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CASE REPORTS

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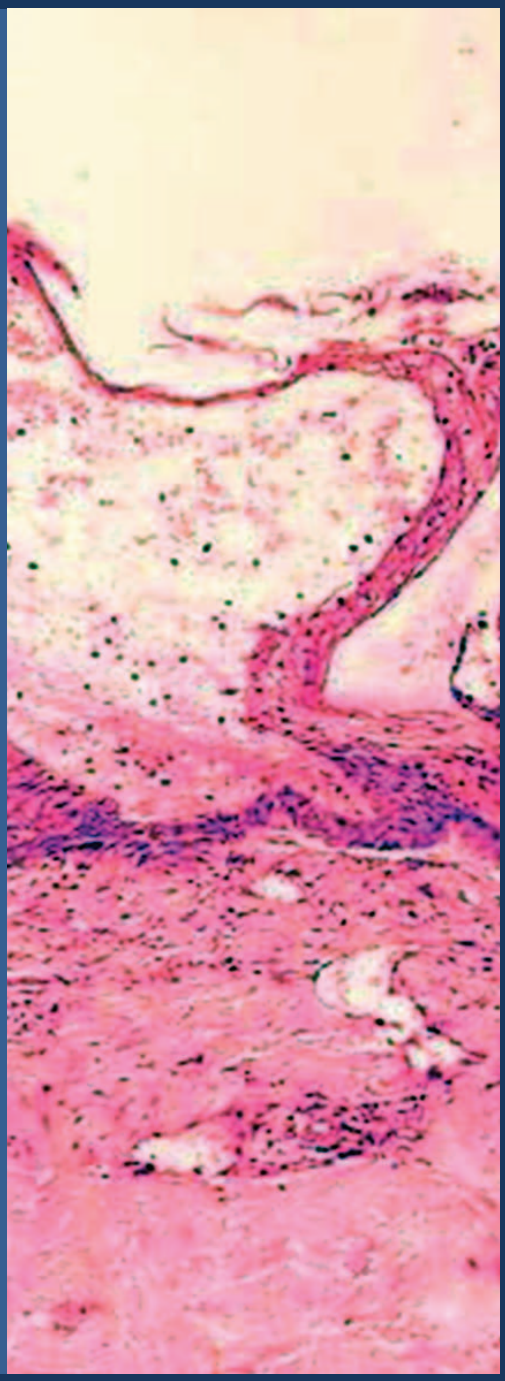

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Evaluation of IHC Ki-67 with Clinical Correlation in Psoriasis

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Abstract

Introduction. Psoriasis is a chronic inflammatory skin disease with hyperproliferation, abnormal differentiation and inflammatory infiltration in epidermis and dermis. Sometimes it is clinically and histopathologically challenging to distinguish psoriasis from other non-psoriatic psoriasiform dermatoses (NPPD) like eczema, pityriasis rosea, pityriasis rubra pilaris, and lichen simplex chronicus. Ki-67 is a non-histone nuclear protein complex that regulates the cell cycle and is the most widely used proliferation immunohistochemistry (IHC) marker. Its levels have been shown to be raised in psoriasis compared to normal skin. **Aim**. To elucidate and compare expression of IHC Ki-67 in psoriasis and NPPD, correlate these levels with clinical variants and disease severity in psoriasis and to observe change in levels with demographic and psoriasis -related variables. **Material and Methods**. Thirty patients, each with clinically diagnosed psoriasis (cases), and NPPD (controls) were enrolled. Biopsy was taken for histopathology and IHC Ki-67 immunohistochemistry. Statistical analysis was performed. **Results**. We found a significantly higher expression of IHC Ki-67 in psoriasis as compared to all types of NPPD. The higher level of Ki-67 in pustular and erythrodermic psoriasis compared to plaque-type emphasizes the greater severity and activity of these forms. The Ki-67 expression was found to increase with increasing body surface area involvement and disease severity (PASI) in chronic plaque type. Pityriasis rubra pilaris had the highest Ki67 expression among NPPD group. **Conclusion**. Ki-67 is a promising tool with diagnostic and prognostic utility in psoriasis, particularly when it comes to its differentiation from non-psoriasis psoriasiform disorders.

Key words: Psoriasis; Ki-67 Antigen; Cell Proliferation; Immunohistochemistry; Biopsy; Severity of Illness Index; Diagnosis; Prognosis

Introduction

Psoriasis is an immune-mediated genetically determined disorder affecting skin, nails and joints with various systemic associations (1). The worldwide prevalence ranges between 0.09% and 11.43% with India contributing 20% of the global burden (2, 3).

Non-psoriasis psoriasiform dermatoses (NPPD) are disorders which simulate psoriasis clinically and histopathologically. A few examples are seborrhoeic dermatitis, pityriasis rosea, pityriasis rubra pilaris (PRP) and lichen simplex chronicus (4). Although a specific diagnosis may be reached by means of characteristic and distinctive histopathological features such as Munro's microabscesses and tortuous, dilated capillaries *(psoriasis)*; alternating horizontal and vertical parakeratosis *(pityriasis rubra pilaris)*; mounds of parakeratosis with extravasation of erythrocytes *(pityriasis rosea)*; and dermal, thickened vertical collagen bundles with orthokeratosis *(lichen simplex)*, the dermatopathologist is often forced to report findings as "non-specific psoriasiform dermatitis", thereby emphasizing the need for more effective diagnostic tools to differentiate between psoriasis and NPPD. Ki-67 antigen is a labile, 345-395 kD non-histone nuclear protein complex. It regulates the cell cycle and is the most widely used proliferation immunohistochemistry (IHC) marker. Its expression has been shown to be increased in psoriatic lesions with respect to non-lesional skin (5). However, there are limited data regarding the comparative expression of this marker in different types of psoriasis vis-a-vis NPPD.

This study attempts to elucidate the difference in IHC Ki-67 expression between psoriasis and non-psoriasis psoriasiform derma-

Table 1. Distribution of patients with psoriasis and non-psoriasis psoriasiform dermatoses (NPPD) according to clinical diagnosis

Clinical diagnosis (Psoriasis)	Number n (%)	Clinical diagnosis (NPPD)	Number n (%)
Plaque psoriasis	10 (33.33)	Pityriasis rosea	10 (33.33)
		Eczema	12 (40.0)
Generalised pustular psoriasis	10 (33.33)	Seborrhoeic	6
		Discoid	3
		Lichen simplex chronicus	3
Erythrodermic psoriasis	10 (33.33)	Pityriasis lichenoides chronica	4 (13.33)
		Pityriasis rubra pilaris	3 (10.0)
		Parapsoriasis (small plaque)	1 (3.33)
Total	30 (100)		30 (100)

toses (NPPD) and to identify any correlation with demographic and disease - related variables in psoriasis.

Material and Methods

A cross-sectional observational hospital-based study was conducted on 30 clinically diagnosed cases with psoriasis and 30 age and gender-matched controls with non-psoriasis psoriasiform dermatoses. After the permission and written informed consent had been obtained from the Institutional Ethics Committee and the patients, respectively, a detailed history was elicited from each patient followed by dermatological and systemic examination. Pregnant and lactating females and patients with doubtful diagnosis or on topical or systemic treatment within two months of enrolment were excluded. Data were recorded in Microsoft Excel Software.

Skin biopsy was taken from the most clinically representative lesion for histopathological examination and immunohistochemistry (using two-step polymer method and mouse monoclonal antibodies against Ki-67)

IHC Interpretation: Expression of Ki 67 was indicated by the presence of yellow to brown granules in the nucleus. Ki 67 positivity index was calculated as the percentage of Ki 67 positive cells.

$$\text{Ki-67 percentage} = \frac{\text{Suprabasal Ki-67 positive cells}}{\textit{Total epidermal Ki-67 positive cells}} \times 100$$

Statistical Analysis

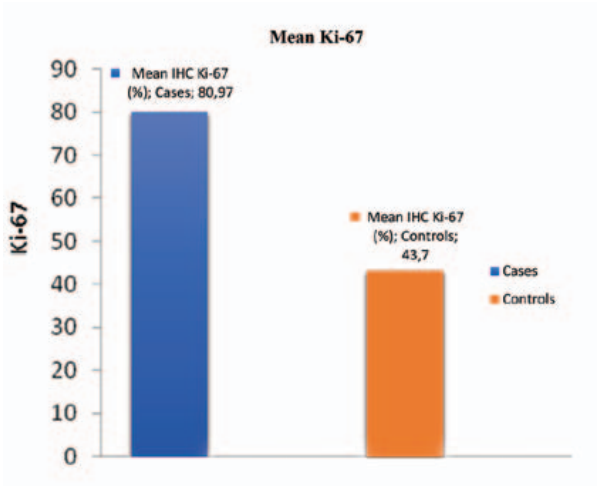
Data analysis was performed using SPSS (Statistical package for social sciences) version 20:0. Qualitative data variables were expressed as frequency and percentage. Chi-square test/Fisher's exact test/Kruskal Wallis test/Mann–Whitney U test/ANOVA test were used to find the association of Ki-67 percentage with various parameters such as the difference between psoriasis and NPPD, correlation with the type and duration of psoriasis, age, gender, treatment history, nail and joint involvement and disease severity (assessed by PASI score and body surface area involvement). p-value <0.05 was considered as significant.

Results

Table 1 depicts the distribution of the 30 psoriasis cases and 30 non-psoriasis psoriasiform dermatoses (NPPD, controls) based on clinical diagnosis (confirmed by clinicopathological correlation). The psoriasis group comprised of 10 plaque, generalized pustular and erythrodermic types each. Maximum number of patients in both psoriasis (22, 73.33%) and NPPD (23, 76.66%) groups was below 50 years of age, their mean age being 35 years (SD 18.66) and 37.17 years (SD 17.43), respectively, without any statistically significant difference. There were three pediatric cases in both plaque and pustular group (mean age 10.16 years). Both psoriasis (57%) and NPPD (70%) groups showed male predominance. Disease duration since its onset ranged between 15 days to 30 years for psoriasis while 90% of the NPPD had duration less than 6 months. Out of 30 psoriatic patients, 16 had previous history of treatment.

Table 2. Mean IHC Ki-67 percentage in psoriasis and non-psoriasis psoriasiform dermatoses (NPPD)

Clinical diagnosis (Psoriasis)	Number n, (%)	Mean Ki-67 value (%)	Clinical diagnosis (NPPD)	Number n,(%)	Mean Ki-67 value (%)
Plaque psoriasis	10 (33.33)	78.50	Pityriasis rosea	10 (33.33)	45.30
Generalised pustular psoriasis	10 (33.33)	82.0	Eczema	12 (40.0)	41.00
Erythrodermic psoriasis	10 (33.33)	82.40	Pityriasis lichenoides chronica	4 (13.33)	47.50
			Pityriasis rubra pilaris	3 (20.0)	51.00
			Parapsoriasis	1 (3.33)	23.00
Total	30 (100)			30 (100)	



Graph 1. Comparison of Mean IHC Ki-67 between Psoriasis (cases) & NPPD (controls)

Nail changes were noted in 22 (73.3%) psoriatic patients while in NPPD only 3 (10%) patients with chronic eczema had pitting and longitudinal ridges. Two psoriatic patients (one each with generalized pustular psoriasis and erythroderma) had joint pain while none from the NPPD group had this complaint.

