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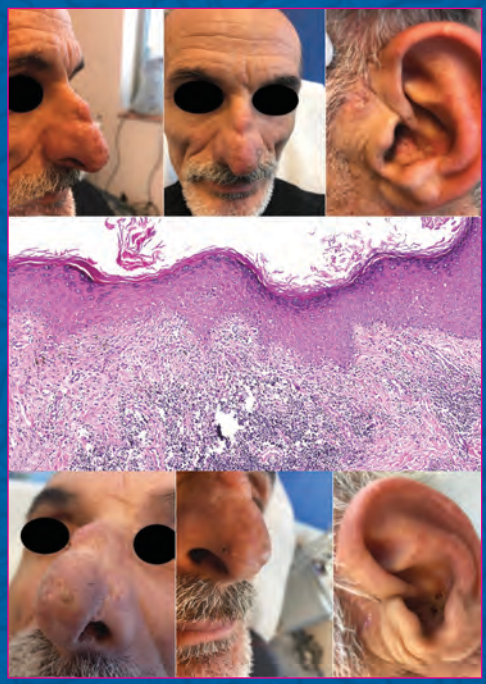

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Review Article

What Is in a Name?—Demystifying "SKINTED"—A Review of Literature from Dermatological Perspective

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Abstract

Surgery of the knee, injury to the infrapatellar branch of the saphenous nerve, traumatic eczematous dermatitis (SKINTED) is a regional dermatitis specific to total knee arthroplasty, occurring postsurgically. It is characterized by an eczematous eruption localized to the knee, mostly the anteroinferior aspect, presenting as pruritic, dry, erythematous, scaly, or at times papulovesicular lesions. Having been known over the past decade by various nomenclatures, the basic pathogenesis has now been agreed upon as a locoregional immune dysfunction because of damage to lymphatics occurring postsurgically. We have described three case reports of typical eczematous lesions occurring after total knee replacement surgery and reviewed the literature for similar cases described across the literature. A PubMed and Google Scholar search pertaining to the articles published with the keywords "SKINTED" and "autonomic denervation dermatitis" was conducted. A total of 10 results were obtained after exclusion of duplicated and irrelevant search results. This yielded one review article, one original article, seven case reports, and two correspondence articles. Based on the review, the authors agree with the concept of Rucco's immunocompromised district, being the most logical explanation for the occurrence of SKINTED. SKINTED should be differentiated from implant eczema occurring because of hypersensitivity to metal implants, which presents as systematized contact dermatitis and has a predefined set of diagnostic criteria.

Keywords: Autonomic denervation dermatitis, immunocompromised district, injury to the infrapatellar branch of the saphenous nerve, surgery of the knee, traumatic eczematous dermatitis (SKINTED)

Introduction

Surgery of the knee, injury to the infrapatellar branch of the saphenous nerve (IPBSN), traumatic eczematous dermatitis (SKINTED) is a regional dermatitis specific to total knee arthroplasty (TKA), occurring postsurgically. It is characterized by an eczematous eruption localized to the anteroinferior aspect of the knee, presenting as pruritic, dry, erythematous, scaly, or at times papulovesicular lesions. This term was first conceived in 2009[1] and, over the years, has been referred to by different nomenclatures, such as autonomic denervation dermatitis, trophoneurosis, neuropathic dermatitis,[2] and posttraumatic eczema. These terms have sometimes been used synonymously and sometimes as different entities. The most recent concept that tries to unify these entities is explained by the theory of "immunocompromised district" (ICD).[3] Surgical incision of the TKA leads to the damage to the locoregional sensory nerves—saphenous nerve being the most important nerve, as well as to the interruption of lymphatic drainage. These factors contribute to a barrier dysfunction as well as immune dysregulation, which in turn predisposes the healed surgical site to develop eczema or even other dermatoses. In the present article, we describe three cases, with similar eczematous eruption post-TKA, and a review of literature for this entity "SKINTED." Our aim of conducting this review is to clarify the etiopathogenesis of this entity and to "declutter" the somewhat confusing

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conundrum of various nomenclatures. Another objective is to differentiate it from a rare, but possible diagnosis of implant eczema.

SKINTED: Report of Three Cases

Case 1

A 68-year-old woman, presented with itchy, exfoliating skin lesions over the right knee, which appeared 4 months after a TKA (cobalt chromium knee implant), indicated for right knee osteoarthritis. There was no history of oozing, pustules, ulcers, or edema over the area or any pain or difficulty during the joint movement. The patient did not have a history of preexisting atopic dermatitis. Cutaneous examination revealed a well-demarcated, erythematous, scaly plaque, over the surgical incision and extending medially. Orthopedic examination did not reveal any restriction of joint mobility, pain, or deformity. X-ray of the knee (anteroposterior and lateral view) was completely normal without any signs of implant loosening. Patch testing was negative for the metals in the implant. Based on the typical clinical morphology and topography of the lesion, a diagnosis of SKINTED was put forward. X-ray of the knee (anteroposterior and lateral view) was completely normal without any signs of implant loosening. Patch testing by Indian standard battery of contact allergens was found to be negative. Rest of the cutaneous examination was normal. Based on the typical clinical morphology and topography of the lesion, a diagnosis of SKINTED was put forward. Topical emollients and moderate potency topical steroid cream (mometasone furoate 0.1%) were given, following which the patient showed clinical improvement in terms of regression of itching, erythema, and scaling. However, during the period of follow-up of 6 months, the patient continued to develop relapses and remission over the same site.

Case 2

A 52-year-old woman presented with itchy plaques, associated with oozing, over the left knee [Figure 1]. She had undergone TKA (cobalt chromium), for osteoarthritis, 5 months before the skin lesions appeared. The lesions initially started as itchy, reddish, slightly edematous plaques, with overlying erosions and papulovesicular eruptions, associated with oozing. They were present over both the medial and lateral aspects of the knee with a central, healed scar.

The patient had recurrent episodes of such lesions over the operated knee, which would resolve partially with treatment, but did not show complete resolution during the course of a 6-month follow-up period. There was a history of postoperative wound infection and postoperative wound gaping, which resolved with antibiotics. X-ray of the operated knee showed a healthy implant, without any signs of loosening. Patch test was negative. There was no pain on joint movement or postoperative deformity of the knee joint. The patient was treated with a combination of topical steroid and antibiotic cream, with a relapsing and remitting course of the skin lesions.

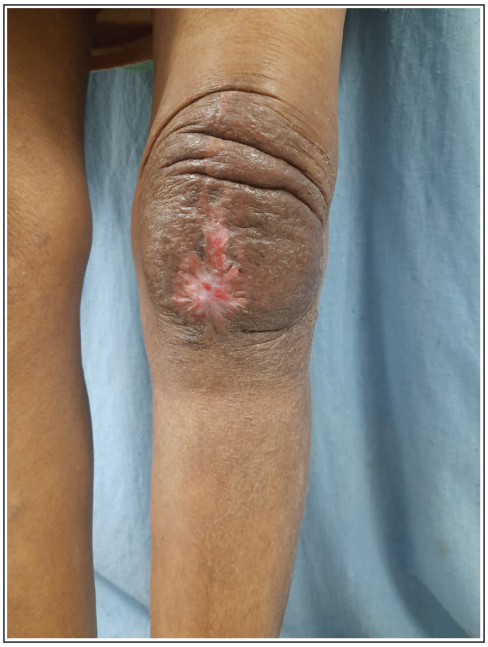

Figure 1: Erythematous, indurated coalescent plaques with oozing present over the left knee, with a central, hypopigmented scar

Case 3

A 53-year-old male underwent TKA of the left knee, with a cobalt-chromium knee implant. After 3 months of an uneventful postoperative course, the patient began developing reddish scaly plaques over the operated knee, associated with severe itching. The patient was atopic and had a past history of chronic eczema over the ankles, which also aggravated simultaneously. The patient was prescribed a topical corticosteroid and emollient, following which the lesions subsequently improved, but with frequent relapses, even on treatment, over the subsequent course of follow-up. Rest of the local and systemic examination, x-ray of the operated knee, and patch testing did not show any abnormal or positive findings.

Discussion and Review of Literature

A PubMed and Google Scholar database search pertaining to the articles published with the keywords "SKINTED" and "autonomic denervation dermatitis" was conducted. A total of 10 results were obtained after the exclusion of duplicated and irrelevant search results. This yielded one review article, one original article, seven case reports, and two correspondence articles. These articles were thoroughly reviewed, and information was collected and condensed, regarding the pathomechanisms and clinical course of SKINTED [Table 1].

Table 1: Literature summary of SKINTED

Type of publication	Results/summary	Remarks/consensus
Brief report/ correspondence[1]	Total number of patients: 55 Clinical presentation: See footnote* Preceded by anesthesia or hypoesthesia Timeline: 3 weeks to 4 months after surgery Distribution of lesions: Exclusively lateral: 75% 25% had involvement of the skin on both sides of incision	The term SKINTED was coined in this correspondence and gained slow popularity The pathogenesis was considered obscure and attributed to barrier dysfunction occurring postsurgery
Case report and literature review[2]	Number of cases: 10 Consisting of various surgical procedures on their lower extremities Clinical presentation: Typical* Timeline: 6 months to 3 years postsurgery Patch test: No significant positive results Hypoesthesia and decreased sweating (demonstrated by starch iodine testing) at the lesional sites	The authors in this study coined the term "autonomic denervation dermatitis" The entity of SKINTED was considered as a subset under the umbrella of autonomic denervation dermatitis
Review article[3]	Total studies reviewed: 8 (one cohort and other case reports and series) 69 reported cases of dermatitis occurring post-TKA Distribution: Lateral to the incision in 30/34 operated knees. Bilateral lesions : six patients No functional limitation	The review focuses on skin lesions occurring in the local area, after knee arthroplasty Since the article has been published in an orthopedic journal, a dermatological viewpoint cannot be derived accurately; however it seems that a majority of cases are SKINTED
Original article[4]	Total number of cases: 203 Estimated incidence of 4.4% Mean duration: 4 months (range: 3–6 months) Clinical presentation: See footnote* Presence of perilesional and marginal hypoesthesia in all patients Complete response, without recurrence in all patients at the end of 6 months	In this article also, SKINTED has been considered as a subset of autonomic denervation dermatitis
Case report[5]	68-year-old patient with eczematous lesions along the lateral margin of incision on both the knees, 9 months postbilateral arthroplasty Managed with topical mid-potent corticosteroid and emollient	SKINTED considered as a subset of autonomic denervation dermatitis
Case report[6]	60-year-old woman B/L total knee replacement Presented with scaly, erythematous to hyperpigmented pruritic plaques 9 months after TKR on the right knee and oozy, erythematous plaques over the left knee, 3 months post-TKR	SKINTED considered as a part of "autonomic denervation dermatitis"
Case report[7]	Two cases Case 1: 70-year-old, arthroplasty—1.5 years back Case 2: 49-year-old woman Localized itchy red lesions with watery discharge over both lower limbs adjacent to surgical scar	SKINTED considered as "autonomic denervation dermatitis"
Correspondence[8]		SKINTED is considered to be a subset of the ICDs of the skin
Case report[9]	Two cases relevant to the present review—one patient developed surgical scars on both the knees after bilateral knee transplant Other patient developed eczema at the site of surgical scar for an operated humerus	SKINTED is considered as a manifestation or a type of Rucco's ICD of the skin

TKR = total knee replacement; *Clinical presentation: xerotic eczematous, discrete to confluent papules and plaques with associated xerosis and scaling, occasionally associated with oozing and fissuring

Table 1: References

[1]Verma SB, Mody BS. Explaining a hitherto nameless condition: "SKINTED." Clin Exp Dermatol 2009;34:e465-6

[2]Madke B, Mhatre M, Kumar P, Singh AL, Patki A. Autonomic denervation dermatitis: A new type of eczematous dermatitis. Clin Dermatol Rev 2017;1:61-4

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[4]Nazeer M, Ravindran R, Katragadda BC, Muhammed EN, Rema DTJ, Muhammed MN. SKINTED: A rare complication after total knee arthroplasty. Arthroplast Today 2020;6:1028-32

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Primary concepts of etiopathogenesis of SKINTED

(a) Sensory denervation and subsequent barrier dysfunction: The pure sensory IPBSN is most commonly resected during TKA.[4] The subsequent hypoesthesia alters the local epidermal barrier function, increases transepidermal water loss, and leads to subsequent xerosis.[1] However, this cannot convincingly explain how sensory loss could trigger eczematous eruptions at the surgical site.

(b) Posttraumatic eczema: Inflammatory response occurring posttrauma has been postulated as a likely trigger for eczema and is likely to occur within 2–4 weeks after any type of mechanical, chemical, or thermal trauma.

(c) Autonomic denervation dermatitis: In 2017, the entity of autonomic denervation dermatitis[5,6] was suggested to include all cases of eczematous eruptions occurring at the site of healed surgical scars. Resection of dermal autonomic nerves following surgical trauma alters the vasomotor and sudomotor responses as well as the cutaneous microcirculation and ultimately disrupts the physiological skin barrier, aided and abetted by resected C-type nerve fibers and an imbalance of various neuropeptides and acetylcholine.

(d) The unifying concept of "ICD": A coordinated crosstalk between the keratinocytes, appendages, Langerhans cells, lymphocytes, mast cells, macrophages, and Merkel cells is necessary for maintaining the homeostasis of skin, which is also a dynamic immune organ. This sectorial impairment of immunological homeostasis of skin, following trauma or any other "stressor" event has been described by the term Ruocco's ICDs. It unites different phenomena such as isomorphic (Koebner) and isotopic (Wolf) responses of skin[7] and is central to understanding SKINTED and many similar types of dermatoses. In surgical scars and their vicinity, the regional lymphatic drainage is hampered, which adversely affects the immune cell trafficking in the surgical site. Also, the transection of autonomic and sensory nerves in the area leads to an altered neurotransmitter signaling. Other similar examples of the ICDs include skin grafts, herpes zoster scars, striae, insect bites, injection sites, sites of radiotherapy, tattoos, sites exposed to chronic friction, and sites of epilation. All these ICDs are vulnerable because they show predilection to develop infections, inflammatory dermatosis, and even tumors.[7]

We agree with the viewpoint that SKINTED is indeed a subset of the ICD. In the three cases that we have reported, the timeline for the development of eczematous lesions was variable, ranging from 2 months to 5 months. In the variable case reports of non-SKINTED ICDs, the onset of second dermatoses ranges from as early as 2 days (the development of new onset lesions of cutaneous B cell lymphoma in a healed herpes zoster lesions, within 5 days) to more than 40 years (the development of basal cell carcinomas in previously irradiated sites with signs of chronic radiation dermatitis).[7]

An important differential diagnosis of SKINTED is implant eczema, which occurs secondary to cobalt-chromium metal implants, and is a common concern prevailing among the orthopedic surgeons. The most important presenting symptoms of implant eczema are painful persistent synovitis and synovial effusion and unexplained implant failure. Cutaneous presentation is variable, ranging from therapy resistant local eczema to a systematized contact dermatitis reminiscent of symmetrical drug-related intertriginous and flexural exanthema. A majority of the reported cases are presumed metal allergy, many of them ultimately being misrepresentations of SKINTED itself.[8] However, there is still a lack of evidence regarding correlation between metal hypersensitivity and implant-related complications.[9] The criteria for metal hypersensitivity to implants are tabulated in Table 2.

