivation of the enzyme tyrosinase by binding with the copper-containing active site of the enzyme
- Mediating the switch mechanism from eumelanin to pheomelanin production as GSH is the major physiologic reservoir of cysteine and increase in cysteine levels results in switching of eumelanogenesis to pheomelanogenesis [Figure 1]

- Quenching of free radicals and peroxides that contribute to tyrosinase activation and melanin formation
- Modulation of depigmenting abilities of melanocytotoxic agents.

GSH for skin whitening is available in both tablet and injectable form. When taken orally, GSH is hydrolyzed by intestinal and hepatic gamma-glutamyl transferase resulting in reduced bioavailability. Even when large oral doses were administered, it was found that most of the absorbed GSH remains within the gut luminal cells and only small and transient increases of GSH could be detected in the general circulation.<sup>[4]</sup> Thus, the effectiveness of exogenously administered GSH is hindered by its instability when crossing cell membranes and its rapid hydrolysis in the circulation by gamma-glutamyltranspeptidase found on the extracellular surfaces of cells.<sup>[5]</sup> On the contrary, intravenous GSH delivers very high doses directly into the systemic circulation, overloading the renal circulation.

Oral GSH is in the "generally regarded as safe" category of FDA and is usually marketed as a food or dietary supplement and hence it does not certainly need to be FDA or Bureau of Food and Drug (BFAD) approved. There are no provisions in the law for FDA to approve

dietary supplements for effectiveness before they reach the consumer. However, FDA has banned the use of intravenous form of GSH for skin whitening in view of commonly reported side effects like skin rashes, Stevens Johnson syndrome, toxic epidermal necrolysis, derangement in thyroid and renal function and severe abdominal pain.<sup>[6]</sup>

Till date there is only one study published in English literature assessing the safety and efficacy of oral GSH as a skin whitening agent.<sup>[3]</sup> It was a randomized, double-blind, two-arm, placebo-controlled study conducted on 60 medical students in Thailand. They found 500 mg/day orally administered GSH, for 4 weeks to cause significant skin whitening when compared to placebo and they observed no significant adverse events. However, there were many flaws in the study-plasma GSH levels were not measured (as bioavailability of oral GSH is low), limited study period of 4 weeks, no follow-up to determine when the skin melanin indices return to their baseline values, medical students were chosen (young, otherwise healthy population) and the study was conducted during their college time to ensure that sun exposures were minimal. Hence, the results may be applicable to only young, otherwise healthy Asian individuals.

The promoters of GSH promote it at a dose of 20 and 40 mg/kg/body weight/day which is divided into two doses with a maintenance dose of 500 mg/day.<sup>[7]</sup> They claim that gradual systemic effect will be seen 1-3 months in medium brown skin, in 3-6 months in dark brown skin, in 6-12 months in very dark skin and in 2 years are more in black skin. Injectable GSH is given at a dose of 900 mg weekly by intravenous or intramuscular method and the sessions can be repeated 2-3 times a week. They claim skin whitening to occur as early as 2-3 weeks.<sup>[7]</sup>

GSH is also combined with many other agents like vitamin C to increase its absorption, N-acetyl cysteine to boost its level, alpha lipoic acid and other antioxidants like vitamin E and grape seed extract. Some oral preparations have dangerous combinations like monobenzone which causes irreversible depigmentation and hydroquinone which is banned by FDA as a carcinogen.<sup>[8]</sup>

### L-cysteine peptide

Another agent promoted for skin whitening is L-cysteine peptide, which is claimed to be 3-5 times more potent

than GSH and is BFAD approved.<sup>[9]</sup> Natural sources of L-cysteine include poultry, yogurt, egg yolks, red peppers, garlic, onions, broccoli, Brussel sprouts, oats, and wheat germ. L-cysteine along with L-glutamic acid and glycine is the rate-limiting precursor in the synthesis of GSH peroxidase and has been found that high concentrations of L-cysteine reduced the tyrosinase activity and produced more pheomelanin by way of cysteinyl dihydroxyphenylalanine (DOPA), the building block of pheomelanin [Figure 1]. The cysteinyl DOPAs can be formed in two ways-directly by nucleophilic addition of cysteine to DOPA quinone or indirectly from GSH DOPA by action of gamma-glutamyl transferase and peptidase.<sup>[10-12]</sup> Hence L-cysteine peptide is promoted as skin whitening agent but without much scientific evidence to support its use for this indication.

### Tranexemic acid

Tranexemic acid (trans-4-aminomethyl cyclohexane carboxylic acid), a plasmin inhibitor, commonly used as a haemostatic agent owing to its antifibrolytic action is also promoted as a systemic skin whitening agent especially as oral or intradermal injections for melasma. The skin whitening effects of tranexemic acid was incidentally found when it was used in the treatment of aneurysmal subarachnoid hemorrhage. It is a synthetic derivative of lysine and its therapeutic role in melasma was first studied by Nijor as early as in 1979, but only limited data exist in the literature regarding its use in melasma. Plasmin, is a protease that enhances the intracellular release of arachidonic acid, a precursor of prostanoid, and also elevates alpha-melanocyte stimulating hormone ( $\alpha$ -MSH) processed from pro-opio-melanocortin. Both arachidonic acid and  $\alpha$ -MSH can activate melanin synthesis by melanocytes. Tranexemic acid by way of its antiplasmin activity depletes the keratinocyte pool of arachidonic acid involved in ultraviolet (UV) induced melanogenesis.<sup>[13-17]</sup>

It has been used at a low dose of 250 mg twice a day for at least 3 months for the treatment of melasma and found to be effective.<sup>[15]</sup> But, it is not safe to use it for a long duration in view of its anti-hemorrhagic property resulting in side effects like venous thromboembolism, myocardial infarction, cerebrovascular accidents and pulmonary embolism. It is contraindicated in patients with acquired defective color vision, an active intravascular clotting condition, and hypersensitivity to tranexemic acid.<sup>[15]</sup> However, there is no scientific

data available demonstrating the role of tranexemic acid as an overall skin whitening/lightening agent. It is even being promoted as intravenous injection for skin whitening at a dose of 500 mg every week for 1 or 2 months and 500 mg every month for maintenance.<sup>[18]</sup> Tranexamic acid has been found to produce good synergistic effect when combined with ascorbic acid or its derivatives and L-cysteine.<sup>[17]</sup>

### Miscellaneous agents

Apart from these, large doses of vitamin C, hyaluronic acid, epidermal growth factor and combinations of multiple natural extracts (natural collagen extracts, bearberry extract, Glycyrrhiza glabra extract, Lycopene, Kelp, olive leaf extract, hawthorn, jujube, sea buckthorn, starch, coix seed, pearl extracts, etc.) are also promoted for skin whitening in the form of food or dietary supplements with no scientific evidence.

Nevertheless, there are few animal studies and *in vitro* studies demonstrating the role of natural extracts like irradiated green tea polyphenol,<sup>[19]</sup> proanthocyanidin-rich extract from grape seeds,<sup>[20]</sup> ellagic acid-rich pomegranate extract,<sup>[21]</sup> and coumarin extracts from the plant *Angelica dahurica*,<sup>[22]</sup> in inhibiting melanogenesis resulting in skin whitening thereby recommending these agents as oral preparations for skin whitening. Procyanidins (pycnogenol, grape seed extracts) and *Polypodium leucotomos* have been found to be effective and safe in the treatment of melasma and to prevent UV A induced pigmentary changes respectively.<sup>[23]</sup> But there are no trials demonstrating their efficacy in the treatment of post inflammatory pigmentation or in improving the general skin color.

### THE SCENARIO IN INDIA

In India, GSH is available as Dr. James GSH whitening pills<sup>[24]</sup> which contains 100% natural pure GSH with alpha T-acids costing 3500/- rupees for 60 capsules of 1000 mg, I-Fair tablets<sup>[25]</sup> which contains GSH in combination with vitamin C, vitamin E, grape seed extract, alpha lipoic acid, and glutathione 900 skin whitening injections<sup>[10]</sup> which contains GSH with vitamin C and collagen. These agents are being advertised in the internet and currently there are no market data available on the use of these agents by Indians. As mentioned in the introduction, most of Indian women's marriage prospects are dominated by skin color paving way for irrational use of these agents by these women and may result in untoward effects.

Hence, well conducted studies, establishing the role of these agents in skin whitening and documenting adverse events is the need of the hour.

### PROBLEMS WITH SYSTEMIC SKIN WHITENING AGENTS

As already mentioned above, these agents are not FDA approved for skin whitening and no scientific evidence exists for their use. In addition, the injectable formulations are counterfeited and given by untrained people illegally and hence associated with the risk of sepsis, air embolism, transmission of human immunodeficiency virus, Hepatitis B, and use of non-sterile preparations that can lead to serious infections.

Another major question that remains unanswered as yet is that whether switching the normal machinery from eumelanin (which is protective against UV radiation) to pheomelanin (which photosensitizes UV-induced deoxyribonucleic acid damage as observed in cultured human melanocytes) by an external agent for long duration would result in an increased incidence of skin cancers.<sup>[26,27]</sup>

As a general rule, the promoters of the systemic skin whitening agents list lactation, heart disease and hypersensitivity as contraindications for all these agents. Since there are not much human or animal studies advocating the role of these agents in skin whitening, there is no data on the relative and absolute contraindications, the appropriate dosing schedule and the long term side effects.

### ECONOMIC CONSIDERATIONS

In India, the dermatology market is worth 1642 crore rupees (\$ 410 million) and fairness-directed skin lightening cosmetic market (which are considered as "fast moving consumer goods") is 1000 crore (\$ 250 million) resulting in a staggering 61% of the total dermatology market.<sup>[28]</sup> Companies manufacturing skin lightening products take advantage of the lax advertising laws and make unsubstantiated claims about their efficacy taking a horrendous toll on the consumers. The high-end skin whitening products are often labeled under the new quasi-pharmaceutical category called cosmeceuticals – a hybrid entity with pharmaceutical and cosmetic properties. This ambiguous labeling strategy allows promoters of high-end skin whitening and anti-aging products to make both pharmaceutical

and cosmetic claims. The marketing trends are designed in such a way so as to blur the lines between cosmetics and food categories and food and pharmaceutical categories, thereby helping in evading the regulatory constraints for these products, eventually enticing more consumers to consume these relatively expensive and poorly regulated products. Thus, their claims can neither be independently verified, nor can potential risks to consumers be assessed.<sup>[29]</sup>

## CONCLUSION

The desire for white and fair skin is a global phenomenon and it is being highly capitalized by both the cosmetic and dermatologic industries. It is an essential role of the dermatologist to make the public aware that skin lightening agents may progressively revert back the facultative color to the constitutive level and normally this color change will not go beyond the constitutive level. If such a change is claimed, it should be considered to be dangerous as such alterations can become non-reversible resulting in vitiligo and may also predispose to other complications like skin cancer as the normal biochemical processes are altered. Till date, systemic skin whitening agents do not have much scientific evidence regarding their use and strict laws should be enforced to ban the use of these agents until well conducted randomized controlled trials are available ensuring the safety and efficacy of these agents.

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## Quiz

# Painless dells on the cheek

A 30-year-old woman presented with a 15-year history of two asymptomatic dells on her right cheek. There was no history of preceding acne or inflammatory skin disease.

Dermatologic examination revealed two 0.5 cm and 0.3 cm-sized, sharply-demarcated, skin-colored papules with cup-shaped central depressions, located on the zygomatic [Figure 1] and mandibular regions of the right cheek. On close inspection, follicular plugging was evident.

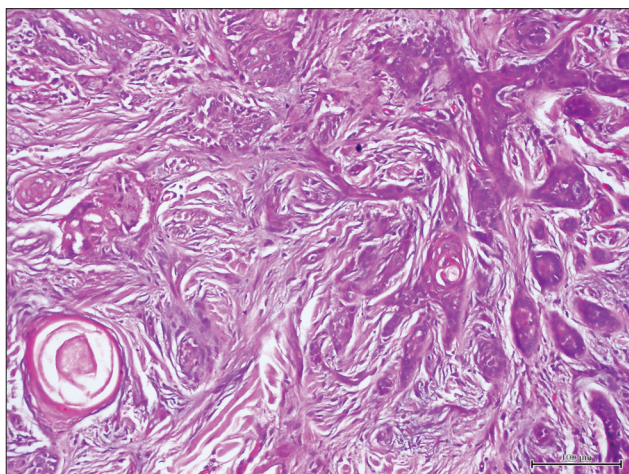
Histopathological examination displayed a partially well-circumscribed tumor in the dermis with an overlying sharp depression. The tumor was composed

of small cords and islands of basaloid cells that showed connection to the follicular infundibulum. Tumor strands were surrounded by a desmoplastic fibrous stroma [Figures 2 and 3]. Several keratinous cysts and foci of dystrophic calcification were also noted. Immunohistochemically, the tumor cells stained positive with anti-pancytokeratin (CK), anti-CK15 and negative with anti-carcinoembryonic antigen (CEA), anti-CK7 and anti-epithelial membrane antigen antibodies. The tumor was focally immunopositive for CK20 antibody, indicating the presence of scattered Merkel cells.