Mean Ki-67 percentage for psoriasis (80.97 $\pm$ 5.58, range 70 – 90%) was significantly higher than for NPPD (43.7 $\pm$ 10.10, range 20% to 59%) (p value < 0.001) **(Table 2 and Graph 1)**. Among different variants of psoriasis, erythrodermic type had the highest levels followed by generalized pustular and plaque **(Graph 2a).** However, this difference was not statistically significant (p value 0.199). Children (< 12 years) with plaque-type had significantly higher Ki-67 expression than their adult counterparts (84.66% vs. 75.85%) while adults with pustular type had insignificantly higher levels as compared to children (83% vs 79.6%). PRP had the highest Ki-67 levels (51%) in NPPD group followed by pityriasis lichenoides chronica, pityriasis rosea and small plaque parapsoriasis **(Graph 2b)**. **Figure 1 (A, B and C)** shows immunohistochemistry staining (IHC Ki-67) observed in the three sub-types of psoriasis. Of all variables analyzed, body surface area (for entire

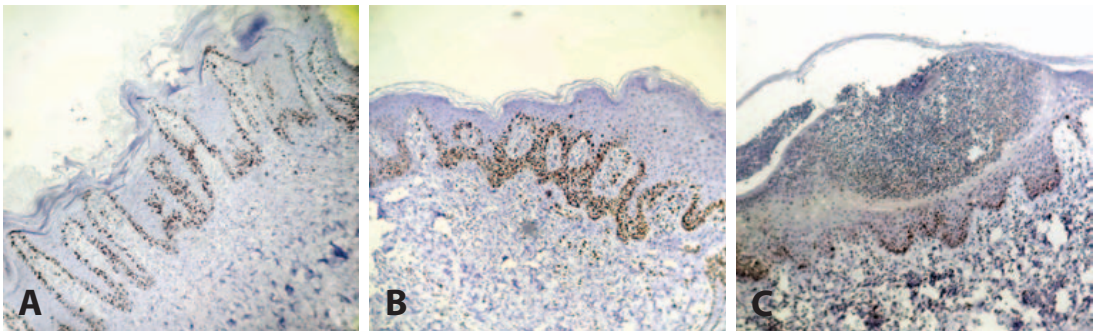


Figure 1. Immunohistochemical staining (IHC Ki-67) in psoriasis: A) Plaque Psoriasis, B) Erythroderma, C) Pustular Psoriasis

Table 3. Correlation of mean value of IHC Ki-67 with body surface area involvement in psoriasis

BSA	Number of patients	IHC (%)		p-value
		Mean	SD	
≤ 30%	3	73.67	3.21	
31% - 50%	1	75.0		0.024
> 50%	26	82.04	5.25	

Table 4. Correlation of mean value of IHC Ki-67 with PASI score in plaque psoriasis

PASI score	Number n, (%)	Mean value of IHC Ki-67 (%)	SD	p- value
< 10	3	75.33	0.57	
>10	7	80.17	6.55	0. 03

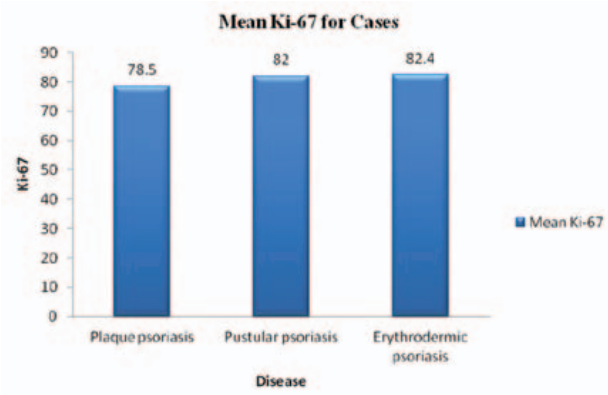
psoriasis group) and PASI score (for plaque-type psoriasis) demonstrated a statistically significant correlation with Ki-67 levels **(Tables 3 and 4)**. The patients with > 50% body surface area involvement (p=0.024) and PASI score > 10 (p = 0.03) had highest Ki-67 levels. Male patients with generalized pustular psoriasis had significantly higher mean Ki-67 levels as compared to female ones (p = 0.021). There was no statistically significant association between Ki-67 levels and other parameters such as treatment history, duration of disease, nail or joint involvement.

Discussion

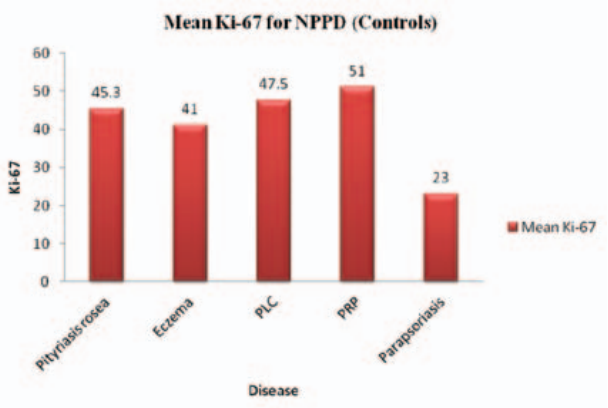
Various dermatoses, either at the onset or during the course of their progression/resolution, manifest lesions that mimic psoriasis leading to delayed or missed diagnosis with implications for management and prognosis.

Histopathologically, psoriasiform reaction pattern is defined as the presence of epidermal hyperplasia with elongation of rete ridges in a regular manner. This encompasses a heterogeneous group of dermatological conditions (6). Psoriasis, the prototype of the psoriasiform dermatoses, is considered to be a disease of dysregulated inflammation, driven and maintained by multiple components of the immune system. The pathologic collaboration between innate and acquired immunity results in the production of cytokines, chemokines and growth factors that contribute to the hyperproliferation and inflammatory infiltrate (4). The common clinical variants of psoriasis are pustular, erythrodermic and plaque type.

Ki-67 is an important marker of active cycling cells (S, G2 and M phases). We found that lesions of psoriasis had higher mean values of IHC Ki-67 than NPPD, confirming a greater degree of epidermal hyperprolifera-



Graph 2a. Mean value of IHC Ki-67 in different types of psoriasis



Graph 2b. Mean value of IHC Ki-67 in different types of NPPD

tion. Our method of IHC Ki-67 staining was similar to Engin Sezer et al. (7) Jun-min et al. stated that the over-expression of Ki-67 in psoriatic lesions suggests an abnormality of cell cycle regulation related to the hyper-proliferation and abnormal differentiation of psoriatic keratinocytes, implying that it may be involved in the pathogenesis of psoriasis (8). In our study, higher levels noted in unstable variants like erythrodermic and generalised pustular are attributable to their greater severity with profound epidermal proliferation as compared to the more stable plaque-type. Our findings are consistent with previous studies that reported higher number of Ki-67 positive keratinocytes in pustular psoriasis as compared with psoriasis vulgaris (9). In the plaque psoriasis group, the highest IHC Ki-67 percentage was seen in a single patient with guttate lesions, suggesting that guttate psoriasis might be associated with increased epidermal proliferation as against the chronic plaque type.

Since the initial documentation of rapid epidermal turnover in psoriasis by Weinstein (10), a large body of evidence has indicated that the cell cycle time in psoriasis is normal and only increased recruitment of epidermal cells may be responsible for the development of psoriatic lesions (5). Our finding of Ki-67 positive inflammatory cells in the epidermis with Ki-67 negative dermal cells is in concordance with the above mentioned hypothesis. In corroboration, Nickoloff and Griffiths proposed that dermal T-cells are in a resting or non-cycling (G0) state and the entry of the T-cells into the epidermis is apparently associated with an important activation event, which involves interaction with the keratinocytes (11). In our study, mean Ki-67 of the three children with plaque-type psoriasis was higher than the adults with the same type. This might indicate higher activity and severity of plaque psoriasis with greater propensity for instability in children. Interestingly, we noted the opposite trend in pustular psoriasis wherein adults had higher mean Ki-67 values. Prakashiny S et al. (12) demonstrated the Ki-67 index of suprabasal epidermal cells as 10-30% in adult psoriasis (6% in normal skin) and 12-28% in childhood psoriasis (8% in normal skin). However, these authors used suprabasal epidermal cell count for calculation, hence the level of expression could not be compared with our study which calculated suprabasal-to-total epidermal cell ratio.

We found significantly higher Ki-67 expression in male patients with erythrodermic and pustular psoriasis in comparison with their female counterparts. Although psoriasis affects adult women and men equally with only slight male predilection, studies assessing the use of systemic and biological treatment in cohorts of patients with severe disease consistently report that men are twice as likely to receive systemic therapy as women, suggesting that they are likely to have more severe disease. Abdou AG et al. (13) have shown nucleolar pattern of Ki-67 expression to be significantly associated with male gender. On the other hand, females with plaque type had higher mean IHC Ki-67 than males, probably due to larger body surface involvement in the small number of females recruited in our study. Psoriasis is an extremely dynamic disorder with multiple fluctuations and the three forms are often inter-convertible. Hence co-relation of proliferation markers with duration is difficult to interpret and explain. We were unable to find any previous studies analyzing this parameter to compare our findings.

Patients with past history of treatment had statistically insignificant lower levels of Ki-67 than treatment-naive patients. According to the standard protocol for psoriasis management followed in our institute, patients are initially prescribed topical corticosteroids, Vitamin D analogs and emollients, while those requiring systemic therapy are prescribed methotrexate or cyclosporine (subject to patient co-morbidity profile and affordability). Miracco et al. (14) and Tursen B et al. (15) have demonstrated that Ki-67 expressions decreased after cyclosporin and etanercept treatment respectively while Van der Velden et al. (16) observed that the number of Ki-67+ cells reduced after topical calcipotriol/betamethasone dipropionate treatment. These reports suggest that Ki-67 expression can be utilized as a prognostic marker to evaluate response to treatment with various topical and systemic modalities.