Table 2: Diagnostic criteria for metal implant hypersensitivity by American contact dermatitis society[1]

Major criteria	Minor criteria
Eruption overlying the metal implant	Unexplained pain and/or failure of the offending implant
Positive patch test to the metal used in the implant	Dermatitis reaction is resistant to therapy
Complete resolution after the removal of the implant	Morphology consistent with dermatitis (erythema, induration, papules, vesicles)
Chronic dermatitis beginning weeks to months after implantation	Systemic allergic dermatitis reaction
	Histology consistent with allergic contact dermatitis
	Positive *in vitro* test to metals (e.g., lymphocytes transformation test)

Noncriteria features: Radiographic images can show osteolytic lesions in the proximity of the femoral and tibial components, which form as a result of the inflammatory response and can lead to aseptic loosening of the implant, loss of tibial posterior slope, and setting of the tibial base plate into varus, as compared to the previous images taken after surgery

Table 2: Reference

[1]Schalock PC, Crawford G, Nedorost S, Scheinman PL, Atwater AR, Mowad C *et al*. Patch testing for evaluation of hypersensitivity to implanted metal devices: A perspective from the American Contact Dermatitis Society. Dermatitis 2016;27:241-7.

Role of predisposing factors in the occurrence of SKINTED: Can it be predicted?

Cicek *et al.*[10] studied the role of autonomic dysfunction in atopic dermatitis and concluded that sudomotor activity controlled by the sympathetic nervous system, as well as unmyelinated fibers that play a role in this activity is affected in patients with atopic dermatitis. The same findings may be extrapolated at the sites of surgical scars, as pointed out by Madke *et al.* This dysautonomia, along with cutaneous dysimmunity, may synergistically play a role in triggering eczematous lesions at the surgical sites. Moreover, an ICD is more liable to be affected by regional recurrence of preexistent dermatoses.[11] It can only be hypothesized that the incidence of SKINTED may be increased in atopic individuals; however, further studies of this entity are required to find out the association.

Summary and Conclusion

Based on the review of available data, the authors conclude that SKINTED represents locus minoris resistentiae or ICD of the skin. Autonomic denervation seems to be an adjunctive factor in the etiopathogenesis by contributing in creating the ICD. The knowledge of this entity alleviates unnecessary stress among the orthopedic surgeons as well as the knee arthroplasty patients. The patients can also be counseled regarding the relapsing and remitting nature of the entity, thus improving overall patient care.

Limitations of this review

Because of limited data availability, a systematic meta-analysis cannot be conducted reliably. Furthermore, we have not been able to shed light on the rate of relapses and recurrence of SKINTED, as well as any predisposing factors that play a role in the occurrence of this entity. A systematic study should be conducted with a reasonable sample size for further insight into the predisposing factors of SKINTED as well as its course and prognosis.

Ethics statement

Informed consent was taken from the patient prior to using data and photograph.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

Data availability statement

Data sharing was not applicable to this article as no datasets were generated or analyzed during the current study.

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Original Article

Relevance of Serum Vascular Endothelial Growth Factor (VEGF) and Serum Interleukin-10 in the Severity of Psoriasis in South Indian Patients: A Case–Control Study

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Abstract

Background: Psoriasis is a chronic inflammatory disorder and is associated with obesity, diabetes mellitus, and hypertension. There is an increased expression of inflammatory cytokines (interleukin [IL]-17, tumor necrosis factor [TNF]-α, IL-22, vascular endothelial growth factor [VEGF]) in the serum of psoriasis patients. Serum levels of IL-10, another anti-inflammatory cytokine, have been found at varying values in psoriasis in different regions of the world. **Aims and Objectives:** The aim of this article is to assess the serum IL-10 and serum VEGF in psoriasis patients with no co-morbidities and healthy controls. **Materials and Methods:** This study was conducted on 46 serum samples (23 psoriasis subjects and 23 healthy controls). After informed consent, 3 mL of serum was obtained and stored at -70°C. The samples were quantitatively assessed for VEGF-A and IL-10 by the enzyme-linked immunosorbent assay. **Results:** This study revealed that the mean (±SD) value of serum VEGF in cases was significantly higher than that in controls (cases = 235.21 ± 138.71; controls = 104.73 ± 36.01 pg/mL). However, levels of serum IL-10, although increased in cases (2.37 ± 1.61 pg/mL) when compared with controls (1.64 ± 0.89 pg/mL), showed no statistical significance. **Conclusion:** In this study, serum VEGF and IL-10 levels were increased in psoriasis when compared with controls but were not significantly related to the Psoriasis Area and Severity Index. The significant correlation between serum VEGF and IL-10 levels in cases when compared with controls suggests their role in the pathogenesis of psoriasis. Persistently increased values in psoriasis patients may lead to the development of comorbidities.

Keywords: Interleukin-10, PASI, psoriasis, vascular endothelial growth factor

Introduction

Psoriasis is a chronic inflammatory disorder which is extremely polymorphic, varying from small nail pits to full blown erythroderma. It is a complex interplay among genetics, immunology, and multiple environmental factors.[1] Globally, the prevalence of psoriasis varies from 0.14% to 1.99%.[2] In India (2010), the prevalence of psoriasis varies from 0.44% to 2.8%.[3] According to the recent data, the countries with the highest number of adults affected with psoriasis were the USA (3.4 million) and India (2.9 million). Psoriasis is now considered a systemic disease with psychological, metabolic, musculoskeletal, and cardiovascular comorbidities.[2] The clinical hallmark of psoriasis, characterized by erythematous scaly plaques, is due to neovascularization in the dermal papillae and psoriasiform hyperplasia of the epidermis.[4] Neoangiogenesis plays an integral role in the immunopathogenesis of psoriasis, with keratinocytes being the source of vascular endothelial growth factor (VEGF).[5,6] Apart from neovascularization, it is known to be involved in epidermal hyperproliferation, leucocyte infiltration in the skin, and also koebnerization in psoriasis.[6,7] With the increased understanding of inflammation in psoriasis, cytokines have been found to play a critical role in its pathogenesis. Psoriatic plaques

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have been shown to contain increased levels of cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), IL-1a, IL-17, and IL-22.[8,9,10] IL-10 is a pluripotent cytokine and exhibits anti-psoriatic activity on different cell populations including antigen-presenting cells and T-cells.[9,10] Further, regulatory B cells produce IL-10, which ameliorate psoriasis.[11] IL-10 is also produced by keratinocytes upon exposure to UV radiation, exhibiting an immunosuppressive effect.[12] There have been many studies conducted in different parts of the world on the serum values of IL-10 in psoriasis, which have thrown up varying findings.[8] Apart from psoriasis, these cytokines are also known to play a role in diabetes mellitus and hypertension.[13-15] The various clinical types of psoriasis and its severity are dependent on the interaction of the cytokines and keratinocytes.[4,11] The Psoriasis Area and Severity Index (PASI) is a clinical tool to assess the severity of psoriasis.[16] It has its own limitations, being subjective and with a poor sensitivity to changes in small areas of involvement with the disease.[8,16] In the present study, an effort has been made to study the relevance of serum VEGF and IL-10 in psoriasis patients with no comorbidities, to delineate the behavior of these cytokines in psoriasis.

Materials and Methods

This was a prospective case–control study conducted in the Department of Dermatology of a tertiary care center in South India. This study was conducted during the period from June 2016 to May 2018 after approval from the Institutional Ethics Committee (EC/DRP/10/05-04-2016). A written informed consent was taken from all the participants recruited for the study.

Study participants

All adult patients (>18 years) with chronic plaque psoriasis with PASI >10 were recruited for the study. These cases were selected after ruling out that they had no comorbidities such as diabetes mellitus or hypertension (confounding factors) and were not on any systemic treatment such as methotrexate, cyclosporine, or phototherapy. Patients who had stopped systemic treatment for a period of 4 months or more at the time of recruitment were also included for the study. Appropriate informed consent was taken from the participants. Patients with psoriatic arthritis and pustular psoriasis were excluded from the study. A detailed history and examination with assessment of severity with PASI score[16] was done for all recruited patients. Routine investigations such as complete blood picture, urine routine, HbA1c (glycosylated hemoglobin), liver function tests, serum creatinine, blood urea, C-reactive protein, chest X-ray, and skin biopsy (in doubtful cases) were done.

Controls

Age- and sex-matched, otherwise healthy subjects who visited Dermatology OPD for the treatment of non-inflammatory dermatoses were recruited for the study after obtaining informed consent. These individuals were also selected after exclusion of comorbidities such as diabetes mellitus or hypertension.

Estimation of serum VEGF and IL-10 by ELISA

An aliquot of 3 mL of peripheral blood serum was collected from all the 23 cases and 23 controls and stored in a refrigerator at -70°C until analysis. Repeated thawing and freezing of samples were avoided. Thus, a total of 46 serum samples were taken for the analysis of serum VEGF and IL-10 levels. Commercially available Human VEGF-A enzyme-linked immunosorbent assay (ELISA) kit (Diaclone, France) and Human IL-10 ELISA kit (Diaclone, France) were used for the quantitative estimation of serum VEGF and IL-10 levels, respectively. The stored serum samples were diluted and measured in duplicate. The reaction was terminated by adding sulfuric acid and the absorbance was measured at 450 nm using a spectrophotometer. The absorbance measured in each well by the ELISA reader was proportional to the concentration of the respective cytokines present in the serum sample.

Statistical analysis

In this study, descriptive statistics comprising mean ± SD were computed for age, body mass index (BMI), PASI score, and cytokine levels. The independent *t*-test was used to compare mean±SD of cytokines levels between cases and controls. Pearson's correlation coefficient was used to assess the correlation between age and cytokine levels and other factors. The level of significance was fixed at $P < 0.05$. The statistical analysis was done using SPSS version 16 software.

Results

On analyzing the results, of the 46 subjects, 23 were cases with moderate-to-severe psoriasis and 23 were age- and sex-matched subjects without psoriasis or any other chronic inflammatory diseases. The mean age of cases and controls was found to be 37.96 years (SD ±11.92) and 38.48 years (SD±12.32), respectively, thus being matched for age and sex. Similarly, the mean of BMI in the cases and controls was 25.3 (±7.67) and 24.7 (±2.87), respectively. The difference in BMI was not statistically significant ($P = 0.774$). Among the cases, 43.47% (10 cases) had BMI ranging from 21 to 30, whereas in healthy controls it was 91.3% (21 controls). In the cases, the mean duration of the disease was 10.17 (±6.7) years. The mean PASI score was 27.54 (±10.48) with 61.5% (8 cases) having score ranging from 10 to 20, followed by 53.8% (7 cases) having PASI score ranging from 31 to 40 [Table 1].

Comparisons of the two groups revealed a significantly higher mean value of VEGF ($P = 0.001$) in cases, whereas the difference in the mean value of serum IL-10 ($P = 0.095$)

Table 1: Demographic and clinical characteristics of cases and controls

	Cases (n=23)	Controls (n=23)
Age (mean±SD, years)	37.96 (±11.92)	38.48 (±12.32)
Male	12	12
Female	11	11
BMI (mean±SD, kg/m^2)	25.26 (±7.67)	24.70 (±2.87)
10–20	7	1
21–30	10	21
31–40	5	1
>41	1	0
Waist circumference (mean±SD), cm	87.5 (±19.5)	88.5 (±14.2)
Duration of disease (mean±SD), years	10.17 (±6.7)	—
PASI score	27.54 (±10.28)	—
10–20	8	—
21–30	5	—
31–40	7	—
>41	3	—

*SD = standard deviation, BMI = body mass index, PASI = Psoriasis Area and Severity Index

Table 2: Cytokines levels in cases and controls

Cytokines	Cases (mean±SD), pg/mL	Controls (mean±SD), pg/mL	P-value
VEGF	235.21±138.71	104.73±36.01	0.001*
IL-10	2.37±1.61	1.64±0.89	0.095

Table 3: Correlation coefficient for serum VEGF and IL-10 among cases and controls

	Serum VEGF	P-value	Serum IL-10	P-value
Age (n=46)	-0.004	0.981	-0.247	0.098
Duration of the disease (n=23)	0.089	0.687	-0.096	0.664
BMI				
Cases (n=23)	0.373	0.080	0.103	0.641
Controls (n=23)	-0.267	0.219	-0.079	0.719
Waist circumference				
Cases (n=23)	0.036	0.872	-0.037	0.866
Controls (n=23)	-0.354	0.098	-0.297	0.169
PASI score (n=23)	0.272	0.209	0.071	0.748
C-reactive protein (n=23)	0.104	0.636	0.303	0.160
HbA1c (n=23)	0.226	0.299	0.006	0.978

BMI = body mass index, PASI = Psoriasis Area and Severity Index, HbA1c = glycosylated hemoglobulin

was not statistically significant [Table 2]. Pearson's correlation of the serum VEGF and IL-10 with age, PASI, BMI, C-reactive protein, and glycosylated Hb was not statistically significant [Table 3]. Pearson's correlation between VEGF and IL-10 showed statistical significance in cases (P = 0.05) but not in controls (P = 0.37).

Discussion

Psoriasis is a chronic inflammatory papulosquamous disease, wherein there is involvement of an array of cytokines and growth factors. This inflammatory process continuing for a prolonged duration, along with environmental factors, results in various systemic diseases such as diabetes mellitus, hypertension, dyslipidemia, and inflammatory bowel disease.[1,17]

In our study, we evaluated serum VEGF and IL-10 levels in psoriasis patients and healthy controls. Serum VEGF is secreted by keratinocytes upon stimulation of epidermal cells by upregulated Th-1 cytokines.[6] A metanalysis done by Zafar *et al.*[13] found that the serum VEGF level is also elevated in diabetic and hypertensive patients who did not have psoriasis. Thus, serum VEGF is likely to be involved in the pathogenesis of psoriasis, diabetes mellitus, and hypertension. Hence, these confounding factors (diabetes mellitus and hypertension) were eliminated in our study.

A study done by Nofal *et al.*[18] showed a positive significant correlation between serum VEGF levels in psoriasis and controls. Andrys *et al.*[5] conducted a study on serum VEGF in psoriasis, which showed increased levels in psoriasis patients compared with healthy

controls, with its levels post treatment also significantly increased. Flisiak *et al.*[19] also found an increased VEGF level after treatment in psoriasis patients when compared with controls. In our study, VEGF levels in psoriasis patients with no comorbidities were significantly increased when compared with controls. The correlation between serum VEGF and other parameters was also studied. In our study, the correlation between serum VEGF value and BMI was higher in cases (P = 0.08) when compared with controls (P = 0.22). Silha *et al.*[20] conducted a study on 58 healthy subjects with differing BMIs, which showed a significant correlation with serum VEGF (P = 0.04). There was no significant correlation between serum VEGF and HbA1c and waist circumference in our patients. Nofal *et al.*[18] also showed a positive significant correlation between high serum VEGF levels and severity of psoriasis. However, in the present study, the correlation between serum VEGF and PASI score was not statistically significant [Figure 1]. This lack of correlation in our study could be because of lower number of patients or a different demographic and ethnic profile. Our results of a high serum VEGF in psoriasis patients suggest a possible role for this factor in angiogenesis occurring in psoriasis. Its increased levels may also be a pointer to the development of metabolic syndrome in psoriasis.[13] However, even though the levels of VEGF are high in psoriasis patients, we did not find it to correlate with the severity of psoriasis.

Serum IL-10 is secreted by keratinocytes and regulatory B-cells, imparting anti-inflammatory action in psoriasis.[6,12] It is seen that there is upregulation of IL-10 receptors on keratinocytes on exposure to ultraviolent B-light.[12] In a study done by Khandpur *et al.*[21] on Th-1 and Th-2 cytokines, it was shown that there was significantly raised IL-10 in both active and stable psoriasis patients. Borska *et al.*[22] conducted a study on 55 psoriasis patients in which they found that IL-10 was significantly high in patients compared with controls. In a study conducted in the northern part of India by Verghese *et al.*,[23] it was found that although IL-10 levels were higher in controls than in cases, it was not statistically significant. In our study, serum levels of IL-10 were increased compared with controls but not in statistically significant numbers. In contrast, other studies have shown either a decrease in or undetectable levels of IL-10, compared with healthy controls.[24-26] Our study, however, did not show any correlation of IL-10 levels with severity of psoriasis as defined by PASI (P = 0.74) [Figure 2]. It is interesting to note that in a study conducted in north India, IL-10 showed a positive correlation with PASI, whereas other cytokines such as IL-2, IL-4, and interferon-γ did not show any correlation with PASI.[19]

In a study correlating serum IL-10 and BMI, conducted on 268 individuals by Nematollahi *et al.*,[15] it was shown that detectable values of IL-10 were seen in individuals with lower BMI. In our study, however, there was no significant correlation between serum IL-10 and BMI in cases (P = 0.64) as well as in controls (P = 0.71).