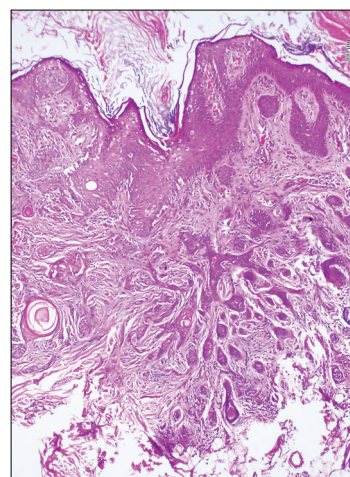
## WHAT IS YOUR DIAGNOSIS?



**Figure 1: A well-circumscribed umbilicated patch on the right zygomatic region**



**Figure 3: Closer view of Figure 2 (H and E, x200)**



**Figure 2: Thin cords and islands of basaloid cells in a dense fibrous stroma (H and E, x100)**

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**Answer****Diagnosis: Desmoplastic trichoepithelioma****DISCUSSION**

Desmoplastic trichoepithelioma (DTE) is a rarely encountered benign adnexal tumor with an estimated incidence of 2 in 10,000 skin biopsies.<sup>[1,2]</sup> The age range varies from 0 to 80. The lesion usually develops on the face of a young woman (71-85%).<sup>[2]</sup> The cheek is the most frequent site of affection (50%).<sup>[1-3]</sup> There is a propensity for DTE development on the right side of the face.<sup>[2]</sup> DTE presents as an asymptomatic, solitary, annular, firm, white to yellowish papule or as a sclerotic plaque smaller than 2 cm. The lesion has a thread-like raised and rolled border and a non-ulcerated central dell.<sup>[1,2]</sup> The clinical appearance may be reminiscent of basal cell carcinoma (BCC).

The histologic portrait in previous reports encompasses narrow strands of basaloid cells, keratinous cysts and desmoplastic stroma.<sup>[2]</sup> The well-demarcated solid tumor is situated symmetrically within the papillary and reticular dermis.<sup>[2,3]</sup> Small basaloid cells with prominent oval nuclei and scant cytoplasm are arranged in slender strands containing one to three rows of cells. There is often a focal connection to the overlying epidermis through the follicular infundibulum. The stroma surrounding the strands of basaloid cells consists of ample homogeneous eosinophilic collagen and multiple horn cysts. There is no cleft between the nests of tumor cells and sclerotic stroma. While palisading is lacking, epidermal hyperplasia may be noted.<sup>[2]</sup> Foreign body granulomas from broken cysts, areas of calcification or ossification might be observed.<sup>[2,4]</sup>

The list of differential diagnostic considerations embraces trichoadenoma, trichoepithelioma, syringoma, sebaceous hyperplasia, granuloma annulare, BCC, microcystic adnexal carcinoma and squamous cell carcinoma.<sup>[2]</sup> Differentiation from morphea-like BCC may be extremely difficult, especially when a lesion is sampled only in part. Immunohistochemical markers may help the pathologist to distinguish DTE and morphea-like BCC. In particular, identification of CK20-positive Merkel cells within the lesion, the presence of CK15 expression in tumoral cells and CD34 expression in peritumoral stroma, along with the absence of CEA androgen receptor and

Periodic Acid-Schiff (PAS) expressions may support a diagnosis of DTE and vice versa.<sup>[2-4]</sup> So far, CK20 is the most reliable immunohistochemical marker in differentiating DTE from morphea-like BCC.<sup>[4]</sup> However, CK 20 expression in DTEs may be focal.<sup>[2-4]</sup>

Once the diagnosis is established, DTE may be clinically followed-up with an expectant policy.<sup>[1]</sup> Cryotherapy, dermabrasion or laser surgery may pose risks of recurrence and/or scar formation. Imiquimod has been used in two cases as an adjunctive therapeutic measure, but without apparent benefit.<sup>[5]</sup> In equivocal cases, the best treatment is complete surgical excision.<sup>[1]</sup> If there is a consideration of microcystic adnexal carcinoma or morphea-like BCC or if tissue preservation is crucial, Mohs micrographic surgery may be recommended.<sup>[1,2]</sup>

**Deniz Duman, Emel Öztürk Durmaz,  
Emel D. Çetin<sup>1</sup>, Şükrü Yazar<sup>2</sup>, Sedef Şahin**

Departments of Dermatology, <sup>1</sup>Pathology, and <sup>2</sup>Plastic, Reconstructive and Aesthetic Surgery, Acibadem University School of Medicine, Istanbul, Turkey

**Address for correspondence:** Dr. Emel Öztürk Durmaz,  
Acibadem Maslak Hospital, Büyükdere Caddesi 40,  
Maslak 34457, Istanbul, Turkey.  
E-mail: emelerkek@yahoo.com

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## Net Letter 1

## Are dermatologists familiar with acronyms?

*Marković Milica, Ivanović Branislav<sup>1</sup>, Bjekić Milan, Sipetic Sandra<sup>2</sup>*City Institute for Skin and Venereal Diseases, Belgrade, <sup>1</sup>Faculty of Philology, Belgrade University, Belgrade, <sup>2</sup>Institute of Epidemiology, School of Medicine, Belgrade, Serbia

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## Net Letter 2

## Familial congenital generalized hypertrichosis

*Neerja Goel, Shalini Rajaram, Bindiya Gupta, Kanika Gupta*

Department of Obstetrics and Gynecology, UCMS and GTB Hospital, Dilshad Garden, Delhi, India

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## Net Letter 3

## Eosinophilic panniculitis after subcutaneous administration of sodium heparin

*Ana Batalla, Elena Rosón, Celia Posada, Ángeles Flórez*

Department of Dermatology, Pontevedra Hospital Complex, Pontevedra, Spain

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## Net Letter 4

## De Sanctis-Cacchione syndrome

*Hema Mittal, Sumit Mehndiratta<sup>1</sup>, Jaya Shankar Kaushik, Tushar Godbole*Department of Pediatrics, UCMS and GTB Hospital, <sup>1</sup>Lok Nayak Hospital, New Delhi, India

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## Net Quiz

## Erythematous indurated plaque lesions on the breast

*Bilge Bülbül Şen, Emine Nur Rifaioğlu, Özlem Ekiz, Tümay Özgür<sup>1</sup>, Seçkin Akkücü<sup>2</sup>, Mehmet Uğur İnan, Asena Çiğdem Doğramacı*Departments of Dermatology, <sup>1</sup>Pathology, <sup>2</sup>General Surgery, Mustafa Kemal University School of Medicine, Hatay, Turkey

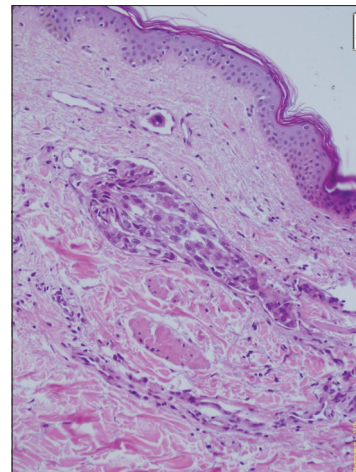
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A 50-year-old female patient, who had retraction of the right nipple for 2 years and erythema in the same breast for 2 months, was referred to our clinic. Mammography and breast ultrasonography performed at the time of onset of nipple retraction were normal. Dermatological examination revealed three erythematous, mildly indurated plaque lesions on the right breast, one of which involved the areola [Figure 1]. The nipple was retracted. The patient had no subjective complaints. The right axillary examination detected several lymphadenopathies, as confirmed by ultrasonography. The histopathological examination of the skin biopsy revealed islands of tumor cells in the dermal lymphatics [Figure 2]. These infiltrations consisted of round-shaped atypical cells with vesiculated nuclei and marked nucleoli. In immunohistochemical studies, strong positive staining by low-molecular weight keratin (LMWCK) and epithelial membrane antigen (EMA) and non-specific staining by vimentin have been detected.

### WHAT IS YOUR DIAGNOSIS?



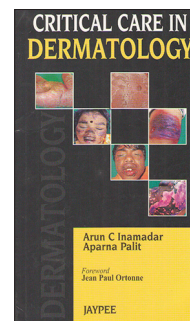
**Figure 1:** Three erythematous plaques on the right breast, one involving the areola



**Figure 2:** Tumor islands consisted of atypical epithelial cells in the lymphatics (H and E, x200)

## Critical Care in Dermatology

**Editors:** Arun C Inamadar and Aparna Palit  
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The book “Critical Care in Dermatology” by Inamadar and Palit is a valuable addition in critical care practice of Dermatology as an easy and handy document. It has a good description of common, uncommon, and rare dermatological emergencies which Dermatologists encounter in their clinical practice. There is a detailed description of each dermatological emergency: how to recognize it; how to assess the severity and details of management. It also gives a good overview of general measures in the management of these emergent situations, which are of critical importance. There is a full chapter dedicated to Fluid, Electrolyte and Nutrition Therapy which is often a challenge for Dermatologists, since many are not familiar with the finer details of these therapies and the detail of the monitoring techniques and procedures during the management of these emergencies. The book also describes sample collection methods from different sites in critically ill patients for appropriate diagnosis and management. The issue of nursing care in Dermatological emergencies, which is an over-sighted aspect in the management of such emergent situations, has been well emphasized and appropriately detailed. The concept of Dermatological Intensive Care Unit is well highlighted in the book with details of necessary equipments needed for such set-up. A dedicated chapter on the Drugs used in Dermatological Emergencies would also be handy for treating physicians, to critically review the different aspects of the drugs including doses, adverse effects, drug interactions etc., Authors have also included a chapter on Drug Therapy in patients with renal and hepatic impairment which may at times be the situations in these patients. A chapter on Drugs in Pregnancy and Lactation appears to be an unnecessary avoidable intrusion in the book. More appropriate would have been the inclusion of management of Dermatological Emergencies in Pregnant and Lactating women which may at times be complex and challenging. At places in the texts, the sentences

are incomplete, lack systematic presentation, and flow. The text matter at places is disjointed. Also there is repetition of texts at different places which could have been avoided. The skin biopsy has often been mentioned as a rapid diagnostic technique which at many centers is often not available for such purpose and there are no histopathological details of the various conditions where biopsy has been recommended or mentioned, to be of help to diagnosis the condition. At places, the tables are appearing before the text which makes reading of the book uneasy. Sometimes, tables appear at different places then the texts, leaving the readers wonders as to why these could not have been placed close to the text. “Why a particular condition is an emergency” good for the beginners to recognize condition as an emergency and manage it appropriately.

Overall, the book may be of value to Dermatologists working in a hospital setting and for trainees. Reducing the number of tiny illustrations on the front page, avoiding shades of color on the top of each page and slightly larger font-size of the text could have made the book more reader friendly.

**Kaushal K. Verma**

Department of Dermatology and Venereology,  
 All India Institute of Medical Sciences, New Delhi - 110 029, India.  
 E-mail: prokverma@hotmail.com

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Seilding V, Hoffmann JH, Enk AH, Hadaschik EN. Analysis of high-dose intravenous immunoglobulin therapy in 16 patients with refractory autoimmune blistering skin disease: High efficacy and no serious adverse events. *Acta Dermato-Venereol* 2013;93:346-9.

High-dose intravenous immunoglobulin (IVIG) have been shown to be effective in treating severe autoimmune diseases that are refractory to standard immunosuppressive therapy. Although considered effective and safe in treating autoimmune blistering diseases, a clear evidence for its therapeutic effect besides case reports and case series is missing.

A retrospective analysis of 16 patients (10 patients with pemphigus vulgaris, 3 with pemphigus foliaceus, and one patient each with paraneoplastic pemphigus, bullous pemphigoid, and paraneoplastic bullous pemphigoid), refractory or relapsing disease under immunosuppressive combination therapy with at least two immunosuppressive drugs and who had received IVIG therapy for at least six full cycles, between January 2004 and July 2011 was done. The mean age and the mean duration from diagnosis to initiation of IVIG therapy was 50.4 years and 40.8 months, respectively. Patients had a mean of 2.9 immunosuppressive drugs prior to initiation of IVIG therapy. High-dose IVIG was administered at a total dose of 2 g/kg body weight intravenously per cycle over 2 days after ruling out the contraindications. Patients received IVIG every 4 weeks, and prior to discontinuation of IVIG the time between the cycles was extended to 5 or 6 weeks.

Efficacy of IVIG therapy was assessed with changes in skin symptoms, changes in autoantibody titers, and tapering of steroid dose. Laboratory blood tests including ant basement membrane antibodies and anti-intercellular epidermal antibodies were routinely performed. To measure efficacy of IVIG therapy, a score for each 6 months during the total period of 24 months was used:

- (Very good) – no skin symptoms; autoantibody titer: No change or lower titer,

- (Good) – skin symptoms ameliorated; autoantibody titer: No change or lower titer,
- (Satisfactory) – skin symptoms unchanged; autoantibody titer: No change or higher titer,
- (Unsatisfactory) – skin symptoms deteriorated; autoantibody titer: No change or higher titer.

By the end of the 24-month observational period, most of the patients were still receiving IVIG. The mean total number of cycles per patient was 38.6. Adverse events were recorded in 87.5% of patients and in 56.3% of total infusion cycles. Headache (43.8%) and fatigue (43.8%) were the commonest side effects recorded. Only one patient reported petechiae after a single infusion cycle. Majority of patients had a very good score (43.8%, 75%, 61.5%, and 58.3%, respectively) in all of the four half-year periods. Also tapering of steroids up to a mean reduction of 75.8% in starting dose was possible without relapse in most patients.

**Comment:** IVIG is prepared from the pooled plasma of donors. Although initially used in the treatment of primary immunodeficiency syndromes, recently its use has been widely explored as an off-label indication in a variety of autoimmune and inflammatory conditions across multiple specialties.