We found that mean IHC Ki-67 increased with increasing body surface area in both overall psoriasis group (with maximum expression in erythroderma followed by generalized pustular psoriasis with > 50% BSA) as well as the plaque-type (maximum in BSA > 50%). PASI score is a universally accepted clinical indica-

tor of disease severity in plaque type psoriasis. We studied plaque patients with PASI score ranging from 5.2 to 44.2 (mean 18.32) and found significantly higher Ki-67 expression in patients with PASI more than 10 as compared to those with PASI under 10, which is consistent with the findings of authors who have noted a positive correlation between clinical psoriatic activity (PASI) and epidermal proliferative activity (17, 18). According to the European S3 Guidelines on the systemic treatment of psoriasis vulgaris, moderate to severe disease is defined as a PASI score >10 and is an indication for systemic treatment (19). Amany et al. (20) concluded that Ki-67 was the most significant variable contributing to clinical severity and claimed that one unit change in Ki-67% can explain 1.2 unit changes in PASI score (with 97% sensitivity, 40% specificity and 25% cut-off value). Contradicting this school of thought, Yazici et al. (21) did not observe any correlation between PASI index and Ki-67, PCNA and ICAM-3 expression in patients treated with methotrexate. They have propounded that the PASI index is a static method of evaluation of the intensity of psoriasis which does not adequately reflect the real activity of the disease process. In the absence of any consensus criteria for severity assessment of generalized pustular and erythrodermic psoriasis, the correlation of Ki-67 with this parameter could not be studied in these variants. Among NPPD, the highest mean value seen in pityriasis rubra pilaris is concordant with its propensity for progression to erythroderma. The epidermal cell kinetic study conducted by Ralfs et al. (22) also demonstrated elevated proliferative indices among PRP patients while Jeng-Feng Chen et al. (23) documented upregulated Ki-67 expression in PRP lesional epidermis compared to the adjacent non-affected skin, supporting the view that PRP results from hyperproliferation of the epidermal keratinocytes.

Strengths – This is probably a novel study of its kind because, despite thorough search through available literature (using search engines: Google, Google Scholar, Pubmed), we were unable to find any other study analyzing the co-relation of Ki-67 with such a comprehensive number of demographic and psoriasis-related parameters.

Limitations – A small sample size of different sub-types of psoriasis could be enrolled due to constraints of feasibility and availability of immunohistochemistry kits. Therefore, although various parameters demonstrated an association with Ki-67 expression, this did not reach statistical significance and hence definitive conclusions could not be drawn. Multivariate-regression analysis would be required to identify and quantify the exact correlation between Ki-67 and study variables. Elicitation of post-treatment Ki-67 expression was not part of the cross-sectional study design.

Conclusion

This preliminary study demonstrates the potential utility of Ki-67 as a diagnostic and prognostic marker in psoriasis, particularly to differentiate it from non-psoriasis psoriasiform disorders. More studies with larger sample size for individual sub-types of psoriasis will further elucidate its role in the pathogenesis and management of this challenging disorder.

Abbreviations

NPPD – non-psoriatic psoriasiform dermatoses
IHC – immunohistochemistry
PRP – pityriasis rubra pilaris
SPSS – Statistical package for social sciences

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Evaluacija IHC Ki-67 sa kliničkom korelacijom u psorijazi

Sažetak

Uvod. Psorijaza je hronično inflamatorno oboljenje kože se hiperproliferacijom, abnormalnom diferencijacijom i inflamatornom infiltracijom u epidermu i dermu. Ponekad je klinički i histopatološki izazovno razlikovati psorijazu od drugih nepsorijaznih psorijazoformnih oboljenja (NPPO): ekcem, *pityriasis rosea*, *pityriasis rubra pilaris* i hronični *lichen simplex*. Ki-67 je nuklerno proteinski kompleks koji reguliše ćelijski ciklus i najviše korišćeni proliferacijski imunohistohemijski (IHC) marker. Dokazano je da su njegovi nivoi povišeni kod psorijaze u odnosu na normalnu kožu. **Ciljevi**. Da se uporedi ekspresija IHV Ki-67 u psorijazi i NPPO, koreliraju ti nivoi sa kliničkim varijantama i težinom bolesti kod psorijaze i da se posmatra promena u nivoima u odnosu na varijabile povezane sa demografskim podacima i psorijazom. **Materijal i metode.** Uzorak se sastojao od 30 pacijenata sa klinički dijagnostikovanom psorijazom (slučajevi) i NPPO (kontrole). Biopsija je urađena za histopatološki pregled i IHC Ki-67 imunohistohemiju. Urađena je statistička analiza. **Rezultati.** Ustanovili smo

značajno višu ekpresiju IHC Ki-67 u prisustvu psorijaze u poređenju sa svim tipovima NPPO. Viši nivo Ki-67 u pustularnoj i eritrodermalnoj psorijazi u odnosu na pločasti tip naglašava veću težinu i aktivnost tih formi. Ustanovljeno je da se Ki-67 ekspresija povećava sa većom zahvaćenom površinom tela i težinom oboljenja (PASI) u hroničnom pločastom tipu. *Pityriasis rubra pilaris* imala je najvišu Ki-67 ekspresiju u grupi NPPO. **Zaključak.** Ki-67 je potencijalni instrument sa dijagnostičkom i prognostičkom primenom kod psorijaze, pogotovo da je razlikuje od nepsorijaznih psorijazoformnih poremećaja.

Ključne reči: Psorijaza; Ki-67 antigeni; Ćelijska proliferacija; Imunohistohemija; Biopsija; Indeks težine bolesti; Dijagnoza; Prognoza

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Assessment of the Quality of Life in Patients with Scabies in an Urban Tertiary Care Centre in North India

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Abstract

Introduction. Scabies is a highly contagious parasitic skin infestation caused by Sarcoptesscabiei mite causing social stigma in patients owing to skin lesions over the exposed body-parts. The present study was aimed at assessing the quality of life in scabies patients. **Material and Methods.** This non-interventional and cross section study included a total of a hundred newly diagnosed scabies cases above 5 years of age. The patients were given the questionnaire on the life quality affected by their disease and a detailed analysis was done afterwards. **Results.** Out of a hundred patients, 52% were females. The age group 21-40 years was most affected: 25.7% of adult patients had moderate effect while 55.9% of children suffered no effect on their quality of life. **Conclusion.** Scabies moderately affected the quality of life of the patients in the present study in the form of feeling of embarrassment, stigmata and shame associated with disease.

Key words: Scabies; Quality of Life; Urban Population; Child; Adult; Sarcoptes scabiei; Social Stigma; Embarrassment; India

Introduction

Scabies is a highly contagious parasitic skin infestation caused by Sarcoptes scabiei mite. In endemic areas with poor resources, the prevalence has been estimated to be 10% in general population and about 50% in children, making it one of the major dermatological concerns in such nations (1).

Besides the skin lesions, scabies causes substantial morbidity owing to secondary infections and post-infective complications such as acute post-streptococcal glomerulonephritis (2). As it is not possible to eliminate scabies, the only option to reduce the burden of the disease is to limit the resultant physical and mental morbidities (3). Morbidity is not only reflected by the degree of clinico-pathological manifestations but it also includes the emotional aspects of the disease process. Both physical and psychological aspects of morbidity may decrease the quality of life (3). Patients with scabies suffer from social stigma significantly because its mode of transmission is mostly by direct person-to-person contact. It is not difficult to imagine, therefore, that scabies has a significant adverse impact on the quality of life (QoL) in such patients. Our aim in the present study was to explore the quality of life in patients with scabies.

Material and Methods

In this non-interventional and cross section study, a total of a hundred patients with scabies were selected among all the newly diagnosed scabies cases who attended dermatology OPD. Clinical diagnosis was made on the basis of characteristic clinical symptomatology and clinical signs of papules, excoriation marks and burrows. All adults and children over the age of 5 years were included in the study. Pregnant and lactating females, children less than 5 year of age and patients having atypical skin lesions and crusted scabies were excluded from the study. Patients who had other chronic skin or systemic disease like psoriasis, atopic dermatitis, diabetes mellitus etc. were excluded from the study. An informed written consent was taken from patients above 15 years of age and caregiver

Table 1. Demographic details of patients

Complaints	Numbers (%)
Itching	95%
Cutaneous lesions	84%
Nocturnal aggravation	82%
Family history	
Present	66%
Absent	34%
Past history	
Present	20%
Absent	80%
Secondary infection	
Present	19%
Absent	81%
Eczematization	
Present	23%
Absent	77%

(informant) consent was obtained in subjects below 15 years of age. Relevant data on demographic details, clinical findings, family history and relevant past history were noted in predesigned proforma. A pre-validated questionnaire about the quality of life impairment was distributed to the patients so as to be filled as a part of the study. Modified Dermatology Life Quality Index Questionnaire (mDLQI) for scabies by Worth et al. was minimally modified as per the requirement of Indian population (4). Subsequently, a detailed analysis of the data was carried out.

Results

Out of total one hundred patients recruited in our study, 48% were males and 52% were females. The two most affected age groups were those ranging in age 21-40 yrs and 5-12 yrs, comprising 37% and 34% of total population, respectively. Amongst these 100 patients, 40% were students, 25% were housewives, 23% patients were employed and 12% were unemployed.

In our study sample, 95% of the patients had itching as the presenting complaint, 82% of the patients had nocturnal aggravation of itching and 84% of the patients had skin lesions in the form of papules, pustules, excoriations and burrows. Past history of similar lesions was present in 20% of the patients and positive family history was found in 66% of the patients.

Most common sites of involvement in decreasing order were inter-digital clefts of hands 62%, genitals 56%, ventral aspect of wrists 44%, inner thighs 42% and trunk 40%. The most commonly observed skin lesion was papules 83% followed by excoriations 77% and the least commonly seen lesion was burrows 9%.

Playing was most commonly adversely affected in 52% of children whereas studying was negatively affected in 47% of the patients as a result of the disease process; 23% of children were teased by their colleagues due to itching and visible skin lesions.

In adults, the feeling of embarrassment was the most common manifestation in 80% of the patients followed by difficulty in working at the work place in 57% of the patients. The least commonly affected domain was feeling of depression which was seen only in 21% of adults.

Table 2. Clinical details of patients with scabies

Age (years)	Numbers (n=100) (%)
5-12	34%
13-20	8%
21-40	37%
41-60	19%
61-80	2%
Sex	
Male (M)	48%
Female (F)	52%
Literacy	
Literate	66%
Illiterate	34%
Occupation	
Student	40%
Housewife	25%
Job	23%
Others	12%

Discussion

Scabies is a contagious parasitic skin infestation affecting an estimated 100 million people annually all over the world. In developing countries, especially those with poor resources, scabies is a major health issue with prevalence of 10% in adults and upto 50% in children. Scabies mainly occurs in people living in tropical countries, areas with scanty water resources leading to poor hygiene and over-crowded conditions such as prisons, hostels and orphanages where cleanliness is often ignored (5). Even an asymptomatic person infested with mites can spread scabies (6).

Transmission of scabies occurs via skin-to-skin contact, which may take as little as 20 minutes, and thus it spreads quickly within families where children and adults share a common linen in a limited sleeping space. In the adult population it may even spread through sexual contact (7).