We assume from our findings that serum IL-10 may have a probable role in psoriasis. There is no significant correlation in the values between psoriasis cases and controls with respect to IL-10 in most of the Indian studies. Because of its anti-inflammatory properties, IL-10 could possibly be used in the treatment of psoriasis.

In our study, there was a significant correlation between VEGF and IL-10 in cases when compared with controls. There are no comparative studies regarding VEGF and IL-10 correlation in psoriasis. On comparing serum VEGF and IL-10 values in cases and controls, it was found that VEGF was a significantly better inflammatory marker in cases.

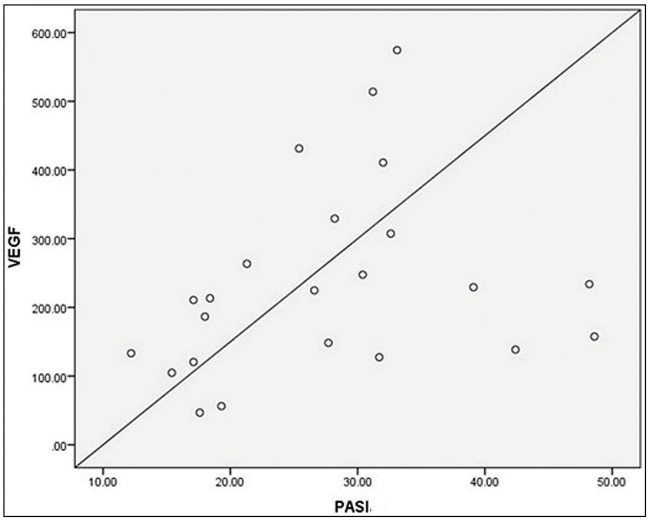

Figure 1: Correlation between PASI score and serum VEGF without systemic treatment

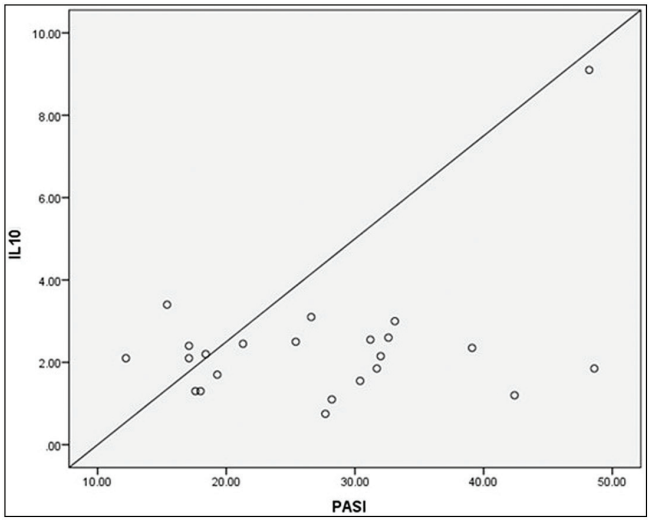

Figure 2: Correlation between PASI score and serum IL-10 without systemic treatment

Limitations of the study

Our study is limited by a small sample size. The small sample size is due to the study being conducted in a single center and because of excluding cases and controls with comorbidities such as hypertension and diabetes mellitus.

Conclusion

Our study was on serum VEGF and IL-10 levels in psoriasis patients with no comorbidities. We conclude that there is a probable role of VEGF and IL-10 in psoriasis as their values show significant correlation in cases when compared with controls. There is a need for further studies on VEGF and IL-10 levels in psoriasis patients pre- and post-treatment. Our study is probably unique as we have studied psoriasis patients with no comorbidities. The increased levels of VEGF and IL-10 even in these cases suggest that inflammation occurs early in psoriasis much before the development of metabolic syndrome. This may help in delineating the role of VEGF and IL-10 in psoriasis.

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Declaration of patient consent

The authors certify that they have obtained appropriate informed written consent from the patients and controls. Patients and controls have also given their consent for publication.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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Original Article

Major Histocompatibility Complex Class I-Related Chain A and Macrophage Migration Inhibitory Factor Gene Polymorphisms in a Turkish Patient Population with Vitiligo

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Abstract

Background: Autoimmunity has been implicated in the etiopathogenesis of vitiligo. **Aim:** We sought to determine whether polymorphisms in the major histocompatibility complex class I-related chain A (MICA) and macrophage migration inhibitory factor (MIF) genes may have a role in the pathogenesis of vitiligo. **Materials and Methods:** We conducted a study including 100 patients with vitiligo and age- and sex-matched 172 control subjects to examine the role of single-nucleotide polymorphisms of MICA gene rs1051792 and MIF genes rs755622 and rs2096525 as risk factors for vitiligo. Real-time PCR combined with the melting curve analysis using fluorescence-labeled hybridization probes was used for genotyping analyses. Mann–Whitney, Kruskal–Wallis, and chi-square (χ^2) tests as well as multivariate logistic regression adjusted for age and gender were used for statistical evaluation. Linkage disequilibrium (LD) and haplotype frequencies were also performed. **Results:** No significant association was observed between the variant alleles of studied genes and vitiligo. Haplotype analysis demonstrated that there was a strong LD between rs755622 and rs2096525 loci of MIF gene ($D' = 0.92$, $r^2 = 0.827$). However, haplotype frequencies in patients were similar to those in controls. **Conclusion:** These preliminary results suggest that the polymorphic variants of MIF rs755622, MIF rs2096525, and MICA rs1051792 genes do not play a critical role in the etiopathogenesis of vitiligo.

Keywords: Gene polymorphism, MHC class I-related chain A, MIF protein, vitiligo

Introduction

Vitiligo is an acquired cutaneous disorder with a 0.5%–2% incidence worldwide, characterized by the presence of depigmented skin macules due to the loss of functional melanocytes from the epidermis.[1] Although the exact etiopathogenesis has not been clearly elucidated yet, autoimmune response triggered by genetic and environmental factors, directed to melanocytes, is the strongest theory. A hereditary immune defect influencing T and B lymphocyte stimulation and causing either antibody-dependent cytotoxicity or direct T-cell destruction is the main alleged mechanism. However, the precise defects in immune tolerance, which mediate this uncontrolled self-reactivity, are still lacking.

The major histocompatibility complex class I-related chain A (MICA), an oxidative stress-inducible antigen, has been found to contribute to the susceptibility and severity of alopecia areata (AA) and vitiligo.[2,3] On the other hand, macrophage migration inhibitory factor (MIF) is reported to have a role[4,5] in vitiligo and AA and a possible biomarker of vitiligo activity and severity.[6,7] Actually, the literature on MIF is mainly on increased levels of it in blood or serum. However, MIF gene polymorphisms have been found to be associated with disease susceptibility in an active nonsegmental vitiligo

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in Mexico, as well.[8] There are many studies on genetic susceptibility genes, which in certain environments may trigger the immune system to attack "self-antigens" of the pigmentary system, resulting in the development of vitiligo. Because melanocytes are specific targets in both AA and vitiligo, in this study, we aimed to analyze if there is an association between specific MICA or MIF polymorphic alleles and vitiligo in a Turkish patient population.

Materials and Methods

The study was approved by the local ethics committee. All the patients and controls were recruited from a single center and all provided written informed consent. A total of 100 patients with vitiligo (53 women, 47 men) were enrolled in the study. Vitiligo patients older than 18 years, showing any clinical picture except segmentary type, and who were not on systemic or topical therapy during previous 2 months were included in the study. Vitiligo was diagnosed on clinical grounds at the Department of Dermatology. The control group consisted of 172 age- and sex-matched dermatology outpatients (88 women, 84 men), with no past history of any systemic, infectious, autoimmune, genetic, or atopic disease. A negative family history for vitiligo was also provided. Patients taking any medication including vitamins were excluded. The main diagnoses in the control group were melanocytic nevus and fibroepithelial polyps.

Peripheral venous blood samples were taken in the morning subsequent to an overnight (12h) fast in EDTA-K_3 tubes for genotype analysis. Genomic DNA was isolated from peripheral blood leukocytes by using High Pure PCR Template Preparation Kit (Roche Diagnostics GmbH, Mannheim, Germany). For the detection of the MIF rs755622, MIF rs2096525, and MICA rs1051792 polymorphisms, light SNP assays were used. Light SNP assays are based on simple probe melting curve analysis. They consist of premixed primers and probes. They were developed and optimized according to NCBI "rs" numbers of mentioned polymorphisms by TIB MolBiol (Berlin, Germany). The detection of polymorphisms was performed in a LightCycler (Roche Diagnostics, Mannheim, Germany).

Mann–Whitney U, Kruskal–Wallis, chi-square (χ^2) tests, and multivariate logistic regression analysis estimating age, gender, and smoking status adjusted odds ratio (aOR) were used for statistical evaluation. The statistical significance for deviations from the Hardy–Weinberg equilibrium (HWE) was determined using the Pearson χ^2-test. These statistical analyses were performed with SPSS statistics for Windows (version 21; SPSS Inc., Chicago, IL, USA). Linkage disequilibrium (LD) and haplotype frequencies were estimated using the Haploview software and compared between cases and controls using a contingency χ^2-test.[9] In addition, the NCSS 2000 statistical package (Kaysville, Utah, USA) was used to evaluate the power analysis.

Results

A total of 272 subjects (100 vitiligo and 172 controls) were included in this study. Table 1 depicts the clinical characteristics of the vitiligo patients including the clinical type of the disease, duration, family history, leukotrichia, stability within 1 year, and associated diseases. The mean ages were 38.6±12.0 years (range = 18–76) and 38.5±9.1 years (range = 18–72 years) for patients and controls, respectively. There was no significant difference among the study and control groups in terms of mean age and sex distribution. We had 85% power to detect an effect size (W) of 0.20 using two degrees of freedom (α = 0.05). The genotypic and allelic distributions of MIF rs755622, MIF rs2096525, and MICA rs1051792 polymorphisms for patients and controls are shown in Table 2. All genotype distributions were in accordance with the HWE among the controls and patients. We did not find any associations between vitiligo and variant alleles of MIF rs755622 (aOR = 0.87, 95% CI = 0.53–1.45), MIF rs2096525 (aOR = 0.80, 95% CI = 0.48–1.34), and MICA rs1051792 (aOR = 0.96, 95% CI = 0.66–1.38). In patients with vitiligo, the evaluation of the relationships between the studied polymorphisms and the disease onset, family history, the clinical type of disease, the presence of leukotrichia, the presence of associated disease, and changes in the vitiliginous area within past 1 year showed no significant difference (data not shown).

Table 1: Characteristics of the patients with vitiligo

	Vitiligo (*n* = 100)
Age (years)	
Mean ± SD	38.6±12.0
Range	18–76
Disease onset	
<40 years, *n* (%)	81 (81.0)
>40 years, *n* (%)	19 (19.0)
Duration, years (mean ± SD)	9.95±11.4
Sex	
Male, *n* (%)	47 (47.0)
Female, *n* (%)	53 (53.0)
Family history, *n* (%)	26 (26.0)
Clinical type of disease	
Focal	25 (25.0)
Acrofacial	25 (25.0)
Generalized	50 (50.0)
Leukotrichia	33 (33.0)
Change in the vitiliginous area within past 1 year	
Newly diagnosed cases, <1 year	21 (21)
Enlargement	49 (49)
No enlargement	23 (23)
Repigmentation	7 (7)
Presence of associated disease	66 (66.0)

Enlargement: Increase in the vitiliginous area within past 1 year

Table 2: Distribution of genotypes and allele frequencies for patients with vitiligo and control group

	Controls, *n* (%)	Patients with vitiligo, *n* (%)	aOR (95% CI)*	*P* value
MIF rs755622 (-173G/C)				
CC	123 (75.5)	74 (74.0)	1.0[a]	-
CG	46 (26.7)	25 (25.0)	1.08 (0.61–1.92)	0.78
GG	3 (1.8)	1 (1.0)	1.54 (0.16–15.28)	0.71
CG + GG	49 (28.5)	26 (26.0)	1.11 (0.63–1.93)	0.73
C allele frequency	0.85	0.87	1.0[a]	
G allele frequency	0.15	0.13	0.87 (0.53–1.45)	0.61
MIF rs2096525				
TT	122 (70.9)	76 (76.0)	1.0[a]	-
CT	48 (27.9)	23 (23.0)	1.30 (0.73–2.31)	0.38
CC	2 (1.2)	1 (1.0)	1.00 (0.09–11.52)	0.99
CT + CC	50 (29.1)	24 (24.0)	1.29 (0.73–2.28)	0.38
T allele frequency	0.85	0.88	1.0[a]	
C allele frequency	0.15	0.12	0.80 (0.48–1.34)	0.40
MICA rs1051792 (129Met/Val)				
GG	76 (42.2)	41 (41.0)	1.0[a]	-
AG	68 (39.5)	48 (48.0)	0.78 (0.46–1.34)	0.37
AA	28 (16.3)	11 (11.0)	1.38 (0.62–3.06)	0.43
AG + AA	96 (55.8)	59 (59.0)	0.90 (0.54–1.48)	0.67
G allele frequency	0.64	0.65	1.0[a]	-
A allele frequency	0.36	0.35	0.96 (0.66–1.38)	0.81

Each *P* value was based on chi-square (χ^2) analysis

aOR = adjusted odds ratio

*Adjusted for age and gender

[a]Reference values for aOR

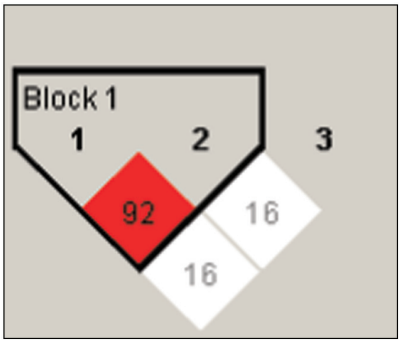

Figure 1: Haplotype analysis and LD patterns (estimated as r^2 and D′) of MIF rs755622 and rs2096525 (block 1). There was strong LD between rs755622 and rs2096525 (D′ = 0.92, r^2 = 0.827) of MIF gene (the number of boxes indicates decimal places of D′)

Lewontin's standardized disequilibrium coefficient (D′) was calculated as a measure for LD between the rs755622 and rs2096525 polymorphisms in the MIF gene [Figure 1]. The rs755622 and rs2096525 were found to be in strong LD (D′ = 0.92, r^2 = 0.827). Haplotype frequencies are shown in Table 3. The most frequent haplotype among the patients and controls was CT (0.860 and 0.837, respectively). There were not any significant differences in the haplotype frequencies between patients and controls.

Discussion

Vitiligo is an autoimmune disease against melanocytes. So far, neither the triggering mechanism of T-cell-mediated destruction of melanocytes nor the gene polymorphisms disrupting regulatory mechanisms are clearly delineated. Research on new molecules is still needed.