Treatment of autoimmune bullous skin diseases can often be challenging. The treatment options primarily comprise systemic corticosteroids and a variety of immunosuppressants. Current treatment strategies are effective in most cases, but side effects of long-term immunosuppressive treatment are a limiting factor in some cases.

In addition, few patients fail to respond or experience frequent relapses. Some of the immunosuppressives have a long latency before benefit begins. The situation becomes all the more problematic in children for the fear of growth retardation. Secondary infection, which may be either systemic or localized to the skin, may

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occur because of the use of immunosuppressants and the presence of multiple erosions. Unlike most therapies for blistering disorders, IVIG is not immunosuppressive and has a favorable side effect profile.

This has allowed its use to expand dramatically over the past decade. It is generally accepted that the use of IVIG should be limited to patients who (1) fail conventional therapy; (2) have side effects or contraindications to conventional therapy that limits its use; and/or (3) have rapidly progressive disease or progressive disease despite conventional therapy.

This study demonstrates tapering of steroids up to a mean reduction of 75.8% from starting dose without relapse in most patients. Most of the reports utilizing IVIG at a dose of 2 gm/kg/cycle have shown a positive clinical outcome, decrease in pathogenic autoantibodies, and a steroid-sparing effect.

It has been well documented that IVIG causes a rapid decline in pathogenic autoantibody levels following which there is often a rebound increase, as in plasmapheresis. It has been hypothesized that use of IVIG along with rituximab or cyclophosphamide would be more beneficial in causing decline in pathogenic antibodies, suppressing the rebound increase and providing a sustained long-term remission with relatively low infectious complication rates.

In general, most published reports on IVIG have been retrospective analysis. There is a paucity of well-designed prospective trials. There is a need for randomized controlled trials for determining the efficacy and adverse effects of IVIG in the treatment of autoimmune bullous skin diseases.

**Castanedo-Cazares JP, Lárraga-Piñones G, Ehnis-Pérez A, Fuentes-Ahumada C, Oros-Ovalle C, Smoller BR, et al. Topical niacinamide 4% and desonide 0.05% for treatment of axillary hyperpigmentation: A randomized, double-blind, placebo-controlled study. Clin Cosmet Invest Dermatol 2013;6:29-36.**

Axillary hyperpigmentation is a frequent cause of cosmetic consultation among dark-skinned women from tropical areas, including Latin America. Currently, there is no widely accepted treatment for the disorder. It is usually treated with bleaching agents because it is considered a variant of inflammatory hyperpigmentation. This was a 9-week, randomized, double-blind, left-right axilla, placebo-controlled trial study conducted to assess the efficacy of

niacinamide 4% and desonide 0.05% emulsions in the treatment of axillary hyperpigmentation.

Twenty-four women aged 19-27 years with hyperpigmented axillae (phototypes III-V) were randomly assigned to receive the study treatments in the axillary region. Improvement was assessed at baseline, then clinically and by colorimetry 9 weeks later. Quantitative evaluation including melanin, inflammatory infiltrates, NKI/BETEB, CD1a, CD68, and collagen type IV content was performed by histochemistry and immunohistochemistry, assisted by computerized morphometric analysis.

Both niacinamide and desonide induced significant colorimetric improvement compared with placebo; however, desonide showed a better depigmenting effect than niacinamide. A good to excellent response was achieved in 24% of cases for niacinamide, 30% for desonide, and 6% for placebo. Side effects, including local erythema, burning, pruritus, infection, and skin atrophy, were absent during the trial. In addition to the associated inflammatory cell infiltrates, a physical discontinuity of the epidermal basal membrane was found which improved after exposure to both drugs and was more evident in the desonide group.

**Comment:** Postinflammatory hyperpigmentation (PIH) is an acquired hypermelanosis occurring after cutaneous inflammation or injury. It can arise in all skin types, but is more frequent in individuals with darker skin (Fitzpatrick skin types IV to VI) as the melanocytes of darker-skinned individuals show an exaggerated response to cutaneous injury. PIH can have a significant psychosocial impact, which is well supported by various epidemiological studies that depict dyschromias. Axillary hyperpigmentation has not been extensively studied due to its primarily cosmetic nature and lack of any major and significant health implications. It has been proposed that axillary skin darkening is best defined as mild PIH, characterized by increased epidermal melanin production, following mild irritation or stimulation of the skin. The treatment of hyperpigmentation in these patients has remained challenging for dermatologists.

Axillary skin is distinctly different from those of other body sites, as it has reduced barrier integrity. Studies have shown cholesterol, ceramide 3, and lactic acid levels to be increased, and natural moisturizing factor amounts to be lower, cornified envelopes to be smaller

indicative of a shorter stratum corneum turnover, compared with the volar forearm.

Although the precise pathogenesis is unknown, it is thought to result from cytokines, inflammatory mediators, and reactive oxygen species. In some individuals, the axillary skin may face additional challenges including leaching of lipids and proteins from the stratum corneum by cleansing surfactants, or additional irritation induced by shaving and plucking which further impairs the natural barrier to exogenous irritants. Histological evaluation of female Filipino axillary skin has revealed that the trauma of underarm hair plucking is associated with melanosome leakage into the dermis and hence increased pigmentation, as well as mononuclear cell and macrophage infiltration.

This study reveals that niacinamide and desonide have depigmenting properties in women with axillary hyperpigmentation along with the added advantage of improvement in the physical discontinuity of the epidermal basal membrane. However, multicentered trials including a large number of patients would be helpful in providing a better interpretation.

**Klein A, Steinert S, Baeumler W, Landthaler M, Babilas P. Photoepilation with a diode laser vs. intense pulsed light: A randomized, inpatient left-to-right trial. *Br J Dermatol* 2013;168:1287-93.**

Photoepilation with lasers or intense pulsed light (IPL, 590-1200 nm) sources is a widely used efficient and safe treatment modality for the removal of unwanted hair. Devices currently in use work on the basis of the selective photothermal destruction of hair follicles, which is based on the principle of selective photothermolysis. This randomized controlled trial (RCT) was undertaken to compare the efficacy, side effects, and patient-rated efficacy of two popular light devices for hair removal, a diode laser (DL) and an IPL source.

IPL and DL treatments were evaluated in 30 participants with a mean age of 33.7 years (skin types II–III) with unwanted axillary hair. Six treatments with each device were carried out at 4-week intervals. The two axillary regions of each patient were randomized to the two competing procedures. After each laser treatment, study subjects were evaluated for immediate side effects, such as burning, edema, and blistering. A visual analog scale (VAS) ranging from 0 to 10 was used for the self-assessment of pain (0 = no pain, 10 = maximum pain) at every treatment visit. The mean score for all six visits was obtained. For the quantitative

evaluation of hair growth, the three regions of interest of each axillary region were photodocumented at each visit with a handheld dermatoscope. Final assessment was conducted 12 months after the last treatment by means of hair counts using close-up photographs. The primary endpoint was reduction in hair growth, analysed on an intention-to-treat and last-observation-carried-forward basis ( $n = 30$ ), and secondary endpoints were patient-rated efficacy, treatment-related pain, adverse effects, and treatment duration.

All participants completed the 3- and 6-month follow-up evaluations (visits 7 and 8), but only 25 volunteers were available for the 12-month follow-up (visit 9). Both devices significantly reduced hair counts. Mean reductions from baseline (3 and 12 months after the last treatment) were 59.7% and 69.2% for DL and 42.4% and 52.7% for IPL treatment ( $P < 0.01$ ), respectively. DL treatment induced significantly more pain [ $3.7 \pm 2.1$  (DL) vs  $1.6 \pm 1.4$  (IPL);  $P < 0.01$ ; VAS] but could be conducted faster [ $33.1 \pm 3.8$  s (DL) vs  $40.1 \pm 5.0$  s (IPL);  $P < 0.01$ ]. No severe side effects were observed for either therapy.

**Comment:** Advances in laser technology have led to the establishment of laser hair reduction as a safe modality for the treatment of unwanted hair on any body part. An ideal patient has thick dark terminal hair, white skin, and a normal hormonal status. There is a paucity of data regarding the safety and efficacy of lasers in dark-skinned individuals.

Studies in the past have compared diode and Nd: YAG laser in terms of efficacy for hair reduction with most of them showing DL to be more comfortable and efficacious. However, without the use of topical anesthetics, patient preference might be based on pain level during the treatment session.

Few studies done in the past have directly compared long-term outcomes of lasers with IPL with both the lasers and light devices showing similar long-term efficacy contradicting the results of this study. Current long-term evidence on efficacy of IPL is sparse. Few trials comparing diode with IPL have shown similar efficacy at 6 months after treatment contrary to the results in this study.

In this study, all sessions were repeated at 4-week intervals. The resting phase for axillary hair tends to be longer when compared with the scalp and beard

hair. Doing the sessions too frequently might lead to a temporary suppression rather than destruction of hair follicle. Controlled trials would be required to differentiate the hair reduction in the long term achieved when sessions are done at 4 weekly intervals versus increasing the gaps after second session.

**Careta MF, Fortes AC, Messina MC, Maruta CW. Combined treatment of earlobe keloids with shaving, cryosurgery, and intralesional steroid injection: A 1-year follow-up. *Dermatol Surg* 2013;39:734-8.**

Earlobe keloids are benign, fibrous proliferations occurring in predisposed persons at sites of cutaneous injury (ear piercing, burns, or surgical procedures). Twelve consecutive patients with earlobe keloids were treated with a combination of surgery and cryosurgery. The surgical procedure consisted of shaving after local anesthesia leaving 1-2 mm of the remaining lesion at the borders. Cryosurgery (liquid nitrogen spray) of the underlying tissue followed it. One cycle of freezing was performed (freezing time 60 s). Patients were evaluated 7 and 30 days after the surgical procedure. At day 30, cases with persistent keloid lesion received adjuvant therapy with intralesional injection of triamcinolone acetonide (10-20 mg/mL). Monthly evaluation was done. The mean posttreatment follow-up was 12 months. Major response, moderate response, and failure was defined as 80%-100% reduction in keloid thickness, 50%-80% reduction in keloid thickness, and improvement of less than 50% or complete relapse after treatment, respectively.

After 1 year, major and moderate response were observed in 9 cases (75%) and 2 cases (16%), respectively; 1 case had relapse 5 months after surgery. The number of intralesional triamcinolone injections varied from none to 4.

**Comments:** Earlobe keloids are benign fibrous proliferations characterized by an excess of collagen deposition. They occur in predisposed individuals at sites of trauma, ear piercing, burns, or surgical procedures. The incidence is higher in blacks and Asians when compared with Caucasians.

They are commonly encountered in day-to-day clinical practice and pose a challenging management problem and distinctive cosmetic implications. Clinically, they appear as shiny, smooth, globular growths on one or both sides of the earlobe. Pruritus, pain, and paresthesias can be another source of distress for some of these patients.

Various therapeutic modalities are available for treatment of keloids. There is no consensus regarding the optimal or best management of keloids. Surgical excision alone has been found to have a low success rate with a high incidence of recurrence in previous studies. Intralesional injection of corticosteroids is one of the mainstays in the management of earlobe keloids. Monotherapy with intralesional injection of steroids has been found to alleviate the subjective symptoms in most of the studies with variable success in improving the objective symptoms.

In the recent literature, surgical excision along with adjuvant therapy is recommended. There is no standardized protocol regarding the administration of intralesional corticosteroids. Some have advocated the instillation of steroids after removal of the sutures followed by weekly or fortnightly injections. Few have also advocated the use of intralesional steroids prior to surgical excision.

Cryosurgery as monotherapy for the treatment of earlobe keloids has shown diverse results. The recently introduced intralesional cryoneedle method has been found to be simpler and safer to use, requiring less postoperative care.

In this study, major response was observed in majority of the cases at 1 year of follow-up with shaving, cryotherapy, and intralesional steroids. The success rate of combination of surgery and triamcinolone acetonide injection has shown great variation across different studies with some exhibiting unsatisfactory response. Here the treatment modality consists of three different treatment techniques. The favorable response illustrated probably reflects the synergism of the combinations. However, in a given patient, the location, size, depth, and duration of earlobe keloids are critical factors in deciding the individualized modality of treatment.

Although this study reveals good comprehensive results, studies dealing with duration of keloids comparing with various treatment responses need to be carried out.

**Poot AM, Diercks GF, Kramer D, Schepens I, Klunder G, Hashimoto T, et al. Laboratory diagnosis of paraneoplastic pemphigus. *Br J Dermatol* 2013. [In press]**

Paraneoplastic pemphigus (PNP) is a multiorgan disease characterized by antibodies against plakins, desmogleins,

and the alpha-2-macroglobulin-like-1 (A2ML1) protein, in association with an underlying neoplasm. This study was undertaken to compare the diagnostic value of different laboratory techniques in the serological diagnosis of PNP by performing immunoblotting, ELISA for envoplakin (EP\_ELISA), anti-Dsg1, anti-Dsg3, BP180, BP230, indirect immunofluorescence (IIF) on rat bladder, radioactive immunoprecipitation (IP), and a nonradioactive combined IP-immunoblot assay on the sera of 19 PNP (median age of 56.6 years) and 40 control patients. The diagnosis of PNP was made if patients fulfilled the revised criteria proposed by Anhalt in 2004 and Zimmerman in 2010.