While scabies can affect people of all socioeconomic status, individuals who are young, elderly, immune-compromised or de-

Table 3. Impairment in quality of life in children

Severity of Impairment in quality of life (n=34)					Sex-wise distribution of impairment (n=34)		
Questions	A (very much)	B (quite a lot)	C (only a little)	D (not at all)	Male (n =22)	Female (n =12)	Total (n = 34)
Feeling embarrassed or ashamed	0	0	1 (2.9%)	33 (97.01%)	0	1 (8.3%)	1 (2.9%)
Affected studies	0	4 (11.76%)	12 (35.29%)	18 (52.94%)	7 (31.8%)	9 (75%)	16 (47%)
Affected playing	0	4 (11.76%)	14 (41.17%)	16 (47.04%)	12 (54.5%)	6 (50%)	18 (52.9%)
Experienced teasing	0	2 (5.8%)	6 (17.64%)	26 (76.47%)	4 (18.1%)	4 (33.3%)	8 (23.5%)
Affected friendship	0	0	2 (5.8%)	32 (94.11%)	1 (4.5%)	1 (8.3%)	2 (5.8%)

Table 4. Impairment in quality of life in adult patients

Severity of Impairment in quality of life (n=66)					Sex-wise distribution of impairment (n=66)		
Questions	A (very much)	B (quite a lot)	C (only a little)	D (not et all)	Male (n =26)	Female (n=40)	Total (n = 66)
Feeling embarrassed or ashamed	4 (6.06%)	31 (46.9%)	18 (27.2%)	13 (19.6%)	19 (73.0%)	34 (85%)	53 (80.3%)
Difficulties at work place	4 (6.06%)	20 (30.3%)	14 (21.2%)	28 (42.4%)	13 (50%)	25 (62.5%)	38 (57.5%)
Sexual relationship	5 (7.5%)	14 (21.2%)	14 (21.2%)	33 (50%)	12 (46.1%)	21 (52.5%)	33 (50%)
Social contacts	0	7 (10.6%)	21 (31.8%)	38 (57.5%)	10 (38.4%)	18 (45%)	28 (42.4%)
Feel saddened/depressed	0	1 (1.5%)	13 (19.69%)	52 (78.7%)	3 (11.5%)	11 (27.5%)	14 (21.2%)

velopmentally challenged ones are at a significantly higher risk of getting scabies and related complications (8).

Sarcoptesscabiei infestation (Sarcoptic mange) results in inflammatory and adaptive immune responses relatively late in the infection (4–6 weeks after initial contact with mite). Given the parasite's long co-evolution with its hosts, it is believed that scabies mites have developed the capability of modulating various aspects of the host immune responses resulting in the delayed onset of symptoms (9).

The rash and itch associated with scabies show features of both type I (immediate) and type IV (delayed) hypersensitivity reactions. The initial inflammatory response as reviewed by Walton et al. (10) towards the mite and its products consists of migration of Langerhans cells and eosinophils with smaller number of monocytes, macrophages and mast cells in the body.

A delayed-type hypersensitivity reaction to mite allergens causes skin inflammation resulting in development of papules and resultant pruritus. Excoriation of the lesions leads to secondary bacterial infections, eczema and long-term health consequences in the form of post streptococcal glomerulonephritis (11).

The most common age group of affected patients in the present study was that between 21-40 yrs in 37% of the patients followed by 5-12 years age group in 34% of the patients. This is in accordance with the study conducted by Nair PA et al. (12) wherein it was found in 44.11% of patients in the 21-40 years age group followed by 39.2% patients in 5-12 years age group. These results in our study are in contrast to the study conducted by Das S et al. (13) wherein 9% of the patients were in the 0-5 years age group, 22% in both 6-15 years and 16-30 years of age group.

A study conducted by Sambo et al. in school going children showed prevalence of scabies in 55.8% of the patients who were in the age group of 5–8 years, whereas 44.2% of the patients were in the age group of 9-12 years (14).

In the present study incidence of scabies was approximately same in both sexes i.e. 48% males and 52% females. A study conducted by Sambo et al. (14) reported equal incidence in both males and females (1:1) whereas in the study by Das et al. males 70% outnumbered females 30% (13).

Positive family history was seen in 66% of the patients in the present study which is in accordance with a study conducted by Nair PA et al. (12) wherein significant positive family history was seen in 59.8% of their patients. Previous episodes of infection with scabies in past was reported in 20% of the patients in our study similar to that found in the study conducted by Das S et al. (13) which reported 25% of cases. Nair PA et al. (12) reported a lower frequency of patients who were infected with scabies in the past 9.8%.

Most of the patients had multiple body sites infected with scabies of which the primary sites in decreasing order were interdigital clefts 62%, genitals 56%, wrists 44%, inner thighs 42% and trunk 40%. These findings are in accordance with a study conducted by Das S et al. (13).

The skin lesions in the present study were papules 83% followed by excoriations 77% and

the least common were burrows 9%. These findings were comparable to the findings of a study conducted by Nair PA et al. (12).

Eczematization and secondary infection was seen in 23% and 19% of the patients respectively which was similar to that in the study conducted by Das S et al. (13) wherein eczematization was present in 24% of the patients, although these values are much lower than the frequencies reported by a similar study conducted by Nair PA et al. (12).

Nocturnal aggravation of itching was reported by 82% of the patients leading to sleep disturbances and this is similar to that reported by Nair PA et al. (12).

Scabies has become an accepted part in developing countries, particularly in areas where scabiesis endemic and most people do not consider infestation a health problem.

In the present study, the most commonly affected domain, as reported by the adult patients, was the feeling of embarrassment 80% followed by difficulty at work 57%, adversities in sexual relationship 50%, disharmony with social contacts 42% while depression was reported by only 21% of the patients.

It was observed in the present study that the two prime activities of children i.e. mainly outdoor sports/games and academics/study were adversely affected owing to intense itching of scabetic sites in 52% and 47% children respectively. This sustains that itching in scabies definitely hampers the quality of life in children.Teasing by fellow companions was seen in 23% of the children. Discord in friendship and social embarrassment due to scabies was reported in 5.8% and 2.9% of the children respectively.

According to the total score obtained by adding individual scores given to each question of the questionnaire, 62.1% of adult patients had mild effect, 25.7% of adult patients had moderate effect while 12.1% of them had no effect on quality of life, whereas a mild effect on quality of life was found in 44.1% of the children and there was no effect on quality of life et all in 55.9% of the children in our sample.

Conclusion

Scabies moderately affected the quality of life of the patients in the present study in the form of feeling of embarrassment, stigmata and shame associated with this disease. All these findings were more frequently observed among adult patients as compared to children. More attention should be paid to this contagious disease, its sequelae and concomitant morbidities despite the disease not being life threatening.

Limitations of this study were small number of cases due to exclusion of pregnant and lactating females, children <5 yrs of age and patients with atypical and crusted lesions.

Abbreviations

QoL – Quality of life
mDLQI – Modified Dermatology Life Quality Index Questionnaire

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Procena kvaliteta života pacijenata sa šugom u urbanoj ustanovi za tercijarnu zdravstvenu zaštitu u Severnoj Indiji

Sažetak

Uvod. Šuga je izuzetno zarazno parazitsko oboljenje kože izazvano *Sarcoptes scabiei* grinjama koje izaziva društvenu stigmu kod pacijenata zbog lezija na koži na izloženim delovima tela. Cilj ove studije bio je da ispita kvalitet života pacijenata sa šugom. **Materijal i metode.** U ovoj neinterventnoj studiji preseka uključeno je 100 novodijagnostikovanih slučajeva šuge kod osoba starijih od pet godina. Pacijenti su dobili upitnik o uticaju bolesti na kvalitet života i onda je urađena detaljna analiza. **Rezultati.** Od 100 pacijenata, 52% su bile žene. Najugroženija starosna grupa bila je od 21 do 40 godina: 25,7% odraslih su imali umereno dejstvo, dok kod 55,9% dece uopšte nije bilo efekta. **Zaključak.** Šuga je umereno uticala na kvalitet života pacijenata u ovoj studiji u obliku osećanja stida, stigme i srama.

Ključne reči: Šuga; Kvalitet života; Urbana populacija; Deca; Odrasli; Sarcoptes scabiei; Stigmatizacija; Stid; Indija

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Disseminated Superficial Actinic Porokeratosis in the Elderly: A Case Report

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Abstract

Currently, most authors believe that disseminated superficial actinic porokeratosis (DSAP) is an inherited or acquired dermatologic disorder of keratinization that occurs in genetically predisposed individuals after adequate exposure to ultraviolet (UV) rays, or immunosuppression. Lesions in DSAP start in sun-exposed areas most commonly in the third or fourth decade of life. The lesions are pink to brownish papules and plaques with a raised scaling ridge, histologically seen as a column of parakeratotic keratinocytes, the cornoid lamella. DSAP is not only the most common, but also the most often overlooked form of porokeratosis (P). Here we present a 77-year-old male with DSAP, who sporadically developed initial skin lesions at the age of 67, at the time when his personal and medical history were significantly long for chronic intensive sun exposure and type 1 insulin dependent diabetes mellitus. We established the diagnosis of DSAP based on personal and medical history, clinical presentation, auxiliary methods such as dermoscopy, and confirmed with pathohistological findings. We advised the patient to avoid sun exposure and to apply photo-protective sunscreens, emollients and keratolytics. After five years of monitoring his changes, we continue to control his lesions for any possible alteration. Although mutations in several genes and data on sun exposure may be responsible for the onset of the disease, most cases of DSPA occur sporadically and without involving the facial skin, as in our case. Lesions usually begin in the third or fourth decade of life. In the elderly, an additional trigger may be present, such as e.g. age-related decreased immune competence. Diabetes mellitus may also be associated with immunodeficiency in the elderly. Recently, DSPA has been a special subtype of DSPA in the elderly. Malignant alteration can occur in DSPA, most commonly in lesions that are long lasting, large, in the elderly, or in lesions in immunocompromised individuals. In conclusion, this is the case of a 77-year-old male person, who sporadically developed the so-called subtype DSPA in the elderly. In addition to UV radiation, the relevant suggestive trigger factors were the immunosuppressive effects of diabetes mellitus and chronological aging.