MICA is a highly polymorphic cell surface glycoprotein of nonclassical MHC class I gene in humans. MICA gene encodes a ligand for NKG2D (NK group 2, member D) receptor, that is expressed mainly on natural killer (NK) cells, γδ T cells, and $CD8^+$ αβ T cells. In this way, MICA attracts cytotoxic or NK cells bearing NKG2D.[10] The role of NK cell activation has been shown in nonsegmental vitiligo,[11] and MICA-interacted $NKG2D^+$ $CD8^+$ skin effector memory T cells were increased in vitiligo skin.[12] On CD8+ αβ T cells and NK cells, NKG2D signaling elicits the target cell lysis.[13-15] Indeed, compared with healthy controls, increased melanocyte-specific CD8+ T cells were found in the blood of patients with vitiligo, and it was correlated with disease activity.[16-18] The upregulation of MICA contributing to melanocyte destruction has been reported in vitiligo.[3]

It is certain that polymorphisms in various genes may reduce the threshold for lymphocyte activation and thereby increase the susceptibility for autoimmunity. The single-nucleotide polymorphism (SNP) rs1051792 causing

Table 3: Haplotype analysis of the MIF rs755622 and rs2096525 polymorphisms in patients with vitiligo and control subjects

Haplotype	Frequency of haplotype	Frequency in controls	Frequency in vitiligo	*P* value
MIF rs755622/rs2096525				
CT	0.845	0.860	0.837	0.48
GC	0.132	0.120	0.139	0.52
GT	0.013	0.015	0.012	0.74

Haplotype frequencies and haplotype association analyses were estimated using Haploview software

a valine (Val) to methionine (Met) exchange at position 129 of the MICA protein is of specific interest. It separates MICA into isoforms that bind NKG2D with high (Met) and low affinities (Val).[19] Thus, it has recently been shown that the MICA-129 Met variant elicits a stronger NKG2D signaling, resulting in a faster costimulation of $CD8^+$ T cells.[19]

Accordingly, MICA-129 (rs1051792) polymorphism was a reasonable suspect, and it was not investigated in vitiligo before. However, MICA-129 polymorphism did not show a statistically significant difference between vitiligo and control group. Some studies had suggested that NK cells may play a trigger role at the beginning of the autoimmune process, so we reanalyzed our patients putting them in two groups, according to the duration of the illness, whether 1 year or longer. Even so, no significant difference was detected between the two groups. Our results do not suggest a role for MICA 129 SNP in the etiopathogenesis of vitiligo.

Macrophage MIF is another regulatory cytokine functioning in innate and adaptive immunity.[20] MIF activates lymphocytes, granulocytes, monocytes/macrophages, and concentrate macrophages at the inflammation loci.[5,20]

Research indicates that MIF is implicated in the pathogenesis of autoimmune diseases by a couple of mechanisms.[21] Macrophage infiltration has been demonstrated in vitiligo lesions, and increased macrophage numbers are also observed in perilesional vitiliginous skin.[22] MIF can inhibit the random migration of macrophages, leading to the accumulation of them at the inflammation area and contribute to the pathogenesis of vitiligo.[5] MIF itself also functions as an initial proinflammatory mediator, which upregulates many cytokines, including TNF-α and IL-6 that have been shown to be increased in vitiliginous skin[5] and serum in vitiligo vulgaris patients.[23] Third, MIF may take part by inhibiting NK cells and causing prolonged inflammation and macrophage infiltration in the area, which all end up with the tissue destruction and the release of new antigens. This is called epitope spreading and is a particular mechanism facilitating the progression of autoimmune reactions.[24]

In vitiligo, MIF levels detected in the peripheral blood mononuclear cells, serum, and the skin of vitiligo patients were associated with disease severity and activity.[5] Recent studies repeated the same conclusion that serum MIF levels were correlated with the severity and activity of vitiligo.[6,7] Likewise, in another controlled study, serum MIF levels in vitiligo patients were associated with the duration and clinical type of the disease.[4]

Genetic factors are known to influence circulating MIF levels and the disease susceptibility. *In vitro* and *in vivo* studies also suggested that rs755622 found in the promoter region of the gene was associated with an increased gene expression and protein levels of MIF.[25] A very recent study showed that MIF polymorphisms rs5844572 and rs755622 were associated with vitiligo susceptibility in active nonsegmental vitiligo.[8]

In this study, we investigated the role of MIF gene polymorphisms (rs755622, rs2096525), but we did not find a statistically significant difference between the two groups in terms of genotype and allele distributions.

In our study, we also performed extended haplotype analysis for the MIF gene loci. The most frequent haplotype among the patients and controls was CT (0.860 and 0.837, respectively). The rs755622 and rs2096525 were found to be in strong LD ($D' = 0.92$, $r^2 = 0.827$). However, there were not any significant differences in the haplotype frequencies between patients and controls.

The main limitation of the study is the lack of serum measurements of MICA and MIF. It is difficult to make an interpretation as the relationship between the three studied genetic polymorphisms of MICA/MIF genes and the serum levels of them cannot be clearly revealed. Moreover, the incriminated SNPs may not be relevant in our study population.

Despite the accumulated data pointing to the important role for MICA and MIF proteins in vitiligo, our results do not support any significant relationship in terms of MICA or MIF gene polymorphisms. The decision to either promote or inhibit autoreactive T cells is probably dependent on a wide variety of factors, which we partially know. Furthermore, the reason causing continuous immune response is also not clear. The identification of new receptors, ligands, or even cell subsets and factors affecting the vulnerability of target cells might help clarify the process.

Conclusions

We studied three genetic polymorphisms of MICA and MIF genes related with NK cell activity, but we were

unable to detect any significant association. Because of the complex nature of the autoimmune processes, we prefer to avoid clear-cut conclusions. Yet, we can at least say these MIF rs755622, MIF rs2096525, and MICA rs1051792 SNPs do not seem to play a critical role in the etiopathogenesis of vitiligo. We think these results should be assessed as preliminary, because of the relatively small sample size, and there is a need for further larger-scale studies including other loci of MIF and MICA genes.

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Conflicts of interest

There are no conflicts of interest.

Author contribution

İEA, İB, PV, SD: Concept and design. İEA: Clinical studies, manuscript preparation. İB, PV, SD: Experimental studies and statistical analysis. İEA, İB, PV, SD: Data analysis, manuscript editing and manuscript review.

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Original Article

Evaluating the Differences Among Dermatologists' Approaches to Abnormal Laboratory Results of Patients Using Oral Isotretinoin Treatment for Acne

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Abstract

Background: Oral isotretinoin is one of the most frequently used treatment options in moderate and severe acne. Abnormal laboratory results may occur during the treatment and there may be differences in approach to these abnormal laboratory results among dermatologists. **Aim:** In this study, we aimed to retrospectively evaluate the differences in approach to abnormal laboratory results and treatment modifications of dermatologists during oral isotretinoin treatment. **Materials and Methods:** Data of 207 patients who had oral isotretinoin treatment for acne between January 2013 and October 2020 were included in this study. Baseline and follow-up laboratory results were reviewed. All treatment modifications were noted and evaluated with relevant literature. **Results:** Among 207 patients, 28 (13.5%) had treatment modifications due to the abnormal laboratory results, and all of them were due to elevation of lipid and liver enzyme levels. The dose was reduced in 24 (11.6%) patients and the treatment was discontinued in 4 (1.9%) patients. Treatment modification was not compulsory in the vast majority of patients (26 of 28) according to the relevant literature. **Conclusion:** The results of the present study showed that unnecessary treatment modifications due to the abnormal laboratory results can be made by dermatologists during oral isotretinoin treatment for acne. Educational programs for dermatologists and more detailed guidelines may prevent these unnecessary treatment modifications.

Keywords: Abnormal, acne, isotretinoin, laboratory, treatment

Introduction

Oral isotretinoin is one of the most effective treatments for the management of moderate to severe acne. Although it has some adverse effects that are generally mild, it is considered a safe treatment option. The most commonly observed adverse effects are mucocutaneous effects related to dryness, such as cheilitis, xerosis of the skin and dermatitis.[1] Abnormal blood tests, including liver function test abnormalities, hyperlipidemia and changes in complete blood count, are other relatively frequent adverse effects.[1,2]

The literature contains little consensus in terms of guidelines for the frequency of laboratory monitoring of patients receiving oral isotretinoin treatment.[3] Moreover, it is unclear when the treatment should be stopped or the dosage decreased in the case of abnormal laboratory results. Due to the different recommendations of various medical resources on oral isotretinoin treatment, dermatologists may also differ in their approach to monitoring and following up with patients using oral isotretinoin. In this study, we aimed to evaluate the responses of dermatologists to the abnormal laboratory test results of patients being treated with oral isotretinoin for acne.

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Materials and Methods

We conducted a retrospective study of the acne patients receiving oral isotretinoin treatment who admitted to Trakya University Hospital between January 2013 and October 2020. The study was approved by the Trakya University Ethics Committee (TUTF-BAEK 2021/258). We evaluated the demographic, clinical and laboratory data of acne patients who received oral isotretinoin for at least 4 months. The laboratory tests were conducted before treatment and monthly thereafter. Patients who completed a minimum of two laboratory tests during the treatment course were included in the study. There was one professor, one associate professor, four assistant professors and five residents in the department of dermatology during the study period. The faculty members had their academic degrees for at least four years. Residents with at least two years of dermatology training were allowed to make treatment modification decisions on their own. Otherwise, treatment modification decisions were made by faculty members.

Laboratory test results of the patients, including complete blood count (CBC), serum lipids (triglycerides [TG], total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C]), liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) were reviewed manually. Patients who have any baseline abnormal laboratory results prior to oral isotretinoin initiation were excluded from the study.

In patients with any abnormal laboratory results, we evaluated and recorded the treatment modifications as followings: no treatment modification, treatment interruption, reduction of dose, and treatment termination. We further reviewed the medical records to identify the reasons for changes in treatment management and evaluated whether the treatment modifications made in these patients were appropriate according to the recommendations in previous literature.[4,5] Values that we used to evaluate the appropriateness of the treatment modifications were, dose reduction if two-to-three-fold elevation in liver enzymes and drug discontinuation if there is more than three-fold elevation in liver enzymes; dose reduction if TG levels exceeds 500 mg/dl and drug discontinuation if TG levels exceeds 800 mg/dl.[4,5] In our literature review, we found no information or recommendation about the modifications that should be made, if total cholesterol and LDL-C level abnormalities occur during the oral isotretinoin treatment.

Results

A total of 207 acne patients using oral isotretinoin were included in the analyses. 150 (72.4%) of the patients were female and 57 (27.5%) were male. The mean age of the patients was 24.99 ± 5.03 years. Treatment modification due to the abnormal laboratory test results occurred in 28 (13.5%) patients, with 24 (11.6%) dose reduction and four (1.9%) treatment termination [Table 1].

There were no treatment modifications due to the CBC abnormalities. All modifications (n = 28, 13.5%) were due to the elevation in serum lipids and liver enzymes. The reasons of the treatment modifications were distributed as following: 10 (4.8%) patients for total cholesterol elevation, six (2.9%) patients for TG elevation, four (1.9%) patients for LDL-C elevation, four (1.9%) patients for ALT elevation, and four (1.9%) patients for AST elevation [Table 1].

Treatment modifications were made in the first month of treatment in four patients (14.3%), in the second month in eight patients (28.6%) and in the third, fourth and fifth months in five patients (17.8%) in each group.

When the patients who underwent a treatment modification (n = 28, 13.5%) were further evaluated, we found that treatment modification was not mandatory in 26 (12.6%) patients according to the literature.[4,5] These patients' laboratory abnormalities were mild-to-moderate and did not meet the abovementioned criteria to make a modification. Treatment modification was appropriate in two (%0.9) patients [Table 1]. These two patients had more than threefold and fivefold liver enzyme elevation; therefore, oral isotretinoin treatment was terminated.

Discussion

In this study, we found that 13.3% of acne patients had their treatment modified, including dose reduction (11.4%) and treatment termination (1.9%), due to abnormal laboratory results during oral isotretinoin treatment. Total cholesterol (4.7%) and TG (2.8%) elevation were the most common reasons leading to treatment modifications. In the majority of the patients who had treatment modification, the laboratory abnormalities were mild, and based on the literature, treatment modification was not compulsory.[4,5] In two patients (0.9%), both of whom had liver enzyme elevations, the decision to modify treatment was compatible with the recommendations provided in the literature.

Table 1: Treatment modificiations made by dermatologists due to the abnormal laboratory results during oral isotretinoin treatment

	High total cholesterol levels	High triglyceride levels	High LDL levels	ALT	AST	Total number (%)
Number of patients with treatment modification (%)	10 (35.7)	6 (21.4)	4 (14.3)	4 (14.3)	4 (14.3)	28 (100)
Number of patients with dose reduction (%)	10 (42)	4 (17)	4 (17)	2 (8)	4 (17)	24 (85.7)
Number of patients with treatment discontinuation (%)	-	2 (50)	-	2 (50)	-	4 (14.3)

It is known that an elevation in serum lipids is the most common laboratory abnormality observed during oral isotretinoin treatment.[2,6] Similarly, the most common reason for treatment modification (4.7%) was the elevation of total cholesterol levels in our study. A systematic review and meta-analysis demonstrated that high-risk or severe abnormalities in total cholesterol levels are rare.[2] However, to our knowledge, there is no specific information or recommendation in the published guidelines regarding the total cholesterol and LDL-C threshold levels that require treatment modification.[3,7] The lack of detailed and clear information on total cholesterol and LDL-C levels in the literature may explain the physicians' dose reductions in the presence of mild to moderate total cholesterol and LDL elevations in our study. We suggest that providing specific values for the total cholesterol and LDL-C levels that should prompt treatment modifications are required in the guidelines, as are currently provided for TG and liver enzyme levels, and that this information would avoid unnecessary treatment modifications by making physicians feel more comfortable with continuing treatment without making any changes. Moreover, providing this information would reduce the number of laboratory tests conducted to check for abnormal values. Thus, both the cost and the stress of blood draws would also be reduced.

In our study, other reasons for treatment modifications included elevated TG levels (2.8%), AST levels (1.9%) and ALT levels (1.9%). The literature provides recommended threshold values for both TG and liver enzymes to indicate when treatment modifications are required during oral isotretinoin treatment.[4,5,7,8] The existence of these kinds of specific criteria undoubtedly has an effect on dermatologists' decision-making processes. However, our study showed that treatment changes were made for some patients who did not meet the published criteria and who had clinically insignificant TG or liver enzyme elevations. Treatment modification was appropriate in only two (0.9%) patients with liver enzyme elevations. There may be several reasons that dermatologists take this approach. First, dermatologists and/or patients may feel anxious about side effects such as hepatitis and pancreatitis due to elevated TG or liver enzyme levels, even though the patient's TG and liver enzyme levels are mild or moderate. Second, current guidelines contain differences that may lead to confusion among dermatologists, resulting in unnecessary treatment changes.[3] A study that assessed dermatologists' actions in response to commonly seen laboratory abnormalities during oral isotretinoin treatment showed that they relied on a wide variety of sources to help them make decisions.[9] These sources included residency training, personal experience, comprehensive drug books, drug company package inserts and evidence-based guidelines. Differences in the information provided by various sources, may lead to difficulties in decision-making and inappropriate treatment modifications among dermatologists. As suggested by Barbieri *et al.*,[10] the provision of education and up-to-date information to dermatologists by dermatology societies on the management of patients using oral isotretinoin would reduce inappropriate treatment modifications.

The present study has some limitations. First, due to the retrospective design of the study, the sources that dermatologists relied on when making the decision to modify patients' treatment could not be evaluated. Second, the single-center design of the study limits the generalization of the findings.