Sensitivities for anti-EP ELISA, rat bladder IIF, immunoblotting (IB), radioactive IP, and nonradioactive IP were 63%, 74%, 89%, 95%, and 100%, respectively, with specificities ranging from 86% to 100%. Low sensitivity and specificity were observed with BP180- and BP230-ELISAs.

**Comment:** PNP is a distinct autoimmune blistering dermatosis occurring in association with various neoplasms. The clinical features consist of recalcitrant, painful oral erosions that may be accompanied by polymorphic cutaneous eruptions and systemic involvement. It is characterized by the presence of autoantibodies against desmoglein 3 (Dsg3) (130 kd), desmoglein 1 (Dsg1) (160 kd), envoplakin (210 kd), periplakin (190 kd), desmoplakin I (250 kd), desmoplakin II (210 kd), bullous pemphigoid antigen 1 (BPAG1) (230 kd), plectin (>400 kd), and a previously unidentified 170-kd protein which has recently been identified as A2ML1, a broad-range protease inhibitor expressed in stratified epithelia.

Histological findings vary considerably according to the clinical presentation and age of the lesions with predominant suprabasal acantholysis in noninflammatory blisters, whereas interface and lichenoid dermatitis in erythematous inflammatory maculopapular lesions. DIF is negative in half of PNP patients and false negatives are also common, attributable to lichenoid lesions and necrotic tissue in the mucosal biopsies. The presence of autoantibodies to plakins is a characteristic feature with highest specificity for envoplakin and periplakin followed by desmoplakins. Plakin autoantibodies, however, have been found in other conditions such as pemphigus vulgaris, pemphigus foliaceus, erythema multiforme,

and toxic epidermal necrolysis, hence demonstration of antiplakin antibodies alone is not sufficient to point toward the diagnosis of PNP.

IP has been found to be the most sensitive and specific test for demonstrating antiplakin antibodies in most of the studies, qualifying as a major diagnostic criteria for PNP. However, tedious nature, cost, and lack of easy availability are the limiting factors. This study shows sensitivity of radioactive IP assay to be superior to IB, IIF on rat bladder, and EP-ELISA. Also, the nonradioactive IP showed marginally higher sensitivity than the radioactive IP. In the absence of IP, combination of IB and rat bladder-IIF may be used as the first serological test for confirming the diagnosis of PNP.

However, more studies with larger number of patients are required to support the findings, which would be of a substantial help in accurately diagnosing this often-fatal disease with a myriad of variable cutaneous morphologies and the morbidity of recalcitrant mucosal lesions.

**Moftah N, Moftah N, Abd-Elaziz G, Ahmed N, Hamed Y, Ghannam B, et al. Mesotherapy using dutasteride-containing preparation in treatment of female pattern hair loss: Photographic, morphometric and ultra structural evaluation. J Eur Acad Dermatol Venereol 2013;27:686-93.**

Female pattern hair loss (FPHL) is one of the most common causes of hair loss, affecting 50% of women in the age of 50 years. Treatment of FPHL is frustrating for both patients and doctors. This study including 126 female patients with FPHL was carried out to evaluate the efficacy and safety of mesotherapy using dutasteride-containing preparation. The patients were classified into two groups: Group I (86 patients) (mean age  $34.1 \pm 6.6$  years) and group II (40 control patients) (mean age  $34.8 \pm 7.2$  years) injected with dutasteride-containing preparation and saline, respectively. Patients received 12 sessions over a period of 16 weeks and were evaluated at the 18<sup>th</sup> week by photographic assessment, hair pull test, hair diameter, and patient self-assessment. Ultra structural evaluation was done for three patients using five of the randomly epilated hairs from the vertex as described by Wyatt and Riggott, before and at the 18<sup>th</sup> week using scanning electron microscope. Photographic improvement was seen in 62.8% of patients compared with 17.5% in control group. Significant improvement in mean hair diameter and

decline in mean number of epilated hairs were seen in group I. Side effects were minimal with no statistically significant difference between the two groups. Ultra structural examination of pretreated hairs revealed absent cuticle in one patient and focal destruction of the cuticle in the second patient, which reappeared in both after therapy. There was a negative correlation between degree of improvement and duration of FPHL ( $P < 0.05$ ).

**Comment:** FPHL is the most common cause of alopecia in women characterized histologically by increased numbers of miniaturized hair follicles. Although medically benign, the impact is predominantly psychological leading to distress, low self-esteem, depression, and impaired quality of life in a significant number of affected females.

The goal of treatment is to arrest the progression of alopecia and stimulate new hair growth. Two main pharmacological options currently widely used are antiandrogens and minoxidil, which need to be continued indefinitely to attain and maintain response.

Mesotherapy has gained a lot of attention in recent past; however, the scientific basis is not established. The US FDA in view of lack of documented evidence has not yet approved it. On theoretical grounds, it can be hypothesized that dutasteride might be more efficacious than finasteride as the latter being a selective inhibitor of type 2 isoenzyme of 5-alpha reductase has the capability to reduce serum dihydrotestosterone levels by about 70%, whereas dutasteride inhibits both isoenzymes inducing more than 90% reduction in the dihydrotestosterone levels. Longer half-life of dutasteride when compared with finasteride has been a limiting factor for the former's use.

In this study, dutasteride administered by meso therapy demonstrated significant increases in target area hair count in comparison to placebo, as early as 12 and 24 weeks. In few studies assessing the efficacy and safety of five alpha inhibitors in androgenetic alopecia, dutasteride was found to be superior to finasteride at 12 and 24 weeks in male pattern hair loss. Also, few reports showed noteworthy response with dutasteride in patients with limited improvement after 6 months of finasteride. This study results reiterate the above findings.

Current treatment options are limited, and even in positive responders a considerable time delay occurs before improvement is apparent. In cases of advanced alopecia (Ludwig grade III) and failure with aforementioned medical therapies, surgical management remains an important option. Dutasteride may be considered as an additional treatment option, following further studies in cases of grade I and II FPHL.

**Sonia Mangal, Muthu Sendhil Kumaran**

Department of Dermatology, Venereology and Leprology,  
Postgraduate Institute of Medical Education and Research,  
Chandigarh, India

**Address for correspondence:** Dr. M. Sendhil Kumaran,  
Department of Dermatology, Venereology and Leprology,  
Postgraduate Institute of Medical Education and Research,  
Chandigarh - 160 012, India.  
E-mail: drsen\_2000@yahoo.com

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Calabrò G, De Vita V, Patalano A, Mazzella C, Lo Conte V, Antropoli C. Confirmed efficacy of topical nifedipine in the treatment of facial wrinkles. *J Dermatolog Treat* 2013; Early Online: 1-7.

There has been an ever-increasing demand for aesthetic procedures to reverse the effects of aging, particularly in the facial area. Recently, topical nifedipine has been found to have anti-wrinkle effects. The aim of this study was to confirm the anti-wrinkle efficacy and tolerability of a 0.5% nifedipine-based topical formulation.

A randomized study was conducted in 20 healthy female volunteers aged between 45-60 years with moderate to moderately severe facial wrinkles and Fitzpatrick's skin phototypes II-IV. Ten volunteers (group A) applied a cream containing nifedipine at a concentration of 0.5%, hyaluronic acid, collagen, and vitamin A and E, and the other 10 (group B) applied a good moisturizer, containing hyaluronic acid, collagen, and vitamin A and E. Patients in both groups were instructed to apply measured amounts (0.1 g) of topical formulations on forehead, nose-geniene, periocular and perilabial wrinkles, twice daily for 3 months after washing the face with the same mild facial cleanser. All parameters were evaluated at baseline (T0), and then 30 (T1), 60 (T2), and 90 (T3) days later. The aesthetic improvement was evaluated by a blinded investigator using the Wrinkle Severity Rating Scale (WSRS) with grade 1 indicating minimum severity and grade 5 indicating maximum severity. In group A, mean WSRS scores at T1 (2.79), T2 (1.99), T3 (1.84) were approximately 1.38, 1.93, and 2.09 times lower than mean WSRS score at T0 (3.85), respectively. In group B, the mean WSRS score at T0 was 3.78, at T1 3.41, at T2 3.42, and at T3 3.36. Post-treatment WSRS score was significantly lower than the baseline WSRS score only in the nifedipine group.

Improvement in skin hydration was found to be more in group A than in group B at the end of the study period of 90 days. Also, the use of nifedipine cream in

group A resulted in significant overall lightening of the skin compared with baseline and the control group. The absence of de-pigmenting agents in the tested product suggests a possible role of nifedipine in skin lightening. No significant change in blood pressure and heart rate were recorded during this study.

**Comment:** Both intrinsic and extrinsic factors influence the aging process. Extrinsic factors include sun exposure, repetitive or exaggerated mimic expressions, gravity, and smoking. Reactive oxygen species (ROS), a byproduct of both environmentally induced and intrinsic aging, lead to a cascade of biochemical reactions within the skin, resulting in the production of matrix metalloproteinases (MMPs) and proinflammatory cytokines. Reduction in collagen and elastin and a loss in hydration are the main structural changes in skin resulting from aging leading to wrinkling. Wrinkles can be divided into four main types: Atrophic crinkling rhytids, permanent elastotic creases, dynamic expression lines, and gravitational folds. Each type usually develops on specific skin regions exhibiting distinct micro-anatomical characteristics. However, the most important pathogenic mechanism is the chronic contraction of mimic muscles.

Nifedipine is a dihydropyridine-type calcium channel blocker that blocks the transmembrane influx of calcium ions into muscle cells inhibiting their contraction, thus accounting for its efficacy in the treatment of facial wrinkles. In nifedipine group, there was a greater improvement in viscoelastic properties of skin, and another significant effect observed was skin lightening. Authors have not provided explanation for the observed skin lightening effect. Its poor percutaneous penetration combined with its rapid metabolism in the skin limits its systemic absorption and side-effects. So, topical nifedipine preparations can prove to be an economical, effective, and convenient means of anti-wrinkle treatment.

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Further in-depth studies are needed to evaluate the anti-aging effects of topical nifedipine over longer treatment period and its possible role not only in skin rejuvenation, but also in the prevention of cutaneous aging by increasing skin hydration and elasticity.

Amerio P, Amoroso G, Bardazzi F, Campanati A, Cassano N, Conti A, et al. Detection and management of latent tuberculosis infections before biologic therapy for psoriasis. *J Dermatolog Treat* 2013;24:305-11.

The biologic agents are highly efficacious in the treatment of psoriasis and psoriatic arthritis. However, their use is associated with an increased risk of developing active tuberculosis (TB). All patients should be screened for latent tuberculosis infection (LTBI) prior to initiating therapy. This article reviews the current recommendations for screening and chemoprophylaxis of LTBI in Italian psoriasis patients treated with biologics.

LTBI is defined by the presence of *Mycobacterium tuberculosis* without clinical symptoms, and bacteriological and radiographic signs of disease. Only about 10% of these patients develop active TB, immunosuppression being a major risk factor for activation. Among the anti-TNF- $\alpha$  agents, the risk of LTBI activation is three to four times higher with the monoclonal antibodies (adalimumab, infliximab, and certolizumab) as compared to etanercept. There are no reports of LTBI reactivation with alefacept. The risk of LTBI with ustekinumab is lower than that observed with anti-TNF- $\alpha$  therapy. However, screening for LTBI is recommended before starting any biologic therapy for psoriasis.

According to the recommendations of an expert working group of Italian dermatologists, screening process for LTBI includes taking complete medical history, chest X-ray (CXR), purified protein derivative skin test (PPD), and interferon  $\gamma$  release assays (IGRAs). History pertaining to age, TB vaccination, previous TB infections, family history of TB, exposure to possible sources of infection, and any recent immunosuppressive or long-term antibiotic therapy should be taken. CXR should be performed in two projections and interpreted by a radiologist (although US National Psoriasis Foundation consensus statement recommends an X-ray only if immunologic tests are positive). Indurations larger than 5 mm are considered positive in the PPD test. Although having good sensitivity, false negatives can result from immunosuppression as a consequence of an autoimmune disease, medication, and age. False positives test can result from vaccination with

bacillus-calmette-guérin (BCG) and exposure to non-tuberculous mycobacteria. A two-step test, also known as a booster PPD, has been suggested, in which a second PPD is administered 1-3 weeks after the first to provoke an anamnestic response to reinforce weakened immune memory. This is useful in older patients or in patients who are at high risk of infection but show a negative result on the first PPD test. *In vitro* immunological tests for LTBI include QuantiFERON and T-SPOT.TB, collectively referred to as IGRAs. These assays correlate better with TB exposure, and they are not influenced by vaccination with BCG or previous exposure to non-tuberculous mycobacteria. They also have a higher specificity. IGRAs employing a cocktail of antigens may be more sensitive than PPD in immunosuppressed patients.

A positive IGRA test is an indication for prophylactic treatment, independent from the results of other tests. The situation is less clear when the IGRA and radiology results are negative, but the PPD is positive. In this case, it is necessary to carefully evaluate the individual situation. If the medical history does not suggest a risk, the PPD result is generally considered a probable false-positive, especially if there is a history of BCG vaccination. However, chemoprophylaxis may still be initiated if a false-negative IGRA result is suspected. If the X-ray results are positive while the other tests are negative, the patient should be referred to a pulmonologist for further evaluation.

For prophylactic treatment, in most cases, isoniazid at a dose of 300 mg/day for 9 months is recommended. The combination of rifampicin/pyrazinamide is not recommended due to the risk of hepatotoxicity. Anti-TNF- $\alpha$  therapy can be started at least 1 month after initiating prophylactic therapy.