Key words: Porokeratosis; Predisposition to Disease; Ultraviolet Rays; Immunosuppression; Aged; Diabetes Mellitus, Type 1; Dermoscopy; Biopsy; Case Reports

Porokeratosis (P) represents a group of rare, acquired or inherited disorders of keratinization showing circumscribed scaling lesions with a raised ridge edge, which is on histology present as a column of parakeratotic keratinocytes, the so-called cornoid lamella. The underlying lesion begins as a 1-3 mm brown conical papule that spreads to 10 mm or more in diameter, with a sharp, slightly raised 1 mm thick keratotic ridge (1-3). Mutations of several genes have demonstrated to be responsible for P, but the pathogenesis of P remains unclear (1, 4-6). Disseminated superficial actinic porokeratosis (DSAP) is the most common form of P in adults. Although most cases of the disease develop sporadically (7), there is familial DSAP that has an autosomal dominant inheritance pattern with incomplete penetrance (3). Apart from several susceptible genetic loci determined for DSAP that were previously identified (5), mutations in the mevalonate kinase gene (*MVK*) on chromosome 12q24 are present in some patients with DSAP. The *MVK* gen encodes the

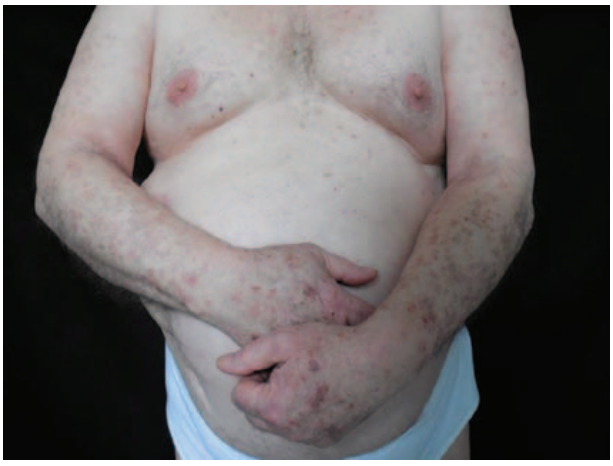

Figure 1. Lesions predominantly in sun-exposed sites of the forearms and hands

synthesis of mevalonate kinase, an enzyme that is part of the cholesterol synthesis pathway which provides protection from UV-induced cell death (6). Thus, DSAP is an inherited dermatologic disorder with lesions appearing in genetically predisposed individuals after adequate exposure to UV radiation or immunosuppression (1, 8).

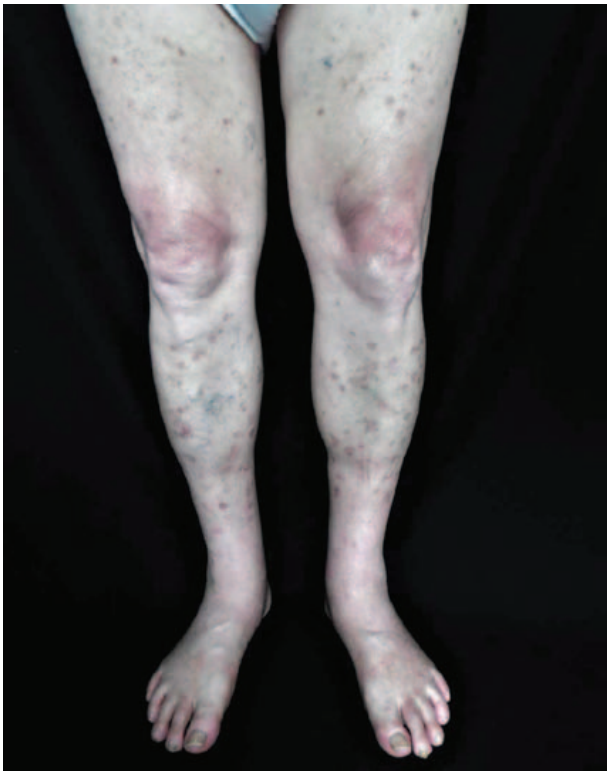

Figure 2. Lesions on the lower limbs

The group of several different porokeratoses includes 6 main types: 1) porokeratosis of Mibelli (PM); 2) linear porokeratosis (LP); 3) disseminated superficial porokeratosis (DSP); 4) disseminated superficial actinic porokeratosis (DSAP); 5) disseminated palmoplantar porokeratosis (DPPP); 6) punctate palmoplantar porokeratosis (PPPP). Besides these main clinical forms, a number of rare morphological forms, such as facial, giant, punched-out, hypertrophic verrucous, reticulate, eruptive pruritic papular, and ptychotropic (manifesting with symmetric verrucous, hyperkeratotic red-brownish plaques of the buttocks and genitalia), has been reported in the literature (9). Different forms of P dermatologists may differentiate solely based on clinical criteria.

Coexistence of several different forms of P has been reported, making final diagnosis somewhat arbitrary (2, 9).

In DSAP, there are numerous skin-colored or brownish-red papules and plaques of variable size, forming a thin peripheral keratotic rim and atrophic hypopigmented center by expanding radially in the sun-exposed sites. It occurs bilaterally and symmetrically. Lesions in DSAP start in sun-exposed areas most commonly in the third or fourth decade of life. The legs, forearms, shoulders, and back are most often affected. The face can rarely be involved. The palms and soles are without lesions. DSAP usually worsens when the affected skin is sun-exposed, and pruritus can intensify (5, 10).

All forms of P can be overlooked, but DSAP, which is also the most common form of P, is most often overlooked (3, 11).

In this case report we present a 77-year-old male with DSAP, who developed initial skin changes at the age of 67, at the time when his medical history was significantly long for type 1 insulin dependent diabetes mellitus

Case Report

A 77-year-old non-atopic Caucasian male was admitted to our Clinic, with a 9-year long history of disseminated skin papules. Widespread lesions first appeared on the lower legs, were initially asymptomatic and then quickly became pruritic. The deterioration occurred a year before admission to the hospital.

The patient denied any personal or family history of previous skin disorders, as well as alcohol intake or cigarette smoking. A review

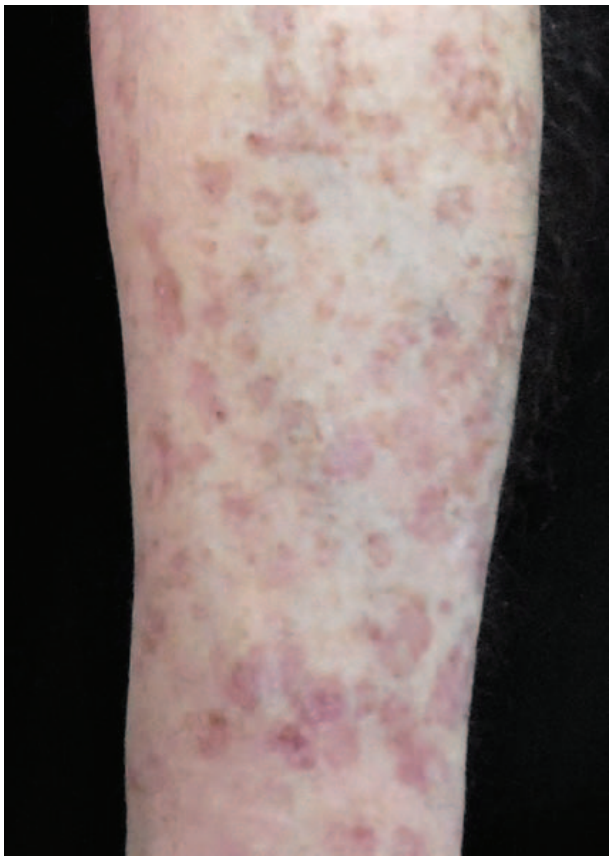

Figure 3. Well-defined erythematous and red-brownish to dark pigmented annular papules and dry plaques up to 1 cm in diameter, with atrophic center

of his medical history was significant for type 1 insulin dependent diabetes mellitus, arterial hypertension, ventricular extra-systolic arrhythmia, and prostate hyperplasia. We continued the treatment of the aforementioned comorbidities at our clinic. The patient also revealed a history of recent and past sun exposure during the performance of his daily activities in the external environment, such as animal husbandry and agriculture for an average of 24 weeks a year for the last 50 years.

At admission, the patient with Fitzpatrick skin phototype II was in good general condition. In addition to the solar lentigines, multiple widespread circular well-defined erythematous and red-brownish to dark pigmented annular papules and dry plaques up to 1 cm and more in diameter were present, with an atrophic center surrounded by a raised, fine keratotic wall and a furrow. The lesions were mostly on the limbs and affected sun-exposed skin of the forearms, upper chest, arms, thighs, buttocks, and legs, sparing the skin of his face, scalp, ears, palms, and soles **(Figures 1-3)**. The diagnosis of DSAP was preliminary considered on clinical ground.

All relevant laboratory findings were within normal limits except for a slight elevation of the erythrocyte sedimentation rate, high blood sugar level, and slightly elevated total prostate specific serum antigen (tPSA).

Additional investigations revealed the following abnormalities: abdominal ultrasound scanning showing calculi in the gallbladder and chest X-rays revealing calcification of the aorta. The cardiologist confirmed the diagnosis of high blood pressure and ventricular extra systolic arrhythmia, and administrated the following therapy: acetyl salicylic acid, propafenone, fosinopril, isosorbide mononitrate, furosemide, and magnesium.

On dermoscopy we saw annular lesions with brown peripheral rim and open pores with plugs, multiple dotted and linear irregular blood vessels, and brown globules in the center. Some lesions had white scar-like center, characteristic annular whitish structures in the form of “white line” or “white track“ along the edge of each lesion. In some parts of the lesion, there was a “double white track” (arrow), sharply demarcated central scar-like area. Tracks were present at the periphery of the lesion along with brown pigmentation (globules and red spots) inside. Structures of single or double “white tracks” and red spots

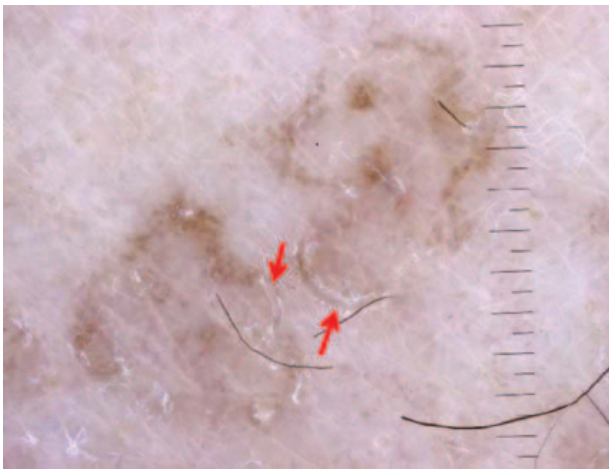

Figure 4. Characteristic annular “white line” or “white track”, along the edge of each porokeratosis lesion and “double white track” (arrow) in some parts of the lesion

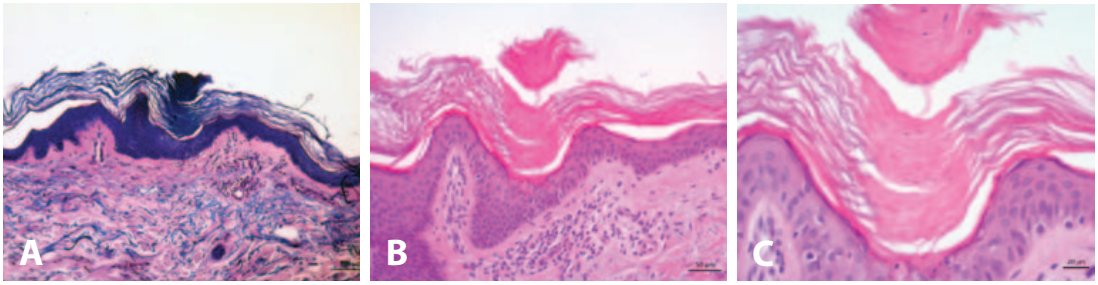

Figure 5. a. The epidermis with slightly flattened rete pegs and orthohyperkeratosis. In the shallowly depressed epidermal part, the thick parakeratotic, vertically oriented column, cornoid lamella. Actinic degenerative changes are present in the dermis (Giemsa x100); **b.** The vertically oriented cornoid lamella without granular layer, with some dyskeratotic and vacuolated keratinocytes. In the dermis variable inflammatory infiltrate is present (HE x200); **c.** At the base of the cornoid lamella, granular layer is absent and some dyskeratotic cells are visible (HE x400)

or globules, corresponded histologically to the cornoid lamella and enlarged blood vessels, respectively **(Figure 4).**

Hystology analysis showed epidermis with slightly flattened rete ridges, orthohyperkeratosis and, a column of parakeratotic stratum corneum cells, the so-called cornoid lamella. The lamella was running vertically through the surrounding cells at the shallowly depressed epidermis, with an almost absent underlying granular zone and some dyskeratotic and vacuolated cells in the spinous and basal layers, respectively. Papillary dermis below lamellae was with extensive actinic degenerative features, dilated capillary blood vessels surrounded with a variably thick dermal lymphocytic infiltrate. Hair follicles and sebaceous glands were missing, while sweat glands extended with regular morphology **(Figures 5a, 5b and 5c).** Clinical, dermoscopic appearance, histological, and laboratory findings were consistent with the diagnosis of DSAP.