In conclusion, the results of the present study show that in some patients who receive oral isotretinoin therapy and have commonly seen laboratory changes, inappropriate treatment changes are made. Providing specific values or threshold levels for abnormal laboratory results in published guidelines and organizing regular educational programs that provide current information on oral isotretinoin management may prevent unnecessary treatment modifications by dermatologists.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Psoriasis Neurodermiformis, Verrucous Psoriasis, and Psoriasiform Keratosis: A Clinicopathological Evaluation

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Abstract

Background: Psoriasis neurodermiformis (PN) and verrucous psoriasis (VP) are two distinct forms of psoriasis characterized by thickened plaques, whose proper description in most dermatologic texts is still lacking. Psoriasiform keratosis (PK) is a recently described clinical entity characterized by a solitary keratotic plaque whose microscopic findings simulate psoriasis. **Aim:** To compare and evaluate the clinical and histological profile of PN, VP and PK, and systematically characterize each of them. **Settings and Design:** This was a prospective, descriptive study done on a total of 51 patients, who were diagnosed with PN, VP and PK based on certain clinical criteria. The study was done at a teaching hospital in eastern India. **Methods and Materials:** The study was carried out on a total of 51 patients presenting with thickened psoriasiform plaques, who visited our outpatient department, over a period of 9 months. They were then carefully evaluated clinically (along with their demographic profile), followed by meticulous microscopic assessment. Each biopsy specimen was then categorically evaluated to enable a precise diagnostic conclusion. **Statistical Analysis:** As all values in our study were qualitative, they were expressed as numeric values and percentages. **Results:** Out of 51 patients, 18 were diagnosed as PN, 19 with VP and 14 with PK. PN demonstrated an equal gender distribution, whereas in VP and PK a male preponderance was apparent. History of past/present psoriasis was positive in only one patient diagnosed with VP. Intensity of pruritus was marked in 88.88%, 21.05% and 14.28% of patients with PN, VP and PK respectively. Dorsa of feet was the commonest site of involvement in PN and VP. In PK, the shin was the predominating site. VP presented clinically as mammillated, verrucous and crateriform phenotypes. PN and PK however, demonstrated single clinical patterns. Microscopically, none of the specimens satisfied all the 7 epidermal criteria set forth by Ackerman. In each slide Trozak's histologic psoriasiform numeric score was >10. **Conclusion:** PN, VP and PK are certainly not as rare as previously considered. Mammillated VP closely mimics PN clinically. Crateriform VP is an extremely rare phenotypic expression encountered. Histological findings of papillomatosis, buttressing and anastomosing rete ridges and a dense dermal lymphocytic infiltrate point more in favor toward VP. Detecting solitary keratotic plaques with a psoriasiform histology should allow clinicians to consider the possibility of PK.

Keywords: Histopathology, psoriasiform keratosis, psoriasis neurodermiformis, verrucous psoriasis

Introduction

Psoriasis is a commonly encountered papulosquamous disorder in all dermatology clinics, throughout the world.

Although chronic plaque psoriasis is the classical phenotype witnessed; there are a number of other clinical presentations of the disease, which the clinician ought to be aware about.

Amongst them, patterns comprising thickened plaques have been specifically identified and studied both clinically and microscopically.

Included within this spectrum, are two variants of psoriasis; namely psoriasis neurodermiformis (PN) and verrucous psoriasis (VP) that have been elaborated in the recent past.[1,2] Of late, another condition referred to as psoriasiform

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keratosis (PK) has been elucidated, which again manifests as a thickened psoriatic plaque.[3] The etiology of PK still remains elusive, and whether it represents a unifocal presentation of psoriasis needs closer evaluation.

Our study was an attempt to analyze PN, VP and PK and determine subtle differences in their clinical and histologic morphologies; thereby allowing a precise conclusion while confronting these entities.

Methods and Materials

This was a prospective, descriptive study conducted over a period of 9 months in the department of dermatology of our institute, after obtaining permission by the institutional ethical clearance committee (Registration number: KMC/IEC/Dept.Res./013/2021-2024DVL).

Only freshly diagnosed patients or patients without any form of treatment for the past 6 months were included in the study.

We were able to get a total of 51 patients during this time frame, of which 18 demonstrated clinical findings of PN, 19 delineated phenotypic features of VP and the remaining 14 expressed characteristics suggestive of PK.

Once patients were enrolled, a written and informed consent was obtained from each of them, following which relevant history concerning the disease was recorded and a complete clinical examination done, which was furthered by a cutaneous biopsy, that was sent for histopathological examination.

Based on certain clinical criteria (that were proposed by the authors of the current study), each patient was designated to one of the three diagnostic entities as stated above; details of which have been elaborated in Table 1. In order to fit a designated entity, fulfillment of each of the aforementioned criterion (as detailed in Table 1), in the respective group was mandatory, the exception being freshly diagnosed cases, wherein the criterion taking into account the responsiveness to topical/intralesional steroids was not required. Table 2 details the number of freshly and previously diagnosed cases (following topical/intralesional steroid therapy and their responsiveness to treatment) of our study subjects.

Biopsy findings were primarily delineated as psoriasiform, based on 7 epidermal criteria originally put forth by Ackerman *et al*,[4] and include neutrophilic microabscesses in the stratum corneum, confluent parakeratosis, hypogranulosis, neutrophilic microabscesses in the spinous layer, slight spongiosis, thinning of suprapapillary plates and regular acanthosis.

This was succeeded by assigning a numeric histologic score as per the grading system designed by Trozak.[5] All slides were then categorically evaluated to determine explicit histological differences in the dermal and epidermal mileu for each of these 3 entities, to enable a precise diagnostic conclusion.

Statistical analysis

As all data in our study were categorical, they were expressed as numeric values and percentages.

Results

Out of the 51 patients studied 18 were clinically diagnosed with PN, 19 with VP and 14 with PK. The salient clinical and demographic profile of each has been outlined in Table 2.

Histologically, we assessed each slide with regard to epidermal and dermal parameters, to identify the existence of major as well as subtle differences in each of the conditions described. These findings have been annotated in Table 3.

Discussion

Our main purpose in conducting this study was an endeavour to delineate the above variants of psoriasis, as their proper description in most dermatologic texts is lacking.

PN, also referred to as lichenified psoriasis, is a variant of psoriasis characterized by accentuated skin surface markings [Figure 1a].[6] It may not be as rare as accounted. More often than not, it could get misdiagnosed as lichen simplex chronicus (LSC) owing to their close clinical approximation. However, there do exist subtle differences between both clinically; meticulous scrutiny of which could be of considerable help [Table 4].

Table 1: Clinical criteria for patient allocation to psoriasis neurodermiformis, verrucous psoriasis and psoriasiform keratosis

Psoriasis neurodermiformis	Verrucous psoriasis	Psoriasiform keratosis
Criteria	**Criteria**	**Criteria**
• Lichenified/leathery pruritic plaques present bilaterally over knees and/or elbows and/or ankle and dorsa of feet	• Verrucous or hypertrophic plaques having an extensor distribution	• Singular lesion or two lesions but unifocal (in a single area)
• Absence of classical scales of psoriasis	• Classical scales of psoriasis may or may not be identifiable	• Absence of classical scaling of psoriasis
• Negative Auspitz sign	• Auspitz sign may be positive or negative	• Auspitz sign negative
• Absence of past or present lesions of psoriasis elsewhere in the body	• History of past or present lesions of psoriasis may or may not be present	• No evidence of psoriasis elsewhere in the body
• Responsive to topical/intralesional steroids	• Responsive to topical/intralesional steroids	• Unresponsive to topical/intralesional steroids

Table 2: Clinical and demographic profile of our study population

Clinical findings	Psoriasis neurodermiformis	Verrucous psoriasis	Psoriasiform keratosis
Gender distribution	Male (9, 50%) Female (9, 50%)	Male (13, 68.42%) Female (6, 31.57%)	Male (10, 71.42%) Female (4, 28.57%)
Age (mean±SD) Range	39.33 ± 22.6 (20 – 60 years)	52.31 ± 23.02 (30 – 74 years)	36.36 ± 28.76 (18 – 60 years)
Duration of lesion (range)	1-5years	6months-5years (in 1 patient 30 years duration)	3months-5years
Number of freshly diagnosed cases	15 (78.94%)	16 (84.21%)	10 (71.42%)
Number of cases who had been treated with topical/intralesional steroids in the past	3 (16.66%) All three patients demonstrated steroid responsiveness, with recurrence of lesions following cessation of steroid therapy. In all these patients lesions recurred after a period of 2-3 months following stoppage of treatment.	3 (15.79%) All three patients demonstrated steroid responsiveness, with recurrence of lesions following cessation of steroid therapy. In all these patients recrudescence of lesions occurred within 3-4 months of stopping treatment.	4 (28.57%) None of these patients responded to topical/ intralesional steroid therapy.
History of past or present psoriasis apart from the lesion described	Negative in all	Negative (18, 94.74%) Positive (1, 5.26%)	Negative in all
Associated comorbidities	Hypertension (2, 11.1%) Obesity (1, 5.5%)	Hypertension (3, 15.78%) Diabetes mellitus (1, 5.26%)	Hypertension (1, 7.14%) Diabetes mellitus (1, 7.14%)
Other associated cutaneous diseases	Nil	Nil	Nil
Associated psychological issues	Nil	Nil	Nil
Intensity of pruritus	Marked (16, 88.88%) Moderate (2, 11.11%)	Marked (4, 21.05%) Moderate (15, 78.94%)	Marked (2, 14.28%) Moderate (7, 50%) Mild (4, 28.57%) Absent (1, 7.14%)
Site(s) of involvement	Dorsa of feet (17, 94.44%) Bilateral knees (2, 11.11%) Ankles (1, 5.55%) Medial malleoli (1, 5.55%) (some patients have involvement of more than one site and so the total number is exceeding 18)	Dorsa of feet (10, 52.63%) Bilateral shins (3, 15.78%) Bilateral shins and dorsa of feet (3, 15.78%) Bilateral knees (3, 15.78%)	Shin (6, 42.85%) Dorsa of foot (4, 28.57%) Knee (3, 21.42%) Lateral malleolus (1, 7.14%)
Auspitz sign	Negative in all	Negative (17, 89.47%) Positive (2, 10.52%)	Negative in all
Nail changes	Nil	Nil	Nil
History of cigarette smoking (no. of patients)	4 (22.22%)	1 (5.26%)	1 (7.14%)
History of alcohol consumption (no. of patients)	3 (16.66%)	1 (5.26%)	1 (7.14%)

Nevertheless, in many cases, this may prove quite challenging, owing to overlapping features that manifest.

Further, absence of Auspitz sign (though not diagnostic, yet a valuable tool) in PN could prevent prompt recognition of the condition. Histopathology therefore becomes mandatory for a precise conclusion.

Despite the presence of overlapping findings in both conditions microscopically, specific features pertaining to both disorders can enable the dermatopathologist in arriving at an end result [Table 4].

Regardless of histological features stated, it has been witnessed that even untreated clinically active psoriatic lesions lack a completely characteristic microscopic architecture.[7] Besides, variable histological findings have been observed even within a single psoriatic plaque, thereby implying that all features of psoriasis may not be viewed very often from just a single specimen.[8] Histological diagnosis therefore relies on an aggregate of attributes; some of which are seen distinctively in psoriasis and others more common to other dermatoses.

Table 3: Histological parameters utilized to evaluate our study subjects

Histological features	Psoriasis neurodermiformis	Verrucous psoriasis	Psoriasiform keratosis
Hyperkeratosis	Marked (11, 61.11%) Moderate (6, 33.33%) Minimal (1, 5.55%)	Marked (13, 68.42%) Moderate (4, 21.05%) Minimal (2, 10.52%)	Marked (3, 21.42%) Moderate (9, 64.28%) Minimal (2, 14.28%)
Parakeratosis	Present: Confluent (10, 55.55%) Focal (3, 16.66%) Absent (5, 27.77%)	Present: Confluent (11, 57.89%) Focal (3, 15.78%) Absent (5, 26.31%)	Present: Focal (5, 35.71%) Absent (9, 64.28%)
Papillomatosis	Present (2, 11.11%) Absent (16, 88.88%)	Present (15, 78.94%) Absent (4, 21.04%)	Absent in all
Hypogranulosis	Present (17, 94.44%) Absent (1, 5.55%)	Present (10, 52.63%) Absent (9, 47.36%)	Present (4, 28.57%) Absent (10, 71.42%)
Acanthosis	Present in all	Present in all	Present in all
Suprapapillary thinning	Present (14, 77.77%) Absent (4, 22.22%)	Present (13, 68.42%) Absent (6, 31.57%)	Present (11, 78.57%) Absent (3, 21.42%)
Spongiosis	Present (11, 61.11%) Absent (7, 38.88%)	Present (15, 78.94%) Absent (4, 21.05%)	Present (12, 85.71%) Absent (2, 14.28%)
Munro's microabscess	Present (13, 72.22%) Absent (5, 27.77%)	Present (14. 73.68%) Absent (5, 26.31%)	Present (2, 14.28%) Absent (12, 85.71%)
Evidence of neutrophils arranged in vertical tiers in the stratum corneum	All negative	All negative	All negative
Spongiform pustules of Kogoj	Present (8, 44.44%) Absent (10, 55.55%)	Present (9, 47.36%) Absent (10, 52.36%)	Present (2, 14.28%) Absent (12, 85.71%)
Pattern of psoriasiform elongation of rete ridges	Regular camel foot elongation of rete ridges (all 18 patients)	Elongated rete ridges with buttressing and anastomoses (all 19 patients)	Regular camel foot elongation of rete ridges (all 14 patients)
Focal excoriations	Absent in all	Absent in all	Present (2, 14.28%) Absent (12, 85.71%)
Dermal inflammatory infiltrates	Predominently lymphocytic in the papillary dermis: -Moderate to dense (5, 27.77%) -Minimal (13, 72.22%)	Predominently lymphocytic in the papillary dermis: -Dense (15, 78.94%) -Moderate (4, 21.05%)	Predominently lymphocytic in the papillary dermis: -Dense (1, 7.18%) -Moderate (7, 50%) -Sparse (6, 42.85%)
Vertical arrangement of collagen bundles in the dermis	Present (10. 55.55%) Absent (8, 44.44%)	Present (7, 36.84%) Absent (12, 63.15%)	No vertical arrangement in all
Evidence of plump fibroblasts	Present (1, 5.55%) Absent (17, 94.44%)	Present (3, 15.78%) Absent (16, 84.21%)	Absent in all
Montgomery's giant cells (clumped endothelial cells)	Absent in all	Absent in all	Absent in all

Likewise, in our study, none of the participants fulfilled all 7 epidermal features as stated above. However, each of these criteria was expounded in significant frequencies amongst our cohorts when carefully taken one by one.

Based on Trozak's histological grading system we scored each slide to obtain a numeric degree of psoriasiform changes.[5]

All our patients with PN demonstrated a numeric psoriasiform grade between 11 and 15 (out of a maximum score of 19), which we consider fitting in making a final diagnosis of psoriasis. Although the apt cut off value has not been determined by Trozak, we regard scores >10 acceptable in making a confirmatory histological diagnosis of psoriasis.

Previous publications regarding the application of Trozak's grading for histopathological evaluation of psoriasis is scant. Literature search revealed only one recent study from India done on classical psoriatic plaques wherein a mean score of 9.44 (in 50 patients) was considered sufficient to label the histological specimen as psoriasis.[9] The reduced utility of Trozak's histologic scoring by most clinicians could be attributed to the fact that in most cases the focus by dermatologists is primarily on clinical assessment scores like the PASI (Psoriasis Area and Severity Index) score, rather than microscopic scoring.

Further the role of histopathology becomes more relevant in atypical phenotypes of psoriasis where clinical diagnosis is not straightforward, thereby warranting scrupulous microscopic assessment in order to obtain a concrete conclusion. In such scenarios, Trozak's grading system could be of substantial value.