**Comment:** The advent of TNF- $\alpha$  inhibitors as a treatment modality in psoriasis is a significant step forward in its management. However, a significant roadblock still remains due to the risk of developing TB in patients with LTBI preventing the optimal utilization of this modality. Animal studies have shown that TNF- $\alpha$  inhibition impairs inflammatory cell trafficking and granuloma formation. Currently recommended screening for LTBI, typically, risk assessment, tuberculin skin testing (TST), and CXR used prior to anti-TNF- $\alpha$  treatment can significantly reduce TB activation rates, but newer screening tests like IGRAs may enhance screening efficacy further.

Patients positive on screening who are treated with isoniazid and subsequently receive anti-TNF- $\alpha$  treatment still have approximately 19% risk for TB.

IGRA test has a better sensitivity and specificity than TST in detection of LTBI and is superior for predicting TB infection, especially in immunosuppressed patients. In a country like India where BCG vaccination is routinely administered to all in infancy, IGRA test has still higher utility, and the requirement for TB chemoprophylaxis can be significantly reduced. A strategy of simultaneous testing to optimize diagnostic sensitivity is suggested in the clinical use of biological drugs. IGRAs performed post-TST was elevated since day 3. So, it is advisable that when using a two-step screening strategy, it is better to perform an IGRA within 3 days after performing the TST.

A higher rate of TST positivity is found in patients of psoriasis being screened for LTBI than the corresponding inflammatory bowel disease (IBD) patients, which may be due to the priming of their clinically healthy skin to overreact to a broad-spectrum of antigenic triggers, including *M. tuberculosis* derived antigens and also there is a higher degree of drug-induced immunosuppression in patients of IBD. It seems reasonable to propose that injection of tuberculin antigens into the unaffected skin of patients with overt plaque psoriasis triggers augmented inflammatory reactions resulting in stronger TST, and adherence to the widely accepted TST-based recommendations for the diagnosis of TB leads to overdiagnosis of LTBI in patients with plaque psoriasis.

In countries, where TB prevalence is very high, the criterion of LTBI diagnosis may be less valuable and the guiding principle for LTBI treatment may not be as strict as in the western countries. Unlike active disease, monotherapy is often used in treating LTBI. The lower bacillary load in LTBI reduces the chances of developing resistant mutants, although this possibility cannot be fully excluded. Isoniazid at a dose of 5 mg/kg (upto 300 mg/day) is used for chemoprophylaxis for a period of 9 months, and the anti-TNF $\alpha$  therapy can be given at least 1 month after initiating prophylactic therapy.

The screening protocols for LTBI need to be applied in a way that there are less false positives so as to avoid denial of treatment to candidates who are eligible for anti-TNF- $\alpha$  therapy. It should also be sensitive enough to identify patients at risk of LTBI activation. The tendency of patients with psoriasis to have higher

number of false-positive TST results and the reduced diagnostic specificity of the TST in BCG-vaccinated populations may greatly diminish the value of traditional screening method of TST in psoriatic patients in India. TST needs to be combined with clinical history and supportive evidence from CXR and IGRA's to help decision-making while screening for LTBI in psoriasis patients being considered for anti-TNF  $\alpha$  therapy.

**Wolosker N, Campos JR, Kauffman P, Yazbek G, Neves S, Puech-Leao P. Use of oxybutynin for treating plantar hyperhidrosis. *Int J Dermatol* 2013;52:620-3.**

Plantar hyperhidrosis (PLH) is an emotionally distressing condition. Several anti-cholinergic drugs have been tried for its treatment in past, but their use is limited by their adverse effects. Oxybutynin is an anti-cholinergic drug, which is primarily used for treating urinary disorders and diminished sudoresis is one of its side-effects. The aim of this study was to evaluate the effectiveness and patient satisfaction with the use of oxybutynin when given at low doses for treating PLH. Thirty-five patients (aged between 18-71 years) with PLH were treated with oxybutynin, of these 30 (female-26, male-4) completed the study. They also had hyperhidrosis at other sites on the body, palmar in 25 (83.3%), axillary in 13 (43.3%), craniofacial in 5 (16.6%), and thoracic and abdominal in 5 (16.6%). During the first week, patients received 2.5 mg of oxybutynin once a day, 2.5 mg twice a day from the eighth to the 42<sup>nd</sup> day, and from the 43<sup>rd</sup> day till the end of 12 weeks, 5 mg twice a day.

At the completion of 12 weeks of treatment, 70% of patients had moderate or great improvement in PLH and more than 60% of patients showed improvement at all of the hyperhidrosis sites. Two-third of patients presented improvement in quality of life (QOL). QOL was much better in 9 (30.0%), a little better in 11 (36.6%), and the same in 10 patients (33.3%). Dry mouth was the most common side-effect (76.6%). Using 5 mg of oxybutynin per day, 66.6% of patients either did not present dry mouth or only presented it mildly, which encouraged the patients to continue with the treatment. Using 10 mg/d, this symptom increased but was tolerated well. Other side-effects reported were headache (10%) and urinary retention (6.6%); however, they were not significant enough to lead to discontinuation of treatment.

**Comment:** Hyperhidrosis is a disorder of excessive sweating beyond what is expected for thermoregulatory needs and environmental conditions. Hyperhidrosis

may be primary or secondary to medications or general medical conditions. Primary hyperhidrosis has an estimated prevalence of nearly 3% of the population. Topical therapy (20% aluminum chloride solution, 15% aluminum chloride in 2-4% salicylic acid gel, and 0.5%, 1%, 2% glycopyrrolate) is generally considered first-line treatment for most cases of focal hyperhidrosis. Other topical agents such as glutaraldehyde, formaldehyde, and tannic acid are seldom used today due to irritancy, skin discoloration, and the availability of better alternatives. For those who fail such treatment, other options available are iontophoresis, botulinum toxin A (BTX-A) injections and surgical or video-assisted endoscopic thoracic sympathectomy. But all these modalities have their limitations.

Only limited data are available regarding the use of oral medications in the management of hyperhidrosis. The various drugs tried include anti-cholinergic drugs: glycopyrrolate (1-2 mg, once/twice daily), oxybutynin (5-15 mg/day) and tolterodine (4 mg/day), and alpha-2-agonists: clonidine (0.6-1.2 mg/d).

Oxybutynin is primarily indicated for urge incontinence where it is used in higher dosage (15 mg/d) and hence leading to a greater incidence of side-effects in these patients. When used in low and progressively increasing doses, it is found to be highly effective for hyperhidrosis with minimum side-effects. There was improvement in hyperhidrosis at all the sites in two-third of the patients. Potential side-effects of oral anti-cholinergics include dry mouth, constipation, nausea, blurred vision, urinary retention, drowsiness, and dizziness. The side effects of oxybutynin are mild as compared to other anti-cholinergics. In this study also, the side-effects were mild and well tolerated by the patients. Because of its rapid resorption ( $T_{max} < 1$  hour), oxybutynin would also be suitable for use 'on demand,' for example, in specific social situations that provoke hyperhidrosis. It is contraindicated in patients with urinary retention, partial or complete obstruction of the gastrointestinal tract, paralytic ileus, gastroesophageal reflux disease, uncontrolled narrow-angle glaucoma and also in those with hypersensitivity to the drug substance. Limitation of the study is that there was no follow up of the patients after the drug was stopped. Treatment of plantar hyperhidrosis is challenging with each therapeutic modality having its own merits and demerits. Treatment of PLH with oxybutynin is a good alternative in patients failing on topical treatment and

not willing for iontophoresis or BTX-A. It has been found to be effective with a minimum of side-effects.

**Tran KD, Wolverton JE, Soter NA. Methotrexate in the treatment of pemphigus vulgaris: Experience in 23 patients. *Br J Dermatol* 2013. [In press]**

Pemphigus vulgaris (PV) is an autoimmune mucocutaneous blistering disorder. The first-line treatment for patients with PV consists of high-dose glucocorticoids, which have greatly reduced the mortality associated with this disease. This is a retrospective chart review of 23 patients of PV who were treated with methotrexate (MTX) between 2001 and 2012. The primary objective was to evaluate the efficacy of MTX in inducing clinical improvement in PV patients, as indicated by the drug's steroid-sparing effect and also to determine if it could be effective as a monotherapy in maintaining symptom control.

All the 23 patients included in the study (before the initiation of methotrexate) were treated with prednisone at a mean maximum dose of 71 mg/day (range 20 to 140 mg/day). Thirteen (56.5%) patients had received non-steroidal immunomodulators other than MTX before. The mean dose of prednisone at the time of initiation of MTX was 35 mg/day (range 10 to 70 mg/day). The initial dose of MTX was 7.5 mg weekly, with increases of 5 to 7.5 mg weekly every 2 to 8 weeks depending on the therapeutic response, until a maximum dose of 15 to 25 mg weekly. Folic acid at a dose of 1 mg/day was prescribed. Concomitant treatment with topical glucocorticoids such as clobetasol propionate ointment, dexamethasone oral rinses and intralesional injections of triamcinolone acetonide 20 mg/mL was continued. Symptom control was defined as either complete clearance of skin lesions, or as "minimal disease activity" exemplified by 1 to 2 new lesions every month that could be controlled with topical therapy and that were not considered to cause considerable distress by the patient. In patients achieving symptom control after addition of MTX, prednisone was tapered. Patients who were successfully weaned from prednisone were then put on tapering doses of MTX.

Of the 23 patients included in this study, 2 (8.6%) developed adverse events after initiation of MTX requiring cessation of the drug, while 21 (91.3%) had improvement in blistering and were able to reduce their dose of systemic corticosteroids. Sixteen (69.6%) patients were eventually weaned completely off prednisone, with a mean time from

initiation of MTX to discontinuation of prednisone of 18 months (range 7-30 months). Five (21.7%) patients experienced a partial steroid-sparing effect requiring a mean maintenance dose of prednisone of 6.75 mg/day. One patient experienced no therapeutic benefit after 2 months of MTX reaching a maximum dose of 25 mg/week. In the 16 patients who were successfully weaned from prednisone, tapering of MTX dose was attempted in 14. Of these 14 patients, the weekly dose of MTX could not be reduced without resulting in a flare of disease in 3 patients, MTX was reduced to 8.75 mg/week (range 5 to 15 mg/week) in 8 patients, and 3 patients were eventually completely tapered from MTX. Of the 3 patients who were completely tapered off MTX, 2 remained in remission for a duration of 3 and 7 months, and the third was in remission lasting for 26 months.

These results were largely unchanged when compared with the subgroup of patients who had previously received other systemic immunomodulators.

**Comment:** High-dose systemic steroids are considered the first-line of treatment for PV. However, the appreciable morbidity associated with systemic glucocorticoids has resulted in the use of other immunosuppressive drugs like azathioprine, cyclophosphamide, mycophenolate mofetil, cyclosporine, and methotrexate. In addition, dapsone, tetracyclines, plasmapheresis, intravenous immunoglobulin (IVIg), and rituximab have been used successfully. Although good results have been reported with biological agents, their high cost is a major limiting factor.

In this study, steroid dose could be reduced in 91% patients and in 69.6%, prednisone was completely tapered. MTX is a safe and efficacious treatment for patients with PV and should be included in the adjuvant therapy armamentarium. Another advantage is that it is a relatively cheap and easily accessible drug with which dermatologists have a vast experience. MTX generally has a delayed beneficial effect on oral lesions, whereas the cutaneous lesions usually respond more rapidly. In patients with severe to moderately severe PV, once the initial disease has been brought under control using high doses of systemic corticosteroids, MTX may be useful in maintaining that control, while allowing a lowering of the corticosteroid dose. It may even be successful in controlling the disease as a monotherapy, but it usually does not lead to complete prolonged remission of the disease.

Most of the studies showing efficacy of MTX in PV have been retrospective case series. Previous studies also suggest that a significant number of patients show clinical improvement with MTX and the drug has steroid-sparing effects. Further prolonged, placebo-controlled or multiple-arm prospective clinical trials are needed in order to further assess the role of MTX in the treatment of PV.

**Tse TW, Hui E. Tranexamic acid: An important adjuvant in the treatment of melasma. J Cosmet Dermatol 2013;12:57-66.**

Melasma is a highly prevalent, chronic pigmentary disorder. Tranexamic acid (TA) is a plasmin inhibitor used to prevent abnormal fibrinolysis to reduce blood loss. This article reviews the rationale use and safety profile of TA as an adjuvant treatment in melasma.

TA has been tried in the treatment of melasma in the oral, topical, and intradermal injection formulation. Eight studies using oral TA (0.5-1.5 g/day) in the treatment of melasma were reviewed. The response to therapy was evaluated after 4-10 weeks of starting the drug. It was concluded that the usual effective dose of TA in melasma can be 250 mg 2-3 times daily, which is much lower than the dose used to reduce excessive bleeding. Clinical response was observed after a period of at least 1 month. Side-effects in the form of gastrointestinal upset and a decrease in the amount of menses were found in a minority of patients (3-4%). No change was found in the coagulation parameters. Recurrence of melasma was seen after stopping treatment in a few patients. It was also found that the duration of the therapy and not the higher dose made the treatment regime more effective.

Since systemic TA has potential side-effects, topical TA has been tried in melasma. Available data in literature on the efficacy of topical TA is scarce, and results are conflicting. Some studies suggest that melasma improves in significant number of patients with topical 2% TA emulsion when applied for 5-18 weeks and no side-effects were observed. While another study showed that topical 5% TA when used for a 12-week period caused more irritation to the applied area without any extra benefit. Recently, topical TA in liposome formulation has been developed to reduce irritation.