Initially, the treatment was topical application of corticosteroids. Although we advised the patient to continue therapy with intermittent systemic retinoid, primarly acitretin and then local calcipotriol or tacrolimus, he was unable to administer this therapy for financial reasons. He no longer had any complaints or subjective problems, and was not worried about his changes even in the cosmetic sense. That is why we recommended him to use emollients and urea-containing keratolytics, avoid sun exposure, and to use photo-protective sunscreens. After 5 years of follow-up, we still regularly control his lesions for any possible alteration.

Discussion

The diagnosis of DSAP encompasses personal and medical history, clinical presentation, auxiliary methods such as dermoscopy, and pathohistological confirmation. Our patient has revealed a history of recent and past sun exposure in his normal daily outdoor activities such as farming. Clinically distinguishing certain forms of disseminated porokeratosis may not be justified (11). Thus, DSP can be clinically similar to DSAP, except that UV rays do not play a role in its formation: the distribution of lesion may be similar to DSAP, but without a history of sun exposure (11). For our patient, chronic intensive sun exposure was a significant risk factor for obtaining DSAP (5). Even more, DSP starts much earlier than DSPA, the former usually between 5-10 years of age and the latter in the third or fourth decade. Our patient developed initial skin changes at the age of 67 years on the photo-exposed skin; however, the skin of his face, palms, and soles was spared. Although changes in DSPA occur on the sun-exposed skin, only 15% of people with DSPA have facial changes (2). The sporadic onset of the disease in our patient may be due to somatic mutations (5).

DSAP occurred at the time when the patient's medical history was significantly long for type 1 insulin dependent diabetes mellitus. P have been associated with hematological malignancies, precancerous diseases, autoimmune diseases, e.g. diabetes mellitus, genetic, and other chronic diseases (4). It is assumed that for the development of DSPA in the elderly, the reported predisposing risk factors are UV radiation, genetic predisposition, immuno-

suppression, infective agents, drugs (e.g. thiazide diuretics), and mechanical trauma (5). It seems that in the case of P of the elderly, in addition to the previously mentioned, the group of other factors can also include age-related decreased immunocompetence (12). Diabetes mellitus may also be associated with deterioration of immune competence of the elderly (13). Thus, apart from UV radiation, immunosuppressive effects of diabetes mellitus and chronological ageing were also present in our patient. Recently, DSPA has been a special subtype of DSPA in the elderly (12, 13). Although the etiology and pathogenesis of P have not been fully elucidated (4-6), it has been proposed that besides genetic predisposition, the proliferation of abnormal clones may be triggered by extrinsic factors such as UV light (5). The centrifugal progress of individual lesions reflects the proliferation and migration of a special clone of abnormal cells (3).

A biopsy of the skin lesion in our patient included the edge of the lesion (1). Histopathological analysis revealed features typical for DSAP, including cornoid lamella, a narrow column of altered or parakeratotic keratin seated in a slight depression in the epidermis. The cornoid lamella is a distinctive feature on the periphery of porokeratotic lesions, but cornoid lamellae may be present in other conditions, e.g. viral warts, some ichthyoses (e.g. hystrix), and naevoid hyperkeratoses. Parakeratotic hyperkeratosis, which is a histological reflection of the cornoid lamella, occurs e.g. in some punctate keratodermas, but the lack of lesions at the margin distinguishes them from true porokeratosis (3). In various forms of P, the epidermal changes (usually of atrophy) are often not striking and the diagnostic cornoid lamella may not be present on the first sections, cut from the block. Therefore, as mentioned previously, all forms of P may be misdiagnosed, but DSAP is the most commonly overlooked one (11).

Dermoscopy can be a useful method for evaluating DSAP, since Nicola et al. proposed dermoscopic features for P lesions: white border circumscribing the lesion; homogenous central white scar-like area; brownish globules or dots; vascular structures: pinpoint vessels or irregular linear vessels crossing the lesion (14). All these criteria were present in dermoscopic finding obtained from our patient.

DSPA usually shows poor therapeutic responses to the applied therapy or, as with our patient, therapy does not seem to be necessary (1, 2, 5, 3). Topical diclofenac shows variable treatment results, but a good safety profile, mostly in the management of P affecting genitalia (1, 5). Ingenol mebutate helps treat hyperkeratosis but not atrophy or hypopigmentation (1). Topical vitamin D analog calcipotriol leads to a favorable response after 6 to 8 weeks (1). 5-fluorouracil produces a robust inflammatory reaction; the clinical response is usually temporal, but a novel approach utilizing 5-fluorouracil chemo-wraps is going on (4). Photodynamic therapy in combination with laser, cryotherapy or other options such as excision, curettage and dermabrasion can give some good results, but not in extensive diseases (1, 15). Lasers, e.g. carbon dioxide laser leaves hyperpigmentation, Q-switched ruby laser does not destroy the cornoid lamella, neodymium:yttrium-aluminum-garnet laser reduces hyperpigmentation and obliteration of the cornoid lamella, fractional photothermolysis does not create too much damage and allows faster healing (16, 17). Grenz ray therapy may help because it blocks cell proliferation by inhibiting DNA synthesis (18). Topical retinoids are preferred over systemic ones due to rapid relapses because of discontinuation of systemic therapy. In addition, oral alitretin caused good therapeutic effects in DSPA, but it is necessary to confirm the duration of the effect even after stopping the therapy (1, 19). Because DSPA is not an inflammatory disease, immunosuppressive agents, such as topical corticosteroids, are usually not effective but may reduce itching (1, 20). Topical cholesterol/lovastatin may prevent the accumulation of toxic products of disturbed mevalonate metabolism (21).

The course of the disease may take a progressive course with potential malignant alteration. Malignant transformation can occur, although its exact cause remains unknown, it may relate to chromosomal instability, reduced immune surveillance, and over expression of mutant p53 in the skin lesions (1, 4). Malignant alteration can occur in DSPA, most commonly in lesions that are long lasting, large, in the elderly, or in lesions in immunocompromised individuals (1, 7). Lesions in DSPA have a 7.5% to 10% risk of malignant

transformation into squamous cell carcinoma or basal cell carcinoma (1, 22). Based on the literature available to us, there are only three published cases of melanoma associated with DSPA (4). Sun protection, use of moisturizers and regular check-ups to rule out malignancy are mandatory as with our patient (5).

Conclusion

This is a case report of a 77-year-old male person, who sporadically developed the so-called subtype DSPA in the elderly. In addition to UV radiation, the relevant suggestive trigger factors were the immunosuppressive effects of diabetes mellitus and chronological ageing.

Abbreviations

P – Porokeratosis
UV – ultraviolet
DSAP – Disseminated superficial actinic porokeratosis
MVK – mevalonate kinase gene
PM – Porokeratosis of Mibelli
LP – Linear porokeratosis
DSP – Disseminated superficial porokeratosis
DPPP – Disseminated palmoplantar porokeratosis
PPPP – Punctate palmoplantar porokeratosis

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Diseminovana superficijalna aktinična porokeratoza u populaciji starih – prikaz slučaja

Sažetak

Diseminovana superficijalna aktinična porokeratoza (DSAP) danas se definiše kao redak genetski determinisani poremećaj keratinizacije pokrenut UV zracima ili imunosupresijom. Započinje u trećoj ili četvrtoj deceniji života pojavom kružnih lezija u vidu ružičastih do smeđih papula i plakova, sa centralnom atrofijom i perifernim keratotičnim rubom sa skvamama koji histološki odgovara stubu parakeratotičnih ćelija tzv. kornoidnoj lameli. Hronična ekspozicija UV zracima u anamnezi i odsustvo lezija na dlanovima i tabanima, odvajaju DSAP od ostalih diseminovanih formi porokeratoze (P). DSAP ne predstavlja samo najčešći oblik P nego i formu bolesti čija se dijagnoza najčešće previdi. Prikazujemo sporadičan slučaj DSPA kod 77 godina starog muškarca, zemljoradnika, kod koga su se prve promene na koži pojavile u 67. godini života. Dijagnoza bolesti je postavljena na osnovu anamneze o hroničnoj ekspoziciji sunčevim zracima, prisustvu diseminovanih promena karakterističnog izgleda sa predilekcijom zahvatanja fotoeksponiranih delova i dermoskopskog pregleda, a potvrđena prisustvom kornoidne lamele u patohistološkoj analizi bioptirane lezije na koži. Promene nisu zahvatale lice, dlanove i tabane, a u anamnezi je dominirao podatak o višedecenijskom prisustvu insulin-zavisnog dijabetesa melitus. Pacijentu je savetovano da izbegava sunce, koristi fotoprotektivne kreme, emolijense i keratolitike. Na regularnim kontrolnim pregledima nisu uočeni znaci alteracije. Iako se smatra da su mutacije opisane na nekoliko gena i genskih lokusa, uz anamnezu o relevantnoj ekspoziciji sunčevim zracima (odgovorni za nastanak oboljenja), najveći broj slučajeva DSAP se javlja sporadično i bez zahvatanja kože lica kao kod našeg pacijenta. Prve lezije se javljaju u trećoj ili četvrtoj deceniji života, a kao najznačajniji deklanširajući faktori, koji mogu izazvati imunosupresiju odgovornu za pojavu oboljenja kod starih osoba, ističu se hronološko starenje i prisustvo dijabetesa mulitus. Nova klasifikacija P podrazumeva postojanje posebnog podtipa DSAP u populaciji starih osoba. Maligna transformacija se može javiti u lezijama DSPA i to najčešće kod starih osoba, u velikim lezijama, onim sa dugim trajanjem ili kod imunosuprimiranih osoba. U zaključku treba istaći da je u radu prikazan sporadičan slučaj muške osobe sa podtipom P nazvanim DSAP u populaciji starih, kod koje su, pored hronične ekspozicije sunčevim zracima, mogući relevantni deklanširajući faktori odgovorni za nastanak oboljenja bili imunosuprimirajući efekti hronološkog starenja i dugogodišnje prisustvo dijabetesa melitus.