As our study dealt with three atypical presentations of psoriasis, histological grading helped us greatly in

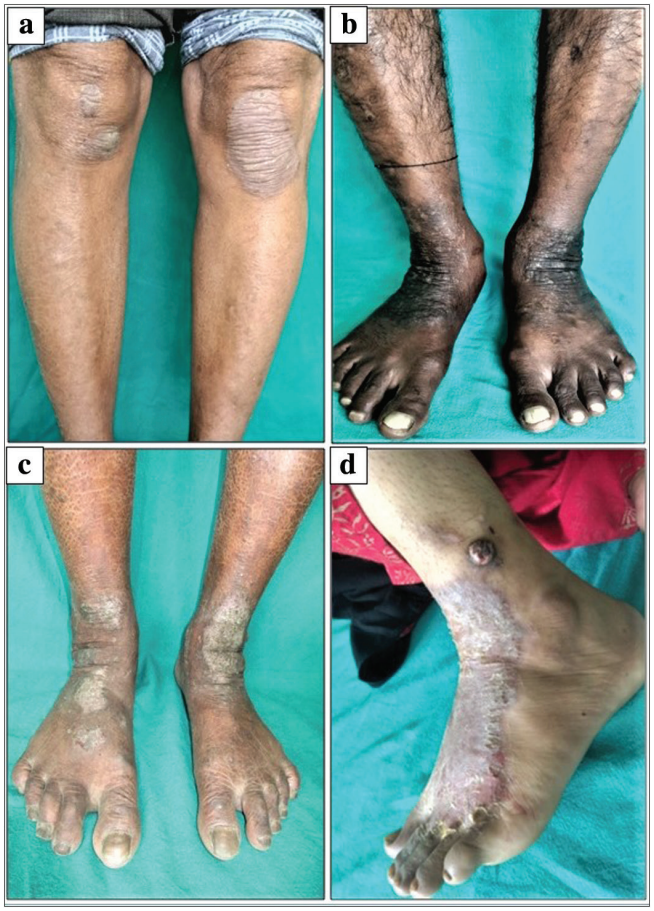

Figure 1: a: Psoriasis neurodermiformis presenting over bilateral knees. The sharper outline and a more keratotic presentation and lack of zonal distribution can be observed. b: Mammillated verrucous psoriasis (VP) over dorsa of feet. c: Classical presentation of VP over dorsa of feet with characteristic verrucous morphology. d: Crateriform VP adjacent to a psoriatic plaque above the left lateral malleoli

evaluating our cohorts. It was only after careful study did we conclude in favor of a score >10 to confer a confirmatory diagnosis of psoriasis microscopically.

Vertically oriented dermal collagen bundles were identified in 10 of our diagnosed patients with PN. Unlike LSC, these bundles were not thickened. This arrangement of collagen bundles has been linked to increased scratching owing to the release of various chemical mediators secondary to activation of the neuro-cutaneous axis involved in psoriasis. Its occurrence therefore should not be an argument to refute a diagnosis of psoriasis.

The mammillated variant of VP can closely mimic PN clinically. VP is a rare variant of psoriasis that requires detailed elucidation. To compound things further, this form of psoriasis presents in four morphological patterns.[2] These include dome shaped papules/plaques, crateriform papules/nodules, annular/oval verrucous plaques and the mammillated phenotype. If the clinician is not acquainted regarding these presentations, there could be a high likelihood of diagnostic discrepancy.

Within our cohorts, 8 (42.11%) presented with the mammillated variant [Figure 1b], 10 (52.63%) were consistent with the verrucous morphology [Figure 1c] and 1(5.26%) displayed features suggestive of crateriform VP [Figure 1d]. In the report by Khalil and colleagues,[2] mammillated VP was the most common presenting morphology and was observed in 67% of their cohorts. The remaining 33% manifested VP in the form of agminated, tan white papules.

Linear verrucous plaques were the characteristic finding in a report from Chennai,[10] and numerous verrucous plaques as the sole morphology of VP was demonstrated in the publication by Wakamatsu *et al.*[11]

Table 4: Distinguishing features (both clinical and microscopic) between psoriasis neurodermiformis and lichen simplex chronicus.

Psoriasis neurodermiformis	Lichen simplex chronicus
Clinical features	
• Plaques are more sharper in outline • Plaques are more keratotic • Plaques do not demonstrate zonal distribution	• Plaques are less sharper in outline • Plaques are less keratotic and more leathery • Plaques usually consist of three zones -a central zone with pronounced skin surface markings -a middle zone composed of multiple small papules -a peripheral zone with pigmentary changes
Histopathologic findings	
Confluent parakeratosis (generally)	Focal zones of parakeratosis
Neutrophilic microabcesses in the horny layer is present in majority of cases	Neutrophilic microabcesses in the horny layer is absent
Hypogranulosis	Hypergranulosis
Thinning of suprapapillary plates is present in majority of cases	Thinning of suprapapillary plates is absent
Elongated rete ridges of even length	Rete ridges more thicker and of less even length
Focal excoriations are absent	Focal excoriations are usually present
Vertically oriented dermal collagen bundles usually absent and if present are not thickened	Vertically oriented thickened dermal collagen bundles are present
Absence of plump fibroblasts in the papillary dermis (usually)	Presence of plump fibroblasts in the papillary dermis
Montgomery's giant cells are absent	Montgomery's giant cells are usually present

Erkek and Bozdogan[12] documented a rare expression of VP in the form of an annular outline of verrucous psoriatic plaques and Garvie *et al.*,[13] reported a phenotype of VP that closely simulated verrucous carcinoma in an 81 year old male.

Crateriform lesions was another rare presentation of VP that was reported by Nakamura *et al.*,[14] in 1994. Following this, to the best of our knowledge no such report of crateriform VP has been published.

Our patient who presented with crateriform VP also displayed lesions of chronic plaque psoriasis. Initially a diagnosis of keratoacanthoma (KA) was contemplated for this lesion, but histology eventually ruled that out.

It would be worthwhile to note that KA has been reported in patients of psoriasis.

In 1961, Vickers and Ghadially reported the first case characterized by multiple KAs emerging over psoriatic plaques treated with coal tar.[15]

A year later, Clendenning *et al.*,[16] in their paper elaborated the occurrence of KAs in a patient of generalized pustular psoriasis.

Almost two decades later, KAs originating at psoriatic treatment sites was again elucidated in two papers; one from India and the other from Canada.[17,18]

Recently, Rehlan and colleagues reported the formation of multiple KAs over healing psoriatic plaques.[19]

Plausible explanations regarding the development of KAs in psoriasis, include tar therapy, immunosuppressive effects of methotrexate, chronic inflammation, phototherapy and epithelial injury as a consequence of psoriasis *per se*.

Interestingly, in all these reports KA developed over a time period that ranged from 4 months to 43 years after the initial presentation of psoriasis, thereby representing a secondary phenomenon.

In our patient, on the other hand crateriform VP and chronic plaque psoriasis presented concurrently.

Further, as crateriform VP is extremely rare, there could be a high likelihood for clinicians to preclude its inclusion in the list of differentials for crateriform lesions. It therefore would be prudent for all dermatologists in being cognizant with this presentation of VP.

Apart from the regular histological findings of psoriasis, epidermal invagination and neutrophilic exocytosis were additional features reported by Nakamura *et al.*,[14] for crateriform VP. In our patient however, neutrophilic exocytosis was not clearly evident. Hyperkeratosis, confluent parakeratosis, scattered neutrophils in the horny layer, a cup shaped epidermal invagination, suprapapillary thinning and elongated rete ridges with buttressing and anastomoses were the predominant findings identified on microscopy [Figure 2a and b].

VP was confined to the lower limbs in all our participants with dorsa of feet (89.94%) being the most common site. In contrast, the study from Tampa, Florida, demonstrated the knees to be the most common site (50%), followed by the elbows (33%) and hands (17%).[2] In the report from Turkey, posterior truncal location of lesions were documented.[12] On the other hand, findings of Rajendran *et al.*,[10] and Wakamatsu *et al.*,[11] closely aligned with our observation of lower limb involvement.

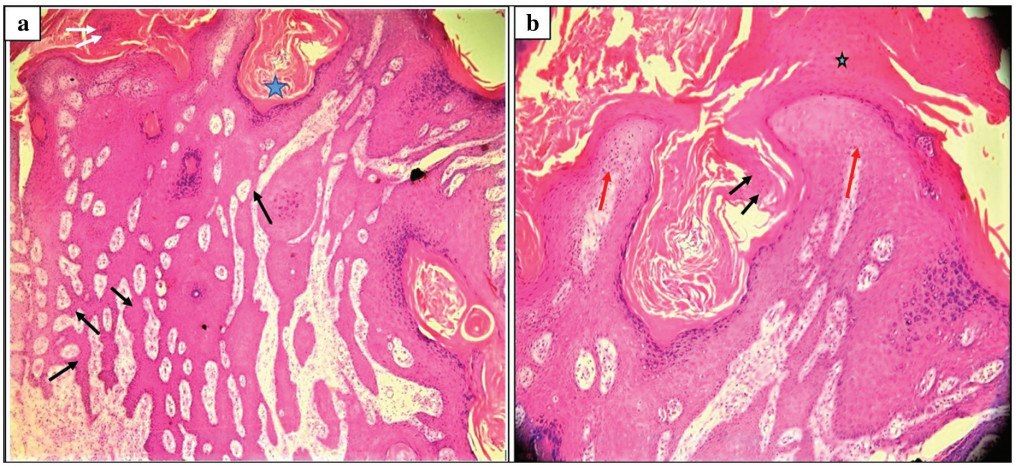

Figure 2: a: Histopathology of crateriform VP demonstrating a cup shaped epidermal invagination (blue star), confluent parakeratosis (white arrows), suprapapillary thinning and elongated rete ridges with buttressing and anastomoses (black arrows) (H&E X100). b: Higher magnification in the histology of crateriform VP illustrating hyperkeratosis, confluent parakeratosis (blue star with black outline), scattered neutrophils in the horny layer (black arrows) and suprapapillary thinning (red arrows) (H&E X200)

Acanthosis, papillomatosis, buttressing of rete ridges, Munro's microabcessess and spongiform pustules of kogoj were seen in 100%, 78.94%, 100%, 52.63% and 47.36% of our VP study subjects respectively. In the study by Khalil *et al.*,[2] similarly acanthosis and buttressing of rete ridges were observed in all their cohorts, whereas munro's microabcessess and spongiform pustules of kogoj were seen in 50% and 92% of their patients respectively.

Further, we observed that spongiform pustules and neutrophills within the stratum corneum in VP were more pronounced than those observed in PN [Figure 3a and b]. Papillomatosis was another significant observation on microscopy in VP [Figure 3c]. Also, unlike the regular camel foot elongation observed in PN, rete ridges in VP demonstrated buttressing and anastomoses as a hallmark finding.

A numeric psoriasiform grade between 11 and 16 was documented in all 19 patients diagnosed with VP.

Diabetes mellitus (DM) has been proposed as a predisposing factor for VP, secondary to the occurrence of microangiopathy and macroangiopathy.[2] Increased susceptibility to the development of VP has also been documented in patients with pulmonary dysfunction and phlebitis, in relation to tissue anoxia.[2] Further, Scavo *et al.*,[20] have reported VP in a patient with chronic hepatitis C treated with interferon. These postulations however need further validation.

Owing to rare reports of VP, a clear pathogenesis remains obscure. It has been propounded that a secondary epithelial response to repeated trauma in patients with preexisting psoriasis or psoriatic diathesis could be the pathogenic mechanism involved.[2]

For PN, constant rubbing over pruritic psoriatic plaques and the development of psoriasis as a consequence of koebnerization secondary to constant friction in patients with LSC are suggested interpretations for its pathogenesis.[1]

PK is a clinical entity that was first illustrated in 2007 by Walsh and colleagues.[3] It is characterized by solitary, unifocal, sharply demarcated keratotic plaques, that demonstrate psoriasiform changes on microscopy [Figure 4a, b, c and d]. Since its initial description, there have been a few more reports reiterating this observation.[21-23] However though, data with regard to PK still remains scant.

The exact etiology of PK remains elusive and has been suggested to be a unique form of epithelial proliferation, culminating in microscopic psoriasiform changes. Further, its inclusion to the list of cutaneous acanthomas has been recommended recently.[21]

Out of our 14 patients, 13 presented with a singular lesion, with one patient having two closely situated keratotic plaques involving the right knee. Majority of our patients were in the 3rd decade, which was in sharp contrast to the observation by Walsh *et al.*,[3] and Mutasim,[21] in which patients belonging to the 7th and 8th decade predominated.

The lower limb was the only site involved in all our participants. This differed from the findings observed by Walsh *et al.*,[3] wherein only 39% of their cohorts demonstrated involvement of the lower limb. In the remaining 61%, sites included the scalp, forehead, neck, shoulder, upper extremities and back. However, with respect to lesional location, findings of Mutasim,[21] Carbone[22] and Pires[23] were in consonance with our findings, allowing us to consider the lower extremity as the commonest site regarding

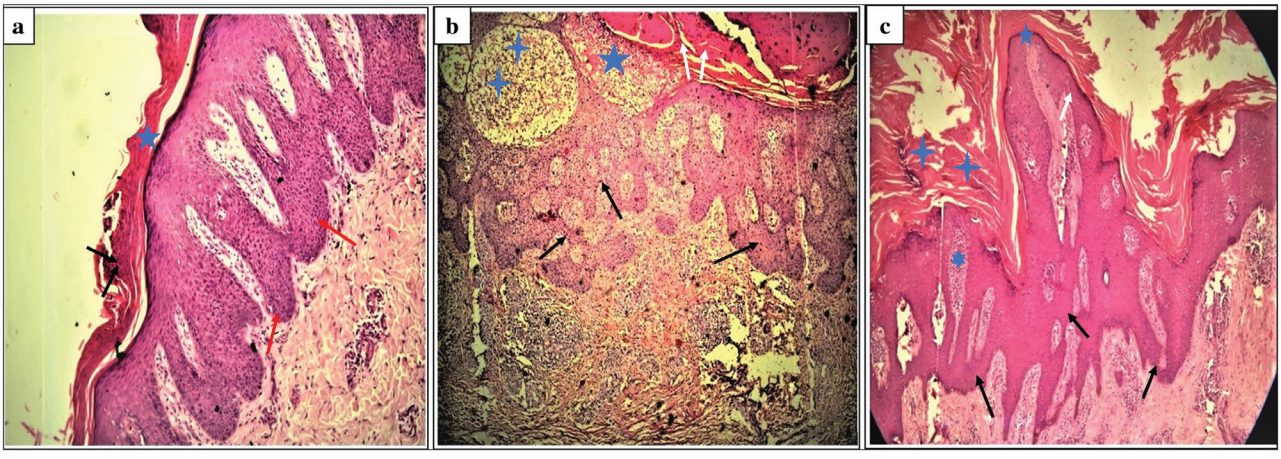

Figure 3: a: Histopathology of psoriasis neurodermiformis showing hyperkeratosis, confluent parakeratosis (five point star), munro's microabscesses (black arrows) and regular camel foot elongation of rete ridges (red arrows) [H&E X100]. b: Histopathology of VP (mammillated variant) showing a more pronounced appearance of confluent parakeratosis (white arrows), munro's microabscesses (five point star) and spongiform pustules of kogoj (four point stars). Rete ridges are showing buttressing and anastomoses with each other (black arrows) [H&E X100]. c: Histopathology of VP (classical verrucous type) showing hyperkeratosis (four point stars), papillomatosis (five point star), suprapapillary thinning (white arrow) and buttressing of rete ridges (black arrows). Dermal lymphocytic infiltrate demonstrate a more dense quality (six point star) [H&E X100]