One study has reported on the efficacy of intradermal injections of TA. The study showed that 85 patients who completed weekly intradermal injections of TA, 0.05 ml TA (4 mg/mL) in the melasma lesion at

1 cm intervals for 12 weeks had significant decrease in the melasma area and severity index (MASI) from 8 weeks onward (8 rated good, 65 rated fair results). No significant side-effect was noted.

**Comment:** The pathogenesis of melasma is multifactorial; genetic predisposition, UV light exposure and hormonal influences being the major etiologic factors.

TA is a plasmin inhibitor used to prevent abnormal fibrinolysis to reduce blood loss. It acts by attaching to the lysine-binding sites of plasmin and plasminogen. It inhibits UV-induced plasmin activity in keratinocytes by preventing the binding of plasminogen to the keratinocytes, thus suppresses the production of prostaglandins (PGs) and UV-induced melanogenesis, through the suppression of the epidermal plasmin activity. Lesser free arachidonic acids and depleted production of PGs reduces the melanocyte tyrosinase activity. This might be the mechanism for the effect of TA on melasma and improvement of post-inflammatory hyperpigmentation. Besides, it also reverses melasma-related dermal changes, such as vessel proliferation and increased number of mast cell.

In the majority of studies showing the efficacy of TA in melasma, the drug has been given orally. Although systemic TA has been reported to be safe for the treatment of melasma, the risk-benefit study must be done on a larger scale. The primary side-effects noted with its use are gastrointestinal complaints (nausea, diarrhea, and abdominal pain). There are also reports of serious complications such as deep venous thrombosis, pulmonary embolism, cerebral artery thrombosis and embolism, and coronary artery thromboembolism.

There is limited published literature on the role of topical TA and intradermal TA injections in melasma. Topical TA may cause irritation and allergy. Therefore, novel topical TA liposome formulations have been developed, but they are not yet commercially available. By injecting TA intradermally, it may be possible to treat the dermal and mixed-type melasma. Intralesional microinjection of TA appears to be a potentially new and promising therapeutic tool that can be easily performed in outpatient settings, with relatively rapid results and without significant side-effects.

Although many agents are available in the therapeutic options of melasma, its management is still challenging and recurrences are common. TA can prove to be a useful adjunct in the treatment of this

difficult to manage disorder of hyperpigmentation. It may also have some synergistic activity when used in combination with the other treatment modalities. But, like other available treatment options, it is not uniformly effective in all the cases. It leads to improvement in pigmentation in many patients, complete clearance in few, and recurrences can occur on stopping the treatment.

**Carbo MA, Pastor MV, Nicolas BR, Sanjuan VP, Estebanez EQ, Carpio EG. Omalizumab in chronic urticaria: A retrospective series of 15 cases. *Dermatol Ther* 2013;26:257-9.**

Chronic idiopathic or spontaneous urticaria (CU) affects around 0.1% of the population and can be highly distressing. It is defined by the presence of daily or almost daily symptoms for more than 6 weeks. Omalizumab is a monoclonal anti-IgE antibody approved for the treatment of severe allergic asthma and is also being tried in CU. This is a retrospective case series of 15 patients with CU treated with omalizumab. Omalizumab was administered at a dose of 150-300 mg subcutaneously every 2-4 weeks; the dosage used was adjusted according to total weight and serum IgE levels. Improvement was assessed after 3 and 6 months of treatment. Complete response was defined as symptom disappearance that could be followed by discontinuation of anti-histamines, and partial response as symptom improvement, but with symptom worsening when attempting to discontinue anti-histamines. After 3 months of treatment, 12 patients responded, with partial response in 9 and complete response in 3. At 6 months, 8 of 10 patients continuing on omalizumab had a complete response and 2 had a partial response. In patients discontinuing the drug, symptoms recurred after 5 weeks without treatment. Only 2 patients reported dizziness or nausea after the injections.

**Comments:** The chronic types of urticaria are divided into physical urticaria (cold, delayed pressure, vibratory urticaria, and urticaria factitia), other urticaria types (aquagenic, cholinergic, contact urticaria, and exercise-induced urticaria/anaphylaxis), and spontaneous urticaria. Chronic spontaneous urticarias may be idiopathic (55%) or autoimmune (45%) as defined by the presence of the immunoglobulin IgG against the alpha subunit of the high affinity IgE receptor, or IgG anti-IgE antibodies.

The first-line drugs for the treatment of CU are second generation H1 anti-histamines. In non-responders,

the dose of the anti-histamine can be increased upto four-fold of the recommended dose or sedating H1 anti-histamine/H2 anti-histamine may be added. The second-line therapies are doxepin, leukotriene receptor antagonist, corticosteroid (short-term only), dapsone, chloroquine, hydroxychloroquine, and sulfasalazine. The third-line treatments include methotrexate, cyclosporine, mycophenolate mofetil, omalizumab, autologous serum therapy, intravenous immunoglobulin, and plasmapheresis.

Omalizumab is a recombinant humanized anti-IgE-IgG monoclonal antibody approved for the treatment of moderate to severe allergic asthma. It blocks the high-affinity Fc receptor of IgE and also reduces the expression of FcεRI on circulating basophils and mast cells, thus reducing their activation and histamine release. In addition to the anti-IgE mechanisms, it also induces eosinophil apoptosis, downregulates inflammatory cytokines IL-2, IL-4, IL-13, and TNF-alpha. This explains the successful results of omalizumab in CU patients even with low levels of serum IgE.

Omalizumab has been shown to be effective in chronic autoimmune urticaria, chronic idiopathic urticaria and various urticaria subtypes such as cholinergic, heat, cold, solar, and delayed pressure urticaria. It is used in doses of 150 mg or 300 mg subcutaneously every second or fourth week, depending on the weight and serum IgE levels. It has been found to be effective in restoring the patient's quality of life and in reducing the

urticaria activity score. Few or no side-effects have been reported with omalizumab therapy. The most frequent adverse events noted are nausea, flu-like symptoms, diarrhea, nasopharyngitis, upper respiratory infection, and headache. Anaphylaxis has very rarely been reported (<0.1%). Omalizumab is an excellent treatment choice for severe treatment-refractory urticaria. It allows for a significant reduction in the dose of anti-histamines, systemic steroids, and other immunosuppressives in patients with CU, thus minimizing their side-effects. The drawbacks with this therapy are the high cost, not uniformly effective in all patients, prolonged treatment, and risk of recurrence on stopping the treatment. Further studies should be performed to confirm its efficacy in urticaria refractory to the conventional treatment.

**Aditi Prashar, Savita Yadav**

Department of Dermatology, Venereology and Leprology,  
PGIMER, Chandigarh, India

**Address for correspondence:** Dr. Savita Yadav,  
Department of Dermatology Venereology and Leprology,  
PGIMER, Chandigarh - 160 012, India.  
E-mail: savita2081@gmail.com

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Sir,

Acronyms were initially introduced during the early 20<sup>th</sup> century, which places them among the relatively new linguistic phenomena with wide spectrum of definitions. The purpose of this study is to analyze the current knowledge of Serbian dermatologists regarding the recognition of acronyms and assessment of familiarity with selected acronyms among practicing dermatologists with the practice experience of various duration.

The anonymous inquiry questionnaire containing poetic letter with 10 hidden acronyms [Appendix 1] has been delivered to 52 certified practicing dermatologists. The final mixture of acronyms hidden in the text included 54-year-old up to 2-year-old acronym. Only 26.7% recognized more than 50% of the hidden acronyms [Figure 1]. Two groups emerged: The “poor” and “good” acronym knowledge group of dermatologists [Table 1]. Dermatologists in the “poor” knowledge group were significantly older with the higher mean age ( $P < 0.05$ ), majority of participants (85.7%) in this group had more

than 10 years of practice. Conversely, up to 79.2% dermatologists in the “good” knowledge group were younger specialists who started to practice within the past decade ( $P < 0.001$ ). Moreover, their own perception of fluency in speaking English ( $P < 0.05$ ) is greater. Gender, type of practice (public vs. private) and the presence or absence of English language education, did not significantly differ between “good” and “poor” acronym knowledge group.

Specific type of acronym was significant for the recognition process so in the “good” knowledge group, terms SAPHO, CHILD, LAMB, DRESS, and KID were significantly more frequently detected by dermatologists. The most frequently detected acronyms in both groups were LEOPARD and SAPHO, respectively.

According to the MedLine and PubMed database search, more than 90 abbreviations were recorded in dermatology regarding the naming of dermatological diseases and syndromes (e.g. SSSS, AD, DLE). Some

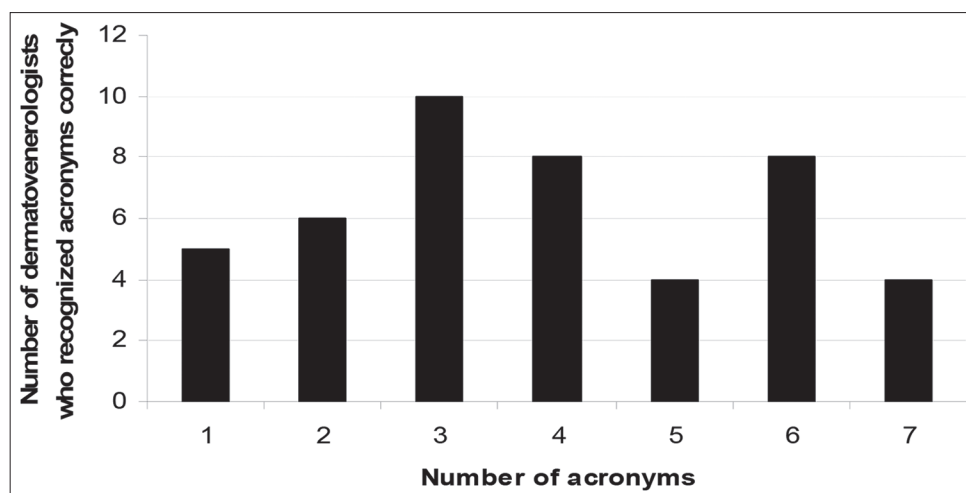
**Table 1: Characteristics of dermatovenereologists according to the number of recognized acronyms**

Characteristics	1-3 acronyms (group I)		4-7 acronyms (group II)		P value
	21	No (%)	24	No (%)	
<b>Total number (45)</b>					
Sex					
Male	5	23.8	3	12.5	0.322*
Female	16	76.2	21	87.5	
Age (mean±SD)	47.38±7.40		41.04±5.51		0.002
Years providing dermatovenereologists care					
<10 years	3	14.3	19	79.2	0.000*
>10 years	18	85.7	5	20.8	
Practice					
Public	16	76.2	22	91.7	0.153*
Private	5	23.8	2	8.3	
Learning english					
Yes	16	76.2	23	95.8	0.053*
No	5	23.8	1	4.2	
Own perceptions of knowledge in english					
Poor	8	38.1	5	20.8	0.050*
Good	12	57.1	11	45.8	
Excellent	1	4.8	8	33.3	

\*P value according  $\chi^2$  test, \*\*P value according t test, SD: Standard deviation

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**Figure 1: Distribution of dermatovenereologists according to the number of recognizable acronyms**

of the commonly used acronyms describing diseases or syndromes in dermatology are (in alphabetical order) AGEF, BIDS, CHILD, CLOVE, COIF, CREST, DRESS, EMPACT, HATS, ILVEN, KID, LAMB, LEOPARD, MIDAS, NAME, PAN, PAPA, PHACES, POEMS, REM, SACRAL, SAPHO, SDRIFE, TEN, and WILD. The first acronym used in dermatology, TEN appeared only 13 years after the official acceptance of the exact acronym definition, and the rise of acronyms in naming of dermatoses and syndromes continued during the past 6 decades.<sup>[1]</sup>

Since, the dermatology is visual i.e descriptive medical specialty one could expect that the theory of visual word recognition would have the greatest impact on identification and memorization of acronyms.<sup>[2]</sup> This might well be supported by study on acronym “superiority effect” which presents that *familiarity* of a word (i.e., with pre-existing lexical representation) has even superior effect on recognition and memory than orthographic regularity (effective spelling of the letter string) when it comes to visual word recognition.<sup>[3]</sup>

The acronymophyllia which appeared in other medical fields could have been easily avoided in dermatology by using three simple rules when creating one: (1) the acronym must have at least three letters and be easily pronounceable, (2) it has to make the communication easier, (3) and to be more readily recognized by the reader compared to the original phrase<sup>[4]</sup> adding the *familiarity* as the most important characteristic. All acronyms elected in the study obey the proposed rules: Surprisingly well- recognized acronym SAPHO could only be explained by Serbian-Greek historical

connections and hence familiarity with Greek goddess Sapho.

Since, its cumbersome to memorize all the acronyms and syndrome names (NAME, LAMB, LEOPARD, Carney syndrome) that refer to almost the same skin lesions: Lentigines and/or ephelides and various benign tumors, all of them being rare, only the oldest acronym LEOPARD was highly recognizable, which emphasizes the significance of the clinical endpoint.<sup>[5]</sup>

The duration of acronym usage and interpretation in dermatology appeared to be important factor in recognition of “older” acronyms but only in case of a half-century old mnemonic words which holds primarily for LEOPARD. Similarly, there was complete ignorance of the 2 year old term WILD.