Ključne reči: Porokeratoza; Predispozicija za bolest; Ultravioletni zraci; Imunosupresija; Stari; Dijabetes melitus tip 1; Dermoskopija; Biopsija; Prikazi slučajeva

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A Rare Case of Acute Generalized Exanthematous Pustulosis with Drug-Induced Liver Injury caused by Pyrazinamide

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Abstract

Acute Generalized Exanthemataous Pustulosis (AGEP) is a rare acute pustular eruption that is mostly induced by drugs. Aside from cutaneous eruptions, systemic symptoms such as leukocytosis, neutrophilia, and internal organ involvement such as liver, kidney, respiratory system, and bone marrow, may occur, although uncommon. Liver involvement usually results in a two- or three-fold increase of liver enzymes and rarely exceeds that. Pyrazinamide is the first-line anti-tuberculosis drug that is potentially hepatotoxic, but rarely shows dermatologic manifestations. We report a rare case of AGEP with drug induced liver injury due to pyrazinamide in a young patient with tuberculosis.

Key words: Acute Generalized Exanthematous Pustulosis; Pyrazinamide; Chemical and Drug Induced Liver Injury; Drug-Related Side Effects and Adverse Reactions; Aspartate Aminotransferases; Alanine Transaminase

Introduction

AGEP is a form of acute pustular eruption with a typical clinical symptom of non-follicular sterile pustules on top of an erythematous base with or without accompanying mucosal involvement (1). The term AGEP was first mentioned in 1980 by Beylot, et al. It was first thought to be a variant of pustular psoriasis due to their similar characteristics (2). In 1968, Baker and Ryan reported 104 cases of pustular psoriasis, and analyzed 5 cases that were thought to be AGEP. In those 5 cases, the analysis showed that there was no history of previous psoriasis and accompanied with pustular symptom with a non-recurrent acute onset, in addition to a history of prior drug administration or infection which were then assumed as the etiologies of AGEP (3).

The incidence of AGEP is rare with an incidence rate of around 1-5 cases per 10.000.000 inhabitants. The distribution is equal in both genders and the average age onset is 56 years old. The etiology of the disease is mostly attributed to drugs such as antibiotics, anticonvulsants, sulfonamide, macrolides, beta lactams, diltiazem, terbinafine, and quinolone. In some cases, viral, bacterial, or parasitic infections can also induce the disease (3, 4).

The characteristic clinical feature of AGEP is pustular rash that occurs 24-48 hours after intake of the culprit drug. It starts with pinhead-sized monomorphic non-follicular sterile pustules on top of an erythematous base on the trunk that then spreads to the extremities and face (3, 5). Sometimes, edema can be seen on the flexural and face. Besides pustules, purpura, vesicles or even bullas may also be found. Mucosal involvement accounts for 20% cases and is usually localized in one area, usually the oral mucosa, and is mild in nature (3).

The above-mentioned dermatological symptoms can also be accompanied by systemic symptoms such as fever (>38°C) with neutrophil dominant leukocytosis. The involvement of internal organs can be in the form of renal insufficiency, hepatocellular, hemodynamic, respiratory and bone marrow abnormalities (3, 5).

Drug induced liver injury (DILI) is a hepatic hypersensitivity as a result of drug administration. This condition is often misdiagnosed due to the limited specific makers available in

laboratories. DILI is classified into two types: the first is directly related to the toxicity of drugs resulting in liver injury, and the second one is an idiosyncratic type which is related to genetic factors and the metabolism of drugs (8).

DILI can manifest as cholestatic, hepatocellular, or mixed symptoms. In cholestatic liver injury, an increase in alkaline phosphatase (ALP) can be seen, while hepatocellular liver injury can show a dominant alanine aminotransferase (ALT) and asparatate aminotransferase (AST). In mixed cases, there is an increase in both ALP and transaminase (9).

Over 1000 drugs have been reported to attribute to this disease. Pyrazinamide is an antituberculosis agent that is hepatotoxic and commonly causes DILI, but it rarely gives a cutaneous manifestation (10).

Among the first-line tuberculosis drugs, pyrazinamide has the highest risk of hypersensitivity. Hypersensitivity reaction can take in the form of skin rash, flushing, anaphylactic shock or immediate reactions. However, as far as we know, AGEP as a result of pyrazinamide has yet to be reported (11).

We report a rare case of AGEP with DILI caused by pyrazinamide in a 25-year-old patient. Provocation test was performed to reveal the culprit drug.

Case Report

A 25-year-old male patient came to the emergency room with a chief complaint of generalized rash and pustules along with fever which developed one day before admission. The patient had been diagnosed with tuberculosis and the treatment for his disease started 20 days before. His treatment regimen included 600 mg isoniazid, 450 mg rifampicin, 1500 mg pyrazinamide, and 1200 mg ethambutol. There was no history of other drug consumption. The patient also experienced nausea and vomitus.

Upon physical examination, the patient looked weak, his body temperature being 38.7°C with icteric sclera. Dermatology examination found pinhead-sized sterile non-follicular pustules on an erythematous plaque accompanied with scales on the face, trunks and upper extremities, without mucosal involvement. The lesions were not tender and Nikolsky sign was negative (**Figure 1).**

Laboratory investigations showed leucocytosis 16.400/mm^3, haemoglobin 15 g/dl, thrombocytes 157.000, neutrophils 86.7%, limphocytes 31.2%, monocytes 16.9%, eosinophils 3%, basophils 2.7%, total bilirubin 9.31 mg/dl, direct bilirubin 6.27 mg/dl, AST 518 U/L, ALT 2679 U/L. Immunoserology test was non-reactive of HbsAg and AntiHCV.

A chest X-ray and an abdominal CT scan demonstrated diffuse milliard nodules on both lungs. Histopathological examination of the skin lesion showed sub-corneal pustules with papillary edema and mixed inflammatory infiltrates consisting mainly of neutrophils and some eosinophils, consistent with AGEP **(Figure 2).**

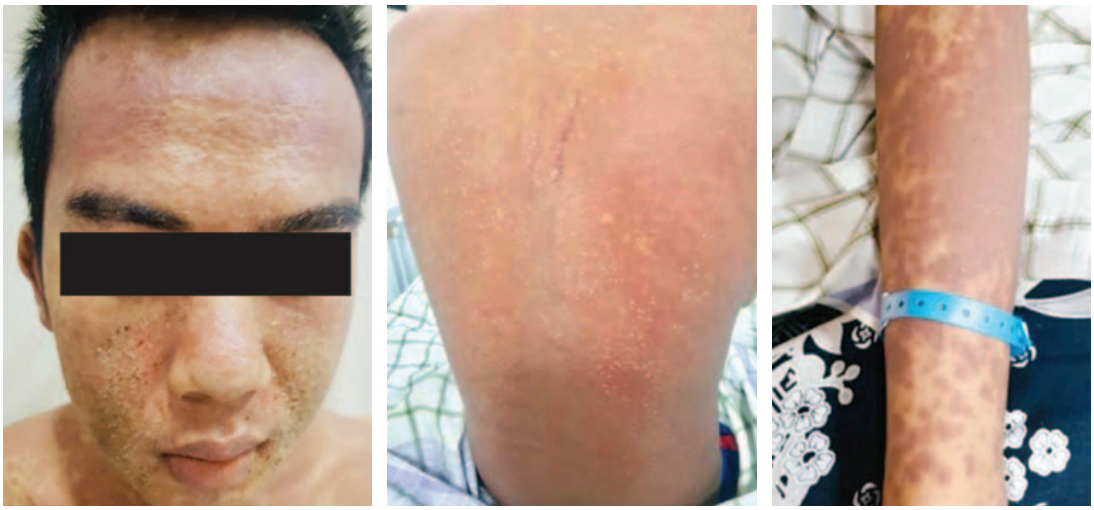

Figure 1. Diffuse erythema with the non-follicular pustules especially on the trunk and upper extremities, with scaly plaques especially on face

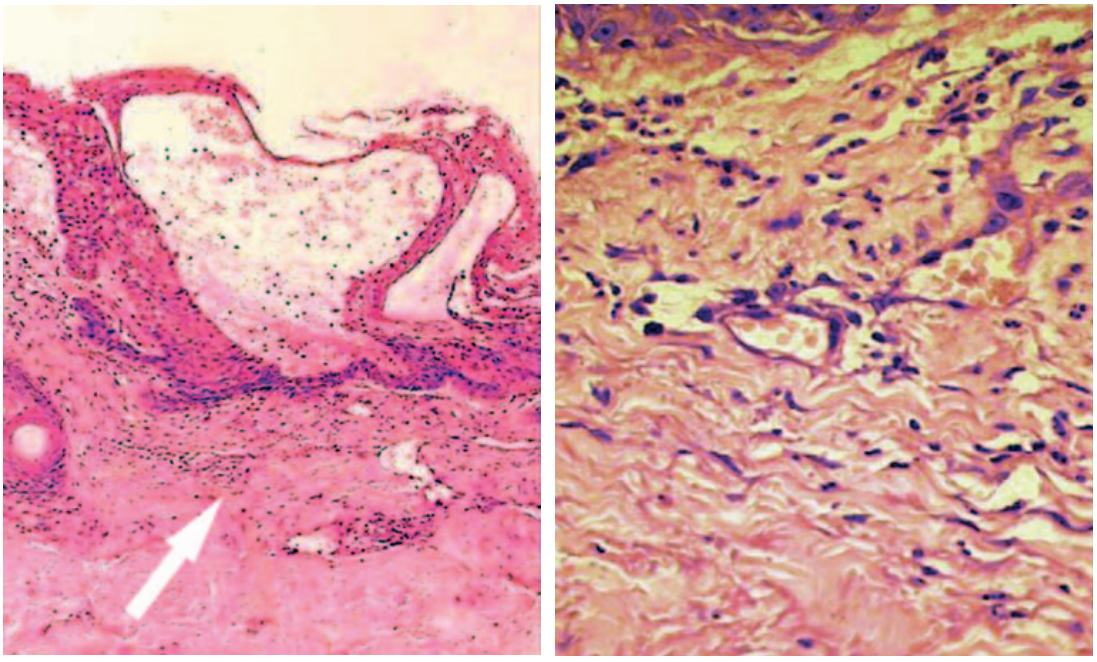

Figure 2. Subcorneal pustules with papillary edema and mixed inflammatory infiltrates of mainly neutrophils and some eosinophils