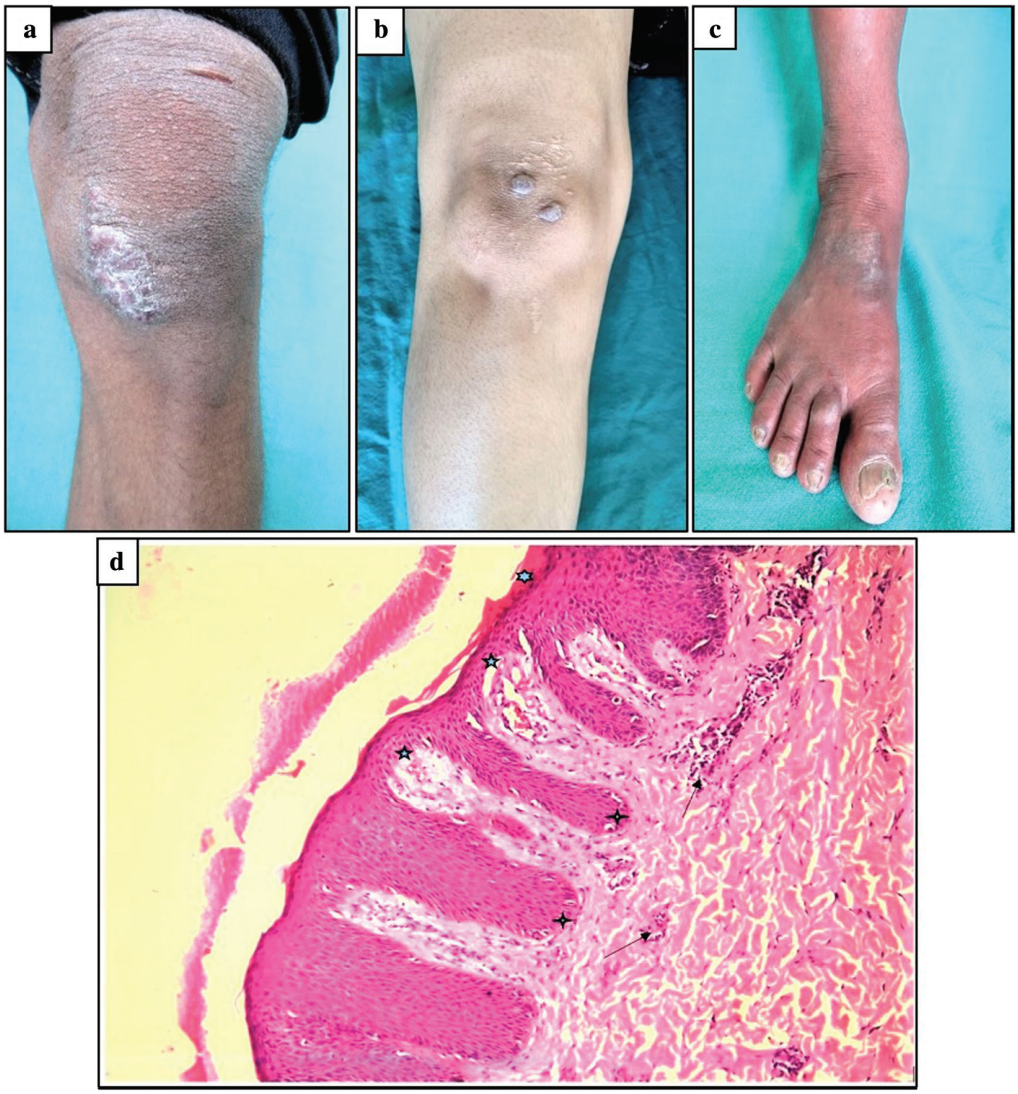

Figure 4: a: Psoriasiform keratosis (PK) over the right knee. b: Psoriasiform keratosis (PK) with two closely situated keratotic plaques involving the right knee. c: Psoriasiform keratosis (PK) with a singular scaly plaque over the dorsa of the right foot. d: Histopathology of PK depicting hyperkeratosis, focal parakeratosis (six point star), suprapapillary thinning (five point stars), camel foot elongation of rete ridges (four point stars) and a mild dermal lymphocytic infiltrate (black arrows) [H&E X100]

the occurrence of PK. Analogous to previous reports, we also considered Bowen's disease, clear cell acanthoma, VP, lichenoid keratosis and psoriasiform eczema as major differentials. In one patient however, owing to a slightly more pronounced thickened texture, possibilities of deep mycosis and tuberculosis cutis were also contemplated, which eventually were ruled out by microscopic examination along with Periodic Acid Schiff staining.

Histologically, parakeratosis was identified in 5 of our 14 patients. This differed from the findings of Mutasim[21] and Walsh *et al.*,[3] wherein parakeratosis was delineated in all their participants. Hypogranulosis was observed in only 28.57% of our patients, in contrast to 69.2% of the subjects in the study from Cincinnati.[21]

Similar to our findings, acanthosis was identified in all histological specimens by Mutasim.[21] Suprapapillary thinning was seen in 78.57% of our participants. This was in contrast to the observation by Mutasim[21] in which none of the slides demonstrated suprapapillary thinning.

The dermal infiltrate in all our patients was composed primarily of lymphocytes. In most of our patients (72.42%), the distribution of inflammatory cells was mild to moderate. This was in consonance with the findings of Walsh *et al.*,[3] and Mutasim.[21]

The numeric histological psoriasiform score ranged from 11 to 13 amongst our PK study subjects.

On comparing PK, with PN and VP, no confusion arose in contrasting it from them clinically.

Histologic overlap though, did occur. Distinguishing VP from PK histologically was not difficult. Certain distinctive findings like anastomosing and buttressing of

rete ridges, papillomatosis, denser dermal inflammatory infiltrate and a more pronounced expression of munro's microabscesses/spongiform pustules of kogoj were more specific for VP and enabled the authors to obtain a concrete histological conclusion.

However, there was considerable overlap between PN and PK microscopically; thereby making clinical correlation essential to arrive at a final/specific diagnosis in these cases.

Conclusion

Although the concept of PN, VP and PK may not be very novel, yet we felt the need to revisit these entities owing to their close similarity with a number of other dermatoses.

Further, because of paucity regarding their representation in medical literature, and their non resemblance to classical psoriatic plaques; often there could be a high likelihood of an incorrect diagnosis.

Moreover, different phenotypes of VP; and the pattern of rete ridges observed under microscopy could further pose a diagnostic challenge to the dermatologist/pathologist if they are not well versed with these findings.

It therefore becomes imperative to adopt a systematic clinicopathological evaluation to arrive at a concrete conclusion.

Besides, we also need to be aware about the fact that it is very unlikely to detect each and every finding of psoriasis in an individual biopsy specimen. Scoring each slide numerically according to Trozak's grading could therefore be of practical significance.

According to our observation, we are of the opinion that any score >10 is acceptable to finalize a histological diagnosis of psoriasis.

Lastly, based on our findings we do not consider PN, VP and PK to be rare entities. This rarity could be attributed to their lower reporting.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Eruptive Lentiginosis in a Young Healthy Woman—Revisiting Causal Associations

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Abstract

Lentigines are hyperpigmented macules, which represent the simplest form of increased melanocytic proliferation. The term "lentiginosis" is applied for the presence of lentigines in an exceptionally large number or in a distinctive configuration. Lentigines evolve slowly, but widespread occurrence over a short period of time is typical of eruptive lentiginosis. We report an unusual case of eruptive lentiginosis in a female patient with no prior systemic disorder or familial pattern, presenting with widespread hyperpigmented macules, symmetrically distributed over the face, neck, upper trunk, shoulders, and both arms and forearms. Clinicohistopathological features were consistent with eruptive lentiginosis. Our case report seems interesting as well as a rare one as it involved an otherwise healthy young woman.

Keywords: Eruptive lentiginosis, hyperpigmented macules, lentigines

Introduction

Lentigines are benign pigmented macules, which are characterized by an increased number of melanocytes, while the term lentiginosis is applied when lentigines are present in relatively large numbers or in a distinctive distribution.[1] Generalized distribution of lentigines has been reported in association with various multisystem disorders of developmental defects. On the other hand, an occurrence without associated systemic manifestations or developmental anomalies, termed as "generalized lentiginosis," has increasingly been reported.[2-4] Lentigines evolve slowly, but widespread occurrence over the short period of time from months to years is typical of eruptive lentiginosis.[1] Eruptive lentiginosis has been linked to various immunosuppressant and immune modulator drugs with the possible hypothesis of altered immune surveillance,[5] as well as drug-induced proliferation of melanocytes in predisposed individuals.[6] We present an unusual case of eruptive lentiginosis in a young woman with no prior systemic disorder or similar familial pattern.

Case History

A 29-year-old woman presented to the outpatient department with widespread hyperpigmented macules located over apparently normal skin of the face, neck, and upper trunk that started 1 year back and progressed rapidly. The patient was housewife and denied having any adverse pregnancy outcome. There was no history of photosensitivity or relatively longer period spent on sunlight, phototherapy, adverse cutaneous drug reactions, or any autoimmune cutaneous or extracutaneous disorders. The patient also revealed noticeable change in the appearance of new lesions after the outbreak of lentigines. During the outbreak of lentigines, macular lesions were initially light brown in color and more scattered, whereas new lesions after outbreak were dark brown and dense. There was no history of similar macules or any atypical melanocytic nevi among family members.

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On examination, numerous light-to-dark brown dense macular lesions of size approximately 1–4 mm present symmetrically over the face, neck, upper trunk, shoulders, both arms and forearms sparing palms and soles, axilla, genitals, and mucous membranes [Figure 1]. Her general and systemic examinations revealed no abnormality. Her routine laboratory investigations, serology, chest x-ray, as well as neurological and hormonal evaluation were all normal. The patient could not undergo genetic analysis because of limited resources.

After complete clinical evaluation, histopathological examination of skin biopsy taken from one larger macule of the left arm showed elongation of rete ridges and relatively increased number of melanocytes at rete ridges with normal distribution of melanocytes in intervening epidermis along with basal layer hyperpigmentation [Figure 2]. Nests of melanocytes, typically found in nevus, were not present in papillary dermis. Clinicohistopathological features were consistent with eruptive lentiginosis. Presently, the patient is on regular follow-up with series of clinical assessment to detect any significant change in numbers or size of macules or newly developed lesions.

Discussion

Lentigines are benign pigmented lesions, commonly start at younger age and are characterized clinically by small-sized multiple brown-to-black macules with well-demarcated edges and histologically by the proliferation of melanocytes in basal cell layers. Multiple lentigines

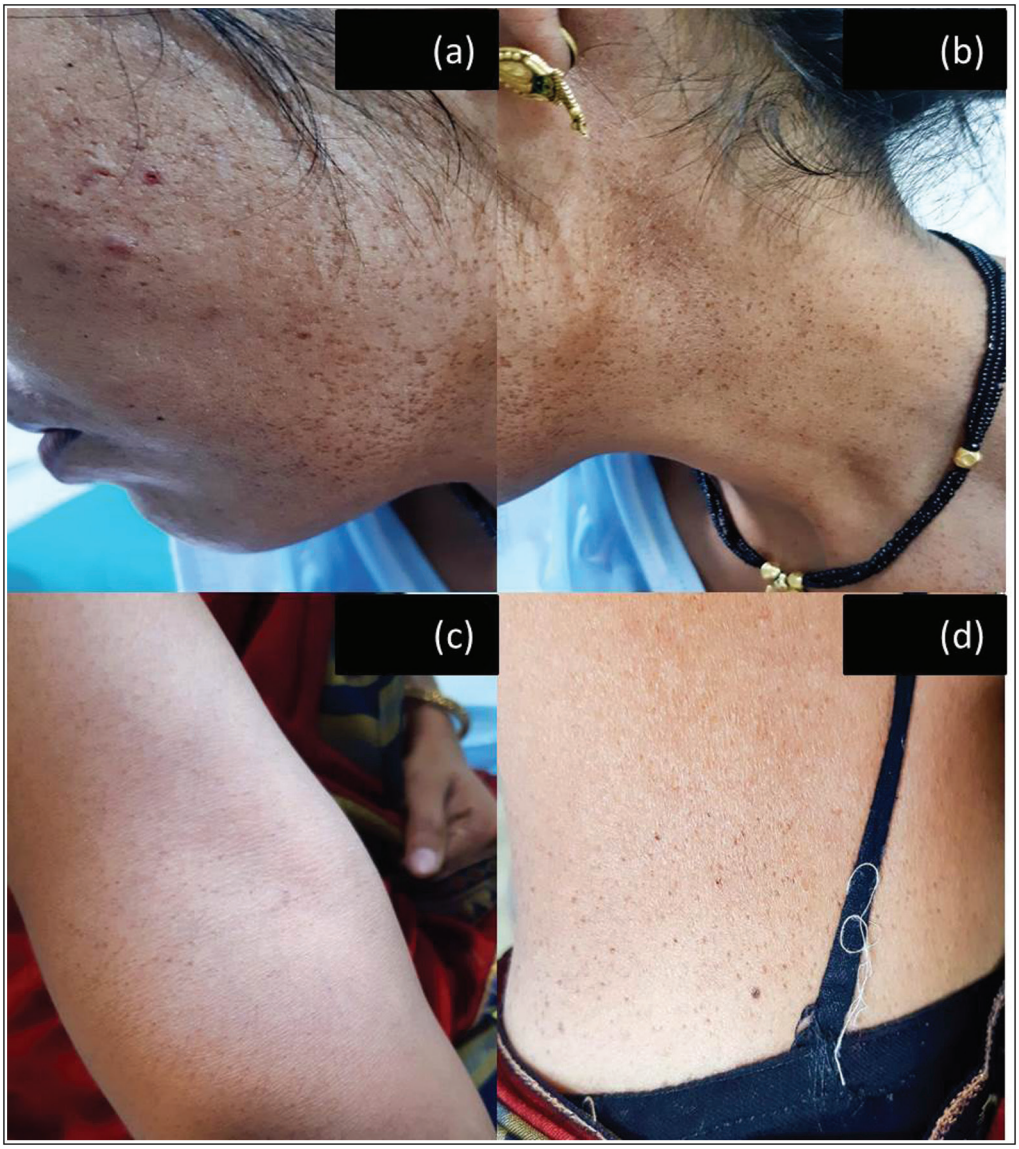

Figure 1: Multiple light-to-dark brown dense macular lesions of size approximately 1–4 mm present symmetrically over (a) the left side of the face, (b) the left side of the neck, (c) arms and forearms, and (d) back

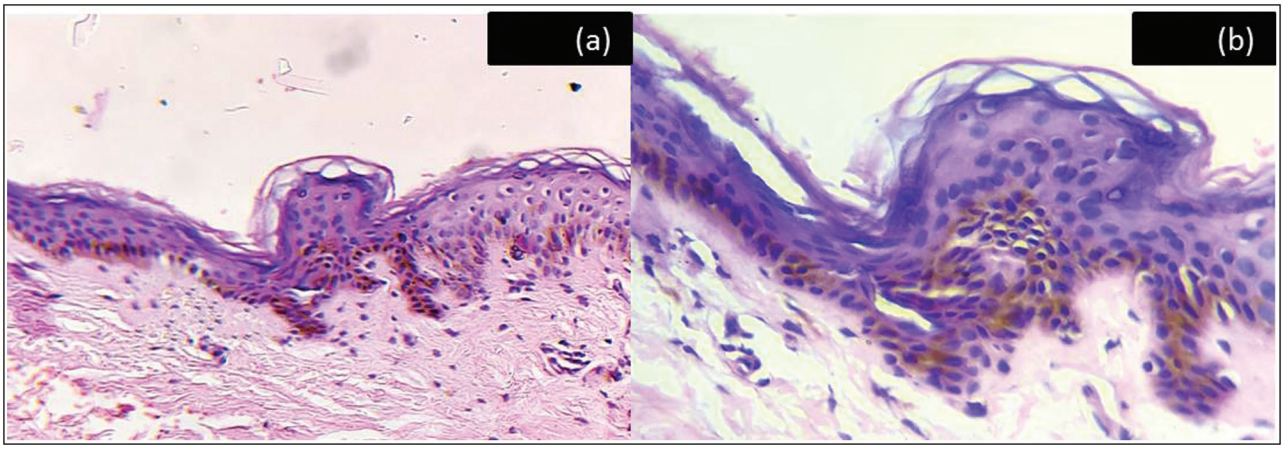

Figure 2: Elongated rete ridges with increased melanocytes and lower epidermis hyperpigmentation: (a) H&E, X100; (b) H&E, X400

may occur as an isolated phenomenon or a part of more complex multisystem disorders namely Noonan syndrome, lentigines, atrial myxoma, and blue nevi syndrome and nevi, atrial myxoma, myxoid neurofibromas, and ephelides syndrome (Carney complex), and Peutz-Jeghers syndrome with relatively early onset of lentigines in these syndromes. The term eruptive lentiginosis, i.e., abrupt onset of lentigines without systemic abnormality, was suggested by Sanderson in 1960 who reported the outbreak of pigmented macular lesions after an episode of measles.[7]

Although eruptive melanocytic nevi may look clinically indistinguishable from eruptive lentiginosis possibly because of extended manifestations of melanocytic proliferation with some continuity,[2] yet the presence of peripheral brown globules on dermoscopy[8] and melanocytic proliferation at dermoepidermal junction and nests of melanocytes in the papillary dermis on histopathology in the former may differentiate it from lentiginosis to a remarkable extent.