Influence of fluency in speaking English on acronym recognition is evidenced in this survey. Word *leopard* have the same written and pronounced version in Serbian unlike the “animal” *lamb*, which remained unrecognized by poor English speakers.

In conclusion, the strongest evidence stands for positive causality between the amount of time spent on acronym usage in dermatology and the extent of visual word recognition, with significant positive influence of the recently gained knowledge through board exam (not more than 10 years of practice), younger age of practicing dermatologist and fluency in English.

## ACKNOWLEDGMENT

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### Appendix 1: Poetic letter with hidden acronyms

Dear Papa,

*I went to the Zoo with our new teacher. Her **name** is **Sapho**, she is Greek. She took her own **child**, Alexander, with us. We saw many **wild** animals, like tigers, wolves, lions and a **leopard**, but most of all I liked a pretty little **lamb**. I was wearing the red **dress** you've bought me for my birthday*

*Zoo ticket was ten Euros*

*All my love to mom and you,*

*Your kid Mary*

Technology of the Republic of Serbia, through Contract No 175402 (2011-2014).

**Marković Milica, Ivanović Branislav<sup>1</sup>,  
Bjekić Milan, Sipetic Sandra<sup>2</sup>**

City Institute for Skin and Venereal Diseases, Belgrade, <sup>1</sup>Faculty of Philology, Belgrade University, Belgrade, <sup>2</sup>Institute of Epidemiology, School of Medicine, Belgrade, Serbia

**Address for correspondence:** Dr. Marković Milica,  
City Institute for Skin and Venereal Diseases,  
Džordža Vašingtona 17, Belgrade 11000, Serbia.  
E-mail: mipopovi@eunet.rs

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Sir,

Hypertrichosis is defined as an abnormal hair growth resulting in an increase in body hair beyond the normal variation for a patient's reference group; excluding androgen-induced hair growth. This should be differentiated from hirsutism, which is increased hair growth in androgen dependent areas.<sup>[1]</sup> It is usually a cosmetic problem, but may be associated with an underlying disorder that requires further investigation. It has been classified into congenital and acquired with further subdivision into generalized or localized hypertrichosis.<sup>[2]</sup> We present a rare case of familial congenital generalized hypertrichosis, which on literature search has been reported in very few families worldwide.

An 18-year-old girl, presented with profuse hair growth over face, arms, legs and back since birth. Her thelarche and menarche were normal and menstrual cycles were regular with normal flow. There was no history of acne, weight gain or voice change. Both her mother and maternal grandmother had a similar history of extensive body hair while her two sisters were normal. On examination, she was phenotypically female with a body mass index of 26. Extensive, soft, black terminal hair, 3-4 cm long was present on the face (shaved), arms, back, buttocks and lower limbs [Figures 1 and 2]. Adult sexual hair was seen in axilla and pubic area.

Hair on chest and abdomen was sparse. There was no hair on palms, soles and mucosal surfaces. Both breasts were normal and there was no clitoromegaly. There were no associated dental anomalies, facial dysmorphism or gingival hyperplasia. Hormone levels were within range (Luteinizing Hormone 4 IU/L, Follicle Stimulating Hormone 3.5 IU/L, Estradiol 54 pg/ml, Thyroid-Stimulating Hormone. 2.2  $\mu$ IU/ml and testosterone 0.9 ng/ml). Uterus and ovaries were normal on ultrasound. A diagnosis of congenital generalized familial hypertrichosis was made. Patient was counseled and referred for full body laser treatment. However as she could not afford the treatment, she continued with shaving and waxing.

Congenital generalized hypertrichosis has terminal hair with typical phenotypic characteristics as described in our patient and has an autosomal or X-linked dominant pattern of inheritance, which has been linked to chromosome x24-q27.1.<sup>[3]</sup> Various mechanisms of hypertrichosis have been described; such as prolonged anagen phase of hair follicles, increased hair follicle density and abnormal vellus to terminal switch mechanism in normal vellus hair bearing areas.<sup>[2]</sup> Terminal hair is medullated, wider than the inner root sheath of the follicle that produces them and the follicle penetrates into the reticular dermis. It can be easily differentiated from the softer



Figure 1: Excessive facial hair (shaved), side profile



Figure 2: Profuse hair on back

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non-medullated lanugo and non-pigmented variably medullated vellus hair.<sup>[4]</sup> Other forms of congenital syndromes with primary generalized hypertrichosis are congenital hypertrichosis lanuginosa (CHL), gingival fibromatosis with hypertrichosis, Cantu' syndrome and hypertrichosis, pigmentary retinopathy and facial anomalies syndrome.<sup>[2]</sup> In CHL, the hair distribution is similar to generalized hypertrichosis except that there is uniform overgrowth of soft lanugo hair with or without facial dysmorphisms (Ambras syndrome).<sup>[5]</sup>

No single method of hair removal is appropriate for all body locations or patients and the one adopted will depend on the character, area and amount of hair growth as well as on the age of patient and their personal preference. Techniques of hair removal can be temporary or permanent.<sup>[2]</sup> Temporary methods can be depilatory such as shaving, cutting or chemical depilators or epilatory such as plucking, waxing or tweezing.<sup>[2]</sup> Patient continued to use these temporary methods. Permanent methods of hair removal include electrolysis, thermolysis or laser treatment. The longer wavelength Nd: YAG laser is considered safest in treating darker skin phototypes.<sup>[6]</sup>

Reporting such rare syndromes not only adds to the database, but pooled data analysis may give us a better insight into patterns of inheritance, epidemiology and associated symptoms.

**Neerja Goel, Shalini Rajaram, Bindiya Gupta,  
Kanika Gupta**

Department of Obstetrics and Gynecology, UCMS and GTB Hospital,  
Dilshad Garden, Delhi, India

**Address for correspondence:** Dr. Bindiya Gupta,  
Department of Obstetrics and Gynecology, UCMS and GTB  
Hospital, Dilshad Garden, Delhi, India.  
E-mail: dr\_bindiya\_gupta@yahoo.co.in

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## Eosinophilic panniculitis after subcutaneous administration of sodium heparin

Sir,

Cutaneous side-effects of heparins are well-known. Among them, nodule development is uncommon. Usually, these nodules reveal calcinosis cutis on histological examination.

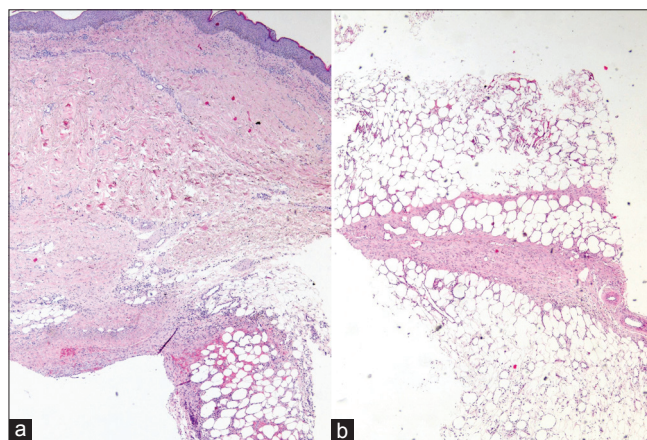
A 66-year-old woman presented with pruriginous lesions on her abdomen, 25 days after initiating oral acenocoumarol and subcutaneous enoxaparin for a pulmonary thromboembolism. On physical examination, multiple tender, poorly delimited, subcutaneous nodules at enoxaparin injection area were evident [Figure 1]. A biopsy and several complementary studies were performed. Hemogram, erythrocyte sedimentation rate, serum chemistry including alpha-1-antitrypsin, lipase, tryptase, angiotensin I-converting enzyme, rheumatoid factor, thyroid hormone function, autoimmunity studies, urinalysis, chest X-ray and purified protein derivative test were all normal, except for slight eosinophilia with normal white cell count. Cutaneous biopsy showed a mainly septal panniculitis [Figure 2]. The inflammatory infiltrate was predominantly composed of eosinophils, together with few lymphocytes and histiocytes, within the thickened septa and lobules [Figure 3]. In the dermis, scant perivascular and

interstitial inflammatory cell infiltrate composed predominantly of eosinophils was evident. Mild overlying spongiosis was also identified. A diagnosis of cutaneous drug reaction with eosinophilic panniculitis induced by heparin was made. Enoxaparin injections were discontinued, which resulted in cutaneous improvement. A positive patch test to enoxaparin confirmed this diagnosis.

The incidence of skin lesions induced by subcutaneous heparin is unknown. Urticaria, angioedema, ecchymosis, cutaneous necrosis, cutaneous induration and eczema-like lesions have been reported secondary to heparin administration. Delayed-type hypersensitivity reactions appear to be the most common mechanism to develop these cutaneous lesions. The presence of nodules or panniculitis caused by heparin has rarely been described.<sup>[1]</sup> The majority of these patients presented with calcinosis cutis or subcutis on histological examination and only one case of eosinophilic panniculitis was reported. Most patients with nodules were receiving treatment with calcium non-fractionated heparins or low molecular weight heparins (LMWH) containing calcium salts. On the other hand, patients with calcinosis cutis following subcutaneous heparin injection usually



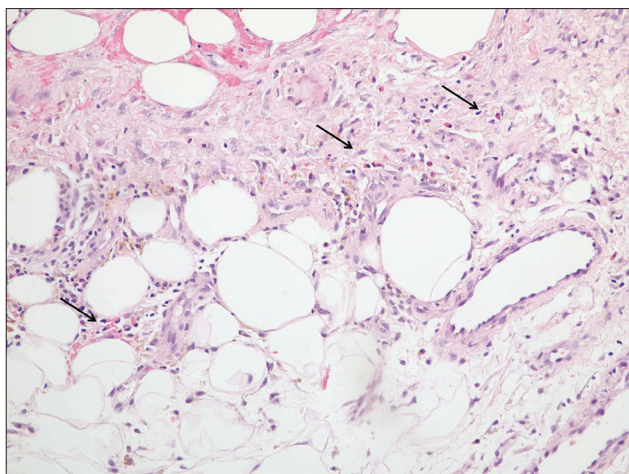
**Figure 1:** Subcutaneous nodules in areas of heparin injection (abdomen)



**Figure 2:** (a and b) Cutaneous drug reaction with eosinophilic panniculitis induced by heparin. Low power view showing inflammatory infiltrate in the upper dermis, thickened septa and lobules (H and E, x40)

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**Figure 3: Detail of numerous eosinophils (arrows) in the inflammatory infiltrate in the septum (H and E, x200)**

suffered from vitamin D, parathyroid hormone or calcium-phosphate disturbances.<sup>[2]</sup> Nodules induced by sodium LMWH have also been found. Funt *et al.* observed nodules in 14 of 426 cancer patients following dalteparin (heparin with sodium salts) injection. These authors described the radiological characteristics of these nodules, but histological studies were not performed.<sup>[3]</sup>

Regarding to acenocoumarol, the absence of reported cases of panniculitis caused by this drug as well as the involution of cutaneous lesions despite continuing with this treatment, helped us to exclude acenocoumarol as a possible cause of the lesions of our patient.

Eosinophilic panniculitis is a rare form of panniculitis characterized by septal and lobular involvement with eosinophilic infiltration. It is believed to be a reactive process that has been associated with a variety of systemic conditions such as gnathostomiasis, leukocytoclastic vasculitis and erythema nodosum.<sup>[4]</sup> In rare instances, eosinophilic panniculitis has been observed as a local phenomenon induced by subcutaneous or intramuscular drug injections including apomorphine, specific immunotherapy, benzathine penicillin and calcium

heparin.<sup>[1,5]</sup> Delayed-type hypersensitivity reactions have also been considered as the cause of these reactions.<sup>[5]</sup>

## CONCLUSION

To the best of our knowledge, this is the first case of eosinophilic panniculitis induced by administration of LMWH containing sodium salts.

**Ana Batalla, Elena Rosón, Celia Posada, Ángeles Flórez**

Department of Dermatology, Pontevedra Hospital Complex, Pontevedra, Spain

**Address for correspondence:** Dr. Ana Batalla, Department of Dermatology. Xestión Integrada Pontevedra - Salnés. Hospital Provincial. C/ Dr. Loureiro Crespo, n2. CP 36002. Pontevedra, Spain.  
E-mail: anacebey@yahoo.es

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Sir,

De Sanctis-Cacchione syndrome (DSC) (MIM #278800) is a rare autosomal recessive disorder with a gene map locus of 10q11, originally described as “xerodermic idiocy.”<sup>[1]</sup> DSC is characterized by cutaneous photosensitivity, microcephaly, mental retardation, short stature, hypogonadism, spasticity, peripheral neuropathy and sensorineural deafness.<sup>[2]</sup> In most of the cases in the literature, hypogonadism has been described, but we report a case of DSC with intact gonadal functions.