Solar radiations and phototherapy are established causes of lentiginosis, as well as cases of eruptive lentiginosis in regressing psoriasis (ELRP) are growing evident.[9] Also, there are limited cases of eruptive lentiginosis reported in the literature, following chemotherapy,[10] azathioprine,[11] and topical immunotherapy.[12]

Most of the previous reported cases of eruptive lentiginosis were either associated with immunosuppressant therapy, topical immunotherapy, or a part of familial eruptive lentiginosis except a case of generalized eruptive lentiginosis in a healthy elderly man reported by Kim *et al.*,[2] but our case seems distinctive in a view that it involved otherwise healthy young woman, a case similar to which has not yet been reported elsewhere to the best of our knowledge [Table 1].

The pathogenesis of eruptive lentiginosis is not clearly understood, but it has been suggested as an exaggerated recovery in pigment production.[9] Surprisingly, we did not find any compensated hyperpigmentary pattern in our case, rather abrupt onset was observed without prior noticeable illness or therapy. Certain mutations in signaling proteins may also predispose patients to initiation and further spread of lentigines as immune modulation will be greater in these individuals.[13] Further, following immunosuppressant therapies, the facilitation of uncontrolled proliferation of melanocytes in genetically predisposed patients has also been suggested.[6] Present case, to our belief, could be the very first sporadic case in family with subsequent contingency in lineage, yet the possibility of unassociated incident cannot be completely ruled out. However, the pathogenesis of familial eruptive lentiginosis without systemic involvement or malignancy and genetic predisposition in the family members is yet to be explicated.[14]

In summary, we hypothesize that the occurrence of our isolated case of eruptive lentiginosis could be due to following probable mechanism:

(a) A part of familial eruptive lentiginosis with possibilities of impending occurrence in subsequent generations[14]
(b) Abrupt reaction pattern of melanocyte proliferation by cytokine surge because of the past unreported brief illness.[15]

These assumptions are a matter of elucidation, and considering the increasingly evident similar cases, further evaluations to help us arrive at final conclusion is the need of an hour.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Table 1: Comparison of the present case with previous case reports

Feature	Our study	Micieli and Alavi (2018)	De *et al.* (2010)	Na *et al.* (2006)
Age (years)	29	29	35	40
Gender	Female	Female	Female	Female
Etiology/ associations	Not known	ELRP after secukinumab	CHOP therapy for non-Hodgkin's lymphoma	Familial
Pathogenesis	A part of familial eruptive lentiginosis, melanocytic proliferation by cytokine surge	Increased number of melanocytes combined with rapid recovery of pigment production in resolving psoriatic plaques, immune modulation, and mutation in signaling proteins	Diminished immune surveillance, immunosuppression-induced melanocytic proliferation, drug-induced	Genetic predisposition, common exposure to in fectious agents, or chemical materials in a family
Family history	Nil	Nil	Nil	Present (similar lesions in daughter)
Distribution	Widespread, sparing lower trunk, lower limbs, palms, soles, and mucosa	On upper extremities and trunk	All four limbs sparing palms, soles, and mucosae	Face, trunk, and extremities sparing palms, soles, and mucosa
Onset	Abrupt	Abrupt	Abrupt	Abrupt
Associated systemic involvement	Nil	Nil	Nil	Nil

CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone.

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Conflicts of interest

There are no conflicts of interest.

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Should Titanium Dioxide–containing Drugs Be Discontinued in Patients with Frontal Fibrosing Alopecia?

Sir,

We read with great appreciation the article published by Aerts *et al*. on frontal fibrosing alopecia of titanium dioxide in 2019.[1] The incidence of this type of cicatricial alopecia, which usually affects postmenopausal women, has increased approximately tenfold over the past decade. Reporting that some sunscreens and cosmetic products may be responsible for the etiology of frontal fibrosing alopecia has caused great concern in dermatologists recommending these sunscreens and in patients using them. Even if patients are not warned about this issue, they access and read these articles on the internet and ask dermatologists questions in this direction. Titanium dioxide is present as a preservative in many drugs used in frontal fibrosing alopecia and other systemic treatments, thus increasing the risk of exposure to this substance. Patients ask their dermatologists about whether these drugs should be avoided.

To answer these questions, we tried to determine titanium dioxide sensitivity in our patients who were diagnosed with frontal fibrosing alopecia based on clinical, trichoscopic, and histopathological findings. For this purpose, patch test with titanium dioxide (Chemotechnique, T-042) was performed on 21 (15 women and 6 men) patients. Six of the female patients are in the premenopausal period. The test results of these patients, whose mean age is 47.14 (age range: 21–68) years, were checked at 48, 72, and 96 hours (according to the guidelines of the British Society of Dermatology), but no positive response was detected.[2] However, the lichenoid reaction may occur early or months or even years after exposure. Therefore, for subsequent readings, patients were instructed on how to check the application sites and to apply to the clinic in case of doubt. However, some late positive reactions may have been overlooked in this study due to non-compliance with our instructions.

In recent years, the sunscreens and some of cosmetic products contain titanium dioxide. A patient with improved frontal fibrosing alopecia has been reported by the removal of this content from sunscreens.[3] In the hair analysis of a different patient, particles containing titanium dioxide were detected.[4] It is suggested that these particles cause a T-lymphocyte-mediated allergic reaction and lead to a lichenoid reaction. However, as in our cases, in eight patients with frontal fibrosing alopecia, no positivity was detected in the patch test with cosmetic products containing titanium dioxide.[5] According to these results, it was thought that titanium dioxide potentiates some contact sensitizers indirectly, not directly. Due to the low sensitivity of the patch test with titanium salts, it is reported that different titanium salts should be used.

It has also been reported that *in vitro* tests such as lymphocyte transformation test or memory lymphocyte immunostimulation method may be used. As there are conflicting results about the relationship between frontal fibrosing alopecia and titanium dioxide, and studies are conducted with a few cases, it is necessary to determine the sensitivity of titanium dioxide in frontal fibrosing patients with *in vitro* tests as well as patch testing. In *in vitro* studies with ionic and nanoparticles, especially ionic forms of titanium dioxide, trigger inflammation.[6] So it is necessary to ask the same question again. Are we, as doctors, trying to treat the inflammation caused by titanium dioxide, which is included in the drugs we give to patients?

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Conflicts of interest

There are no conflicts of interest.

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New-Onset Lichenoid Dermatitis Following Excision of Squamous Cell Carcinoma: Coincidence or Association?

Dear Editor,

Squamous cell carcinoma (SCC) is the second most prevalent skin cancer worldwide. SCC's most substantial risk factors include ultraviolet exposure, fair skin, and immunosuppression. Treatment of SCC is principally surgical, but adjuvant chemoradiotherapy is also used.[1] Lichenoid dermatitis, the most common of which is lichen planus, is among the prevalent clinical and histological examples.[2] To the best of our knowledge, this is the first presentation of lichenoid dermatitis developing after the excision of SCC.

A 67-year-old man with a history of well-differentiated SCC (first diagnosed 2 years earlier) several times excised from the nose and ear but without lymph node, local, or distant metastasis. The patient presented with hyperkeratotic lesions at the last excision sites that developed during the previous 6 months. Dermatologic examination showed erythematous brown hyperkeratotic plaques on the tip and dorsum of the nose, preauricular area, and external ear canal [Figure 1A]. In addition, there were hypertrophic and atrophic scars at the SCC excision sites [Figure 1A]. Ulceration and telangiectasia were not observed. Multiple biopsies obtained from all the lesions were reported as lichenoid dermatitis, with orthokeratosis, hypergranulosis, and irregular acanthosis of the epidermis, but no tumor cells [Figure 1B]. The lesion's spontaneous regression was noted within 2 weeks of the biopsies [Figure 1C]. After 7 months of follow-up, the patient showed no signs of relapse or any likely lesions elsewhere.

The pathophysiology of lichenoid dermatitis is still obscure. On the basis of the relationship between lichenoid dermatitis and paraneoplastic pemphigus, various hypotheses have been proposed about the relationship between lichenoid dermatitis and malignant neoplasms. Lichenoid eruptions may be seen before or after signs or symptoms of the underlying malignancy. A chronic lichenoid reaction pattern may predispose some patients with cancer to develop humoral autoimmunity against basement membrane components. Moreover, cancer might indicate a cell-mediated immune response and give rise to lichenoid dermatitis. Accordingly, autoreactive T cells would respond opposite the ordinarily inactive basement membrane constituents.[3]

In the literature, a case of biopsy-proven lichenoid dermatitis was reported in a patient following basal cell carcinoma (BCC) excision, which was suggested to develop due to the immune response to BCC removal in the excision area. However, considering the relationship between lichenoid dermatitis and BCC detection, the triggering stimulus (BCC) may no longer be detected in a biopsy specimen. Instead, it may be isolated, coexisting with BCC, or be mistaken for BCC, and it may even mask occult BCC.[4] In another case, it was reported that lichenoid dermatitis developed while receiving vismodegib therapy for BCC. It has been claimed that molecular and immune mechanisms cause the formation of lichenoid dermatitis.[5] However, the relationship between lichenoid dermatitis and SCC is unknown.

In our patient, it was observed that lichenoid dermatitis developed in the scar areas. Although it is not clear why lichenoid dermatitis develops after scarring, it is thought that the Koebner phenomenon, which expresses the development of new lesions in post-traumatic areas, is one of the possible provoking factors.[6] In the literature, giant cell lichenoid dermatitis has been reported in herpes zoster scars in a bone marrow recipient. It has been suggested that the varicella-zoster virus may have initiated the hypersensitivity reaction in this patient. It has also been suggested that the patient's immune status may have affected the morphology.[7]

As a result, lichenoid dermatitis might be a paraneoplastic manifestation and can occur before, during, or after malignancy; therefore, additional research is necessary to discern the association between lichenoid dermatitis and SCC; more clearly, patients should be closely monitored.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

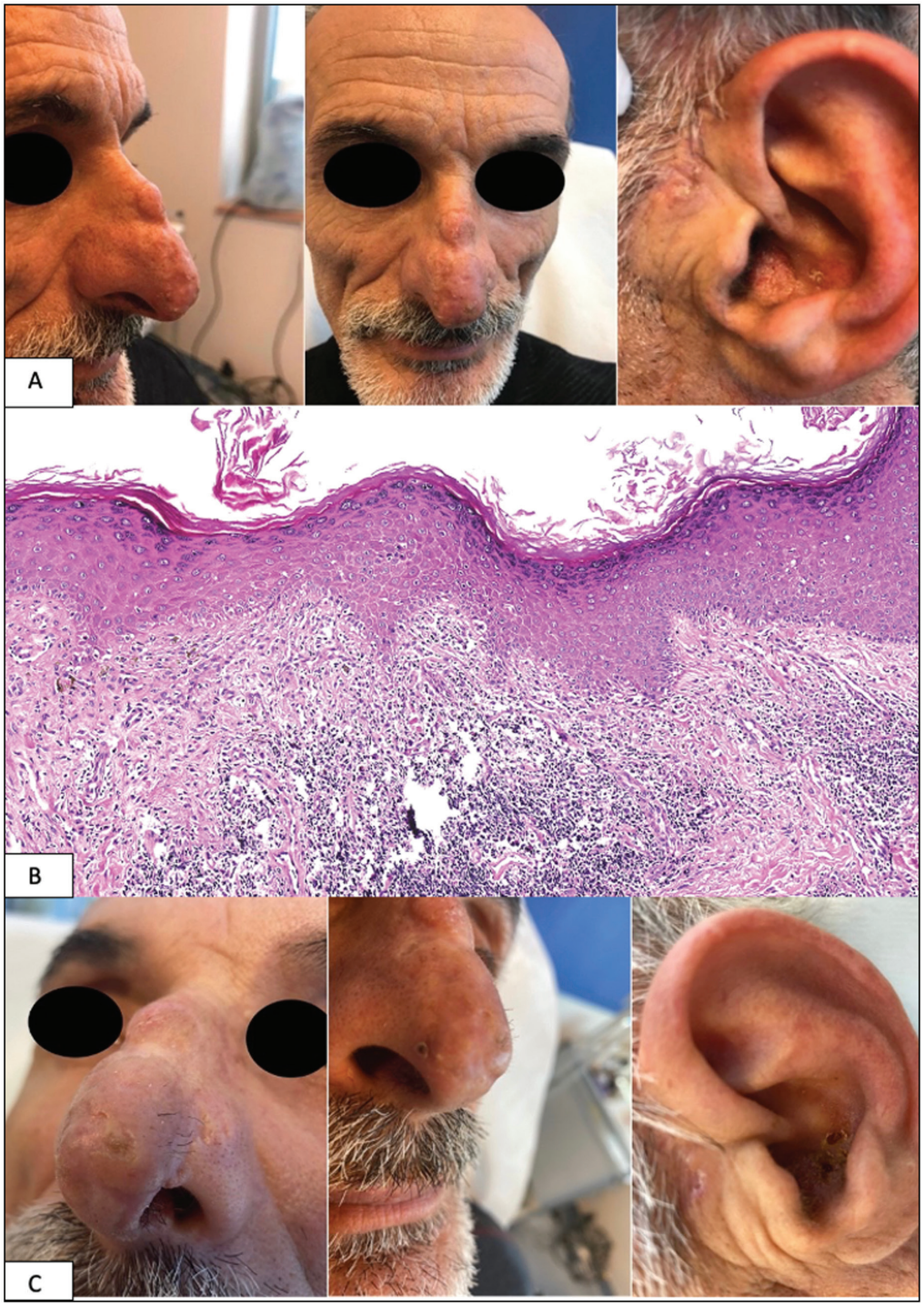

Figure 1: (A) Hyperkeratotic plaques on the nose, preauricular area, and external ear canal. (B) Lichenoid tissue reaction resembling lichen planus. Note orthokeratosis, hypergranulosis, and irregular acanthosis of the epidermis. Note the hydropic degeneration and eosinophilic colloid bodies at the basal cell layer (H&E, X200). (C) Regressed hyperkeratotic plaques on the nose and preauricular area. Note the crust on the external ear canal

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