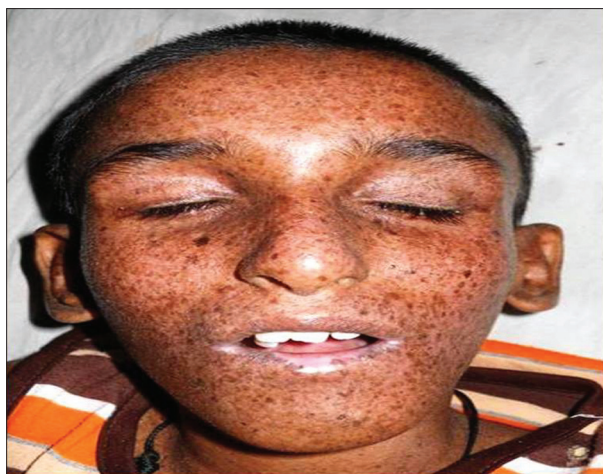
A 10-year-old boy presented with multiple episodes of myoclonic seizures and progressive, rapid loss of milestones, cognition, vision and hearing for the past 6 months. There was a history of persistent drooling of saliva, nasal regurgitation of feeds with episodes of choking and coughing with attempted solid feeds. The child was confined to bed and gave no indications for thirst, hunger, bladder or bowel needs. There was no response to auditory and visual stimuli. Past history suggested dry and scaly skin and photosensitivity (since infancy) and developmental delay (developmental quotient 0.33; revised Denver Developmental Scale II). The child was a third in birth order, product of a third degree consanguineous marriage with high maternal (40 years) and paternal (45 years) age, born at term with an uneventful neonatal period. Other siblings were unaffected and there was no family history of photosensitivity, seizures or mental retardation. On examination, the child was emaciated with a weight of 15 kg (<3<sup>rd</sup> percentile), length of 122 cm (<3<sup>rd</sup> percentile), body mass index of 10.1 (<3<sup>rd</sup> centile) and head circumference of 45 cm (<3<sup>rd</sup> percentile). Facial features were suggestive of “Old man look” with an elongated face, micrognathia, pinched nose and crowded caries teeth. The skin lesions were noted over the face, neck, upper chest and exposed parts of limbs and consisted of scaling, erythema, crusting with patches of hyperpigmentation [Figure 1]. He had fixed contractures of the ankle, knee, elbow and wrist joints [Figure 2]. The genitals, including the penis and testes, were normal with a stretched penile length of 4.5 cm (–2.5 standard deviation = 3.7 cm)

and Tanner’s sexual maturity rating (SMR) of stage 2. Examination of the central nervous system revealed that the child had spontaneous eye opening without focusing, motor response of localization to pain and incomprehensible vocal response. Fundus examination revealed the presence of salt and pepper retinopathy. Brainstem evoked auditory response revealed severe sensory-neural hearing loss. Pharyngeal reflex (gag reflex) was weak suggestive of bulbar involvement. On examination, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 7<sup>th</sup> and 12<sup>th</sup> cranial nerves were normal. Motor system examination showed a decrease in muscle bulk, increased tone, reduced power (1/5) and contractures at knee, ankle, elbow and wrist joints. The elicitation of deep tendon reflexes were masked by fixed contractures. There were no abnormal movements and no cerebellar or meningeal signs. Examination of the abdominal, respiratory and cardiovascular systems revealed no other abnormalities. Laboratory investigations showed a normal hemoglobin (Hb 12.1 g/dl), serum creatinine (0.8 g/dl), serum albumin (3.5 g/dl), alanine aminotransferase (24 IU/L) and alkaline phosphatase (120 IU/L). Skeletal survey showed a bone age of 11-12 years. Contrast-enhanced computed tomography (brain) revealed dilated lateral ventricles, atrophy of cerebral and cerebellar cortex and hydrocephalus (ex-vacuo) with no intracranial calcifications [Figures 3 and 4]. Nerve conduction velocity of upper and lower limb suggested axonal neuropathy. Electromyography revealed a decline in motor unit recruitment and other nonspecific changes. Based on the constellation of above features, a diagnosis of DSC was established.

The child was advised protection from sun exposure by the use of protective clothing, eyeglasses, broad spectrum sunscreens containing para-aminobenzoic acid esters and skin emollients. Seizures were controlled with sodium valproate (25 mg/kg) and lamotrigine mg/kg (2.5 mg/kg/day). Physiotherapy was initiated to prevent the worsening of contractures. Child was on regular follow-up for next 6 months. Seizures were controlled with no further progression of neurological illness.

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**Figure 1: Elongated face with erythema, scaling and crusted lesions**



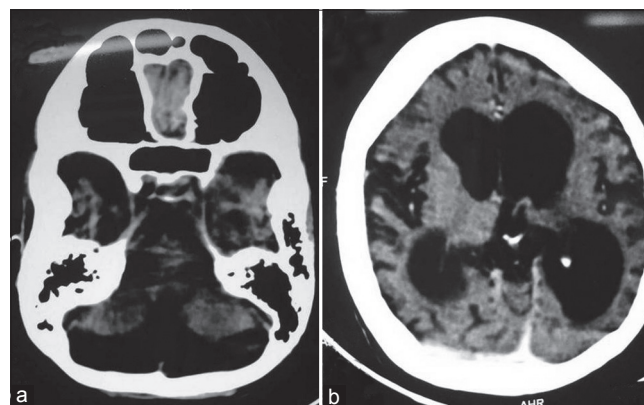
**Figure 3: X-ray of skull Anterio-Posterior view showing prominent mastoids and no intracranial calcifications**

Xeroderma pigmentosa (XP) results from defects in the excision repair of ultraviolet (UV) induced deoxyribonucleic acid (DNA) damage. Defects in nucleotide excision repair (NER) results in inherited neurocutaneous syndromes such as XP, Cockayne syndrome and trichothiodystrophy. There is a complex relationship between NER mutations and clinical features. Seven xeroderma pigmentosum genes, XPA through XPG, have been identified. Conversely, different mutations in one gene can lead to different clinical disorders with variation in systemic involvement.<sup>[2,3]</sup> The gene locus implicated in DSC is ERCC6, which is located at 10q11, which is also called Cockayne syndrome-B gene.<sup>[4]</sup>

Among the variants of XP, patients with DSC have the greatest UV sensitivity and the poorest DNA repair. The neurological manifestations in XP have been hypothesized to be secondary to defective DNA repair



**Figure 2: (a and b) Contractures at elbow, wrist, knee and ankle along with lesions on upper chest, hands and legs**



**Figure 4: (a and b) Computed tomography scan of patient showing cortical and cerebellar atrophy with ex-vacuo hydrocephalus**

in the neuronal cells resulting in neuronal death or dysfunction. Although neurological symptoms appear in the first two decades of life, late presentation in adults has also been reported.<sup>[5]</sup> The common neurological manifestations of DSC are progressive neurological deterioration, peripheral neuropathy and sensorineural deafness observed in 18% of cases.<sup>[6]</sup> Other manifestations include microcephaly, choreoathetosis, cerebellar and extra pyramidal syndromes.<sup>[7]</sup> The late onset of neurological complaints and the relative preservation of gonads and sexual maturity in our case depict sparing of cells from UV induced damage. Early intervention and appropriate protection from sunlight started early in the illness could have a significant impact in delaying the onset of neurological symptoms. There are very few cases reported with complete manifestations of this syndrome. However, many patients have one or more of its neurological features. The features that favored a diagnosis of DSC in our case were mental retardation, microcephaly, cutaneous photosensitivity, stunting, spasticity, contractures, sensorineural deafness and peripheral neuropathy. However, unlike the classical

DSC, our child had normal gonads and sexual maturity staging at the time of presentation. In the absence of cataract, optic atrophy, skeletal dysplasia and basal ganglia calcifications, Cockayne syndrome was ruled out.

Diagnosis of DSC is mainly based on clinical features. Chromosomal breakage studies, complementation studies and gene sequencing to identify the specific gene complementation group are supportive. The mainstay of treatment is adequate sun-protection and regular follow up for the early detection of cutaneous malignancies. This condition is not curable and lesser than 40% patients with severe manifestations survive beyond the second decade of life. A multidisciplinary approach, involving a Neurologist and an Ophthalmologist, is required to deal with the associated conditions. A novel approach to photo protection is to repair DNA damage after UV exposure by the delivery of a DNA repair enzyme into the skin by means of specially engineered liposomes. T4 endonuclease V has been shown to repair cyclobutane pyrimidine dimers resulting from DNA damage.<sup>[8]</sup> Gene therapy for XP is still in a theoretical and experimental stage. The earlier onset of disease is associated with a poorer prognosis. Parental counseling plays a significant role in the reduction of future recurrence as prenatal diagnosis is possible by amniocentesis or chorionic villous sampling.

**Hema Mittal, Sumit Mehndiratta<sup>1</sup>,  
Jaya Shankar Kaushik, Tushar Godbole**

Department of Pediatrics, UCMS and GTB Hospital, <sup>1</sup>Lok Nayak Hospital, New Delhi, India

**Address for correspondence:** Dr. Sumit Mehndiratta,  
Department of Pediatrics, Lok Nayak Hospital,  
New Delhi - 110 002, India.  
E-mail: drsmehndiratta@gmail.com

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## Erythematous indurated plaque lesions on the breast

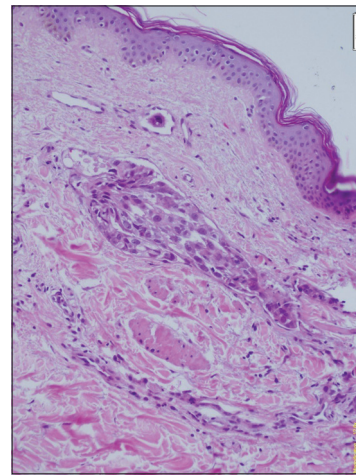
A 50-year-old female patient, who had retraction of the right nipple for 2 years and erythema in the same breast for 2 months, was referred to our clinic. Mammography and breast ultrasonography performed at the time of onset of nipple retraction were normal. Dermatological examination revealed three erythematous, mildly indurated plaque lesions on the right breast, one of which involved the areola [Figure 1]. The nipple was retracted. The patient had no subjective complaints. The right axillary examination detected several lymphadenopathies, as confirmed by ultrasonography.



**Figure 1:** Three erythematous plaques on the right breast, one involving the areola

The histopathological examination of the skin biopsy revealed islands of tumor cells in the dermal lymphatics [Figure 2]. These infiltrations consisted of round-shaped atypical cells with vesiculated nuclei and marked nucleoli. In immunohistochemical studies, strong positive staining by low-molecular weight keratin (LMWCK) and epithelial membrane antigen (EMA) and non-specific staining by vimentin have been detected.

### WHAT IS YOUR DIAGNOSIS?



**Figure 2:** Tumor islands consisted of atypical epithelial cells in the lymphatics (H and E, x200)

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**Answer: Carcinoma erysipeloides****DISCUSSION**

The rate of skin metastasis in internal malignancies varies from 0.7 to 10%.<sup>[1]</sup> The skin metastases may occur as a result of lymphogenous, hematogenous spread, or direct invasion of surrounding tissue by tumor cells. Skin metastases usually occur as a finding of the spread or the recurrence of internal malignancies; however, they may rarely be an initial finding of an undetected malignancy.

Carcinoma erysipeloides (CE) is a rare cutaneous metastasis, which results from the lymphatic spread of an inflammatory carcinoma. While it is mostly related to breast cancer, it may also result from other tumors.<sup>[2-4]</sup> In our case, a solid mass lesion was also detected in the right breast, and the biopsy performed at the General Surgery Department was reported as invasive ductal carcinoma.

In the differential diagnosis of CE, erysipelas, cellulitis, radiation dermatitis, and contact dermatitis should be considered. The exact diagnosis of CE is made by histopathology. The dermal lymphatic invasion is considered as the characteristic feature of CE.

Other than breast cancer, nipple retraction may occur due to periductal mastitis, ductal ectasia, tuberculosis, sarcoidosis, fungal infections, and granulomatous inflammatory diseases, including Wegener's granulomatosis and idiopathic granulomatous lobular mastitis.<sup>[5]</sup> In our case, nipple retraction began 2 years ago, and the laboratory examinations performed at that time revealed no pathology. Therefore, nipple retraction was not considered to be associated with breast cancer.

In general, CE develops several months or years after the diagnosis of primary carcinoma. CE is an indicator of poor prognosis, and patients often die within few months of its diagnosis. CE developing as an initial sign of undiagnosed tumor is rare.<sup>[2]</sup> Interestingly, in our patient, CE was diagnosed before the diagnosis of breast cancer.

In cases of CE, treatment of primary tumor is sufficient. Surgical treatment is not recommended. Systemic chemotherapy and hormonal therapies

alone or in combination with radiotherapy represent the basic treatment options.<sup>[2]</sup> We also referred our patient to the general surgery and oncology departments for planning the treatment of primary tumor.

**CONCLUSION**

While the skin metastases generally occur after the diagnosis of primary tumor, they may also develop prior to diagnosis. The skin invasions can be clinically confused with other disorders. This may result in delayed diagnosis of the malignancy and decrease in survival. Our case demonstrated the importance of non-specific skin lesions such as erythema in diagnosis of breast cancer. Therefore, the dermatologists should be careful with respect to cutaneous metastases, even if the patient's medical history does not include malignancy.

**Bilge Bülbül Şen, Emine Nur Rifaioğlu,  
Özlem Ekiz, Tümay Özgür<sup>1</sup>, Seçkin Akküşük<sup>2</sup>,  
Mehmet Uğur İnan, Asena Çiğdem Doğramacı**

Departments of Dermatology, <sup>1</sup>Pathology, <sup>2</sup>General Surgery,  
Mustafa Kemal University School of Medicine, Hatay, Turkey

**Address for correspondence:** Dr. Bilge Bülbül Şen,  
Department of Dermatology, Mustafa Kemal University, Tayfur Ata  
Sokmen Medical School, Serinyol, Antakya, Hatay 31005, Turkey.  
E-mail: bilgebulbul@yahoo.com

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