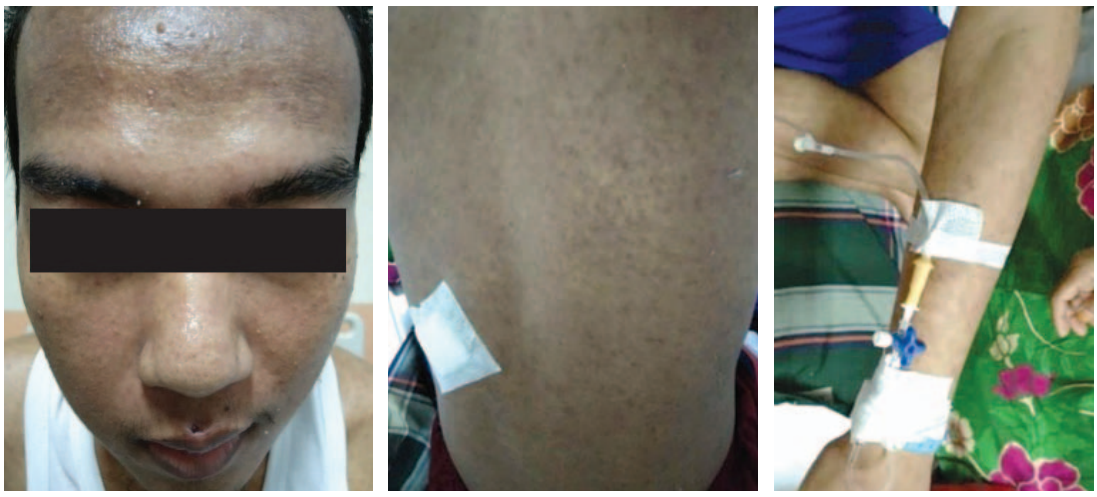

Figure 3. Significant improvement on day 7, with hyperpigmented macules and desquamation on the face

Based on the history taking and physical examination, the patient was diagnosed with AGEP and DILI. The tuberculosis treatment was temporarily stopped and intravenous methylprednisolone 125 mg twice a day, oral antihistamine and topicalemollient were administered. The lesions improved after 7 days of treatment and subsequently, the corticosteroid treatment was stopped. Liver enzymes level also improved AST 140 U/L dan ALT 110 U/L (**Figure 3**).

Discussion

AGEP is a rare but severe cutaneous drug reaction with a distinct clinical symptom of pinhead-sized pustules on top of an edematous erythema base that typically starts to appear from skin folds such as the axillae, inguinal and inframammary region that rapidly spread to other areas such as the trunk and extremities. In 20-25% of cases there is usually a mild and localized mucosal involve-

ment (4). The patient in this case experienced similar symptoms with no mucosal involvement found.

Onset of AGEP is usually 24-48 hours after the initial drug exposure (rapid onset), but in one case, delayed symptoms were found (3 weeks after initial drug exposure) (5, 12). In our case, the symptoms started 20 days after the initial drug exposure but rapid generalized progression happened in 1-2 days. According to literature the pathophysiology of AGEP resulted from a delayed hypersensitivity reaction on certain drugs that activates specific CD4 and CD8 T-cells. The CD8 T-cells utilizes perforin/granzyme B and fas ligand followed by T-cell migration to the skin surface that resulted in keratinocyte apoptosis and the formation of vesicles on the epidermis (1).

Systemic symptoms were also observed in this patient, with fever >38°C, leukocystosis >10.000/mL, an increase in C-reactive protein, and a dominant increase of neutrophils (>7.000/mL) compared to eosinophils (3, 4). Systemic involvement is rare and does not always occur in AGEP. A retrospective study by Hotz et al. showed that out of 58 AGEP patients only 17% (10 cases) experienced systemic symptoms involving one organ, while 6 patients experienced systemic symptoms involving two organs (6). There is also the possibility of multiorgan involvement such as renal insufficiency, hepatocellular abnormality, respiratory failure, hemodynamic abnormality and bone marrow involvement. Hepatocellular dysfunction in AGEP manifests as an increase in liver enzymes such as aspartate aminotransferase and alanine aminotrasnferase twice the usual normal range (6, 7). In a 5-year retrospective study done by Chiptrapassorn, et al. of 25 AGEP patients in Thailand, 52.6% experienced fever, 68.4% experienced leukocytosis and neutrophilia, 10.5% experienced eosinophilia, and 2.3% experienced hepatocellular abnormalities. None experienced renal or lung abnormalities (1).

Hepatic involvement in AGEP is rare and can be marked with double increase of aspartate aminotransferase and alanine aminotransferase enzymes, while cholestatic abnormalities can show an increase of alkaline phosphatase (ALP) and/or gamma-glutamyltransferase (GGP) twice the normal range (2, 6). In our case, the increase of ALT and AST reached up to five times the normal levels with a notable increase in bilirubin. This led to hepatocellular DILI.

DILI is described as the increase of ALN >5x upper normal limit (UNL); increase of ALP 2x UNL, or an increase of ALT $\geq$3X UNL with a simultaneous increase of bilirubin >2x UNL. Liver injury can also give hepatocellular description, where increase of ALT is $\geq$5x UNL or R>5X, R is the comparison ratio between ALT and ALP. AST is not considered diagnostic for DILI but may prove useful when ALT is not available (13).

Of all antituberculosis drugs, pyrazinamide is often associated with hepatocellular liver injury due to its hepatotoxicity. Some studies reported an increase of transaminase enzyme after using pyrazinamide. A study performed by Jason et al. showed that among 114 tuberculosis patients consuming pyrazinamide for 2 months, 16% experienced an increase of liver enzymes while, 7.9% experienced a five-fold increase of liver enzymes, and 5.3% experienced systemic involvement (10). 58% of patients experienced a four time increase of transaminase after consumption of pyrazinamide and ethambutol. A different study reported that 41% of patients experienced a five time increase of transaminase after consuming ofloxacin and pyrazinamide. The hepatotoxicity of pyrazinamide is due to the activity of 5-Hydroxy-Pyrazionic acid (5-OH-PA), a toxic metabolite of the drug. These findings suggested that hepatotoxic effect of pyrazinamide has to be seriously considered.

Pyrazinamide is the most common culprit drug to cause cutaneous manifestation compared to other antituberculosis drugs (11). Oral provocation test was done and it was confirmed that pyrazinamide was the culprit drug. To our best of knowledge, pyrazinamide-induced delayed reaction with significant increase of transaminase has not been reported so far.

The patient was treated with short-term systemic corticosteroids and the administration of pyrazinamide was discontinued as soon as it was suspected to be the culprit drug. Short-term, high-dose corticosteroid was administered due to the severe clinical condition. Topical emollient was given to improve the skin barrier function and to treat the desquamation that often happens especially on the face.

Conclusion

AGEP is a rare but severe cutaneous drug reaction, and can involve the internal organs, especially the liver. Drug-induced liver injury is a type of hepatocellular manifestation that can be induced by drugs, especially pyrazinamide, the most hepatotoxic antituberculosis drug. This case shows a rare case of Pyrazinamide-induced AGEP with severe hepatic involvement.

Abbreviations

AGEP – Acute Generalized Exanthemataous Pustulosis
DILI – Drug induced liver injury
ALP – alkaline phosphatase
AST – asparatate aminotransferase
GGP – gammaglutamyltransferase
UNL – upper normal limit

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Redak slučaj akutne generalizovane egzantematozne pustuloze sa oštećenjem jetre izazvanim pirazinamidom

Sažetak

Akutna generalizovana egzantematozna pustuloza je retka akutna pustularna erupcija koju uglavnom izazivaju lekovi. Pored kutanih erupcija, sistemski simptomi, poput leukocitoze i neutrofilije mogu biti zahvaćeni i unutrašnji organi kao što su jetra, bubreg, respiratorni sistem i koštana srž, mada ne tako često. Zahvaćenost jetre obično rezultira dvostrukim ili trostrukim povećanjem enzima jetre i retko prevazilazi taj nivo. Pirazinamid je antituberkulozni lek prve linije koji je potencijalno hepatotoksičan, ali retko ispoljava dermatološke manifestacije. Ovde prikazujemo slučaj generalizovane egzantematozne pustuloze sa oštećenjem jetre izazvanim lekom toprazinamid kod mladog pacijenta sa tuberkulozom.

Ključne reči: Akutna generalizovana egzentematozna pustuloza; Pirazinamid; Oštećenje jetre izazvano hemikalijama i lekovima; Neželjena dejstva i reakcije izazvane lekovima; Aspartat aminotransferaze; Alanin transaminaza

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DERMOSCOPY OF THE MONTH
Bednar Tumor – a Case Report

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Abstract

Bednar tumor is a rare pigmented type of the dermatofibrosarcoma protuberans characterized histologically by the coexistence of two distinct cell populations, including spindle-shaped cells and melanin-containing dendritic cells. We report dermoscopic features of Bednar tumor observed in a 54-year-old female patient. The dermoscopy of Bednar tumor revealed a multicomponent pattern composed of a homogeneous blue-gray pigmentation with shiny white lines, structureless light-brown pigmented areas and a peripheral pigment network. The dermoscopic features observed in the present case are consistent with reported dermoscopic descriptions of Bednar tumor. Although dermoscopy may be suggestive of the diagnosis of Bednar tumor, pathohistological examination remains a gold standard for diagnosis.

Key words: Dermatofibrosaroma; Diagnosis; Dermoscopy; Skin Neoplasms; Case Reports; Treatment Outcome

Introduction

Dermatofibrosarcoma protuberans (DFSP) is a slow-growing fibrohistiocytic tumor of a low-grade to intermediate malignancy, with a high propensity for a local recurrence and a low rate of distant metastasis (1-4). The pigmented DFSP, also known as Bednar tumor, is a unique subtype of DFSP, characterized histologically by the coexistence of two distinct cell populations, including spindle-shaped cells and particular melanin-containing dendritic cells (1). It has been reported in approximately 1 to 5% of DFSP and has a predilection for the back and shoulders of young to middle-aged adults, with sporadic cases reported in the pediatric age group (1, 5). Herein, we report dermoscopic features of a rare case of Bednar tumor.

Case Report

A 54-year-old woman presented with a 1-year history of solitary asymptomatic nodule on her right forearm that had demonstrated a slow but progressive enlargement over the previous 3 months. Her personal and family history regarding skin cancers was unremarkable. The patient did not report any recent medical history of the local trauma of the affected area. The clinical examination revealed a slightly elevated dark-blue to partially brown nodule of firm consistency, measuring 8x10 mm **(Figure 1 A).** Dermoscopically, the lesion displayed a multicomponent pattern composed of a homogeneous blue-gray pigmentation with shiny white lines, structureless light-brown pigmented areas and a peripheral patchy pigment network (**Figure 1 B).** Based on the clinical and dermoscopic appearance of the lesion, our provisional diagnoses were: atypical dermatofibroma, combined nevus, blue nevus and melanoma. The surgical excision with margins of 2-3 mm was performed. The histopathological examination revealed a storiform arrangement of the spindle-shaped cells admixed with the melanin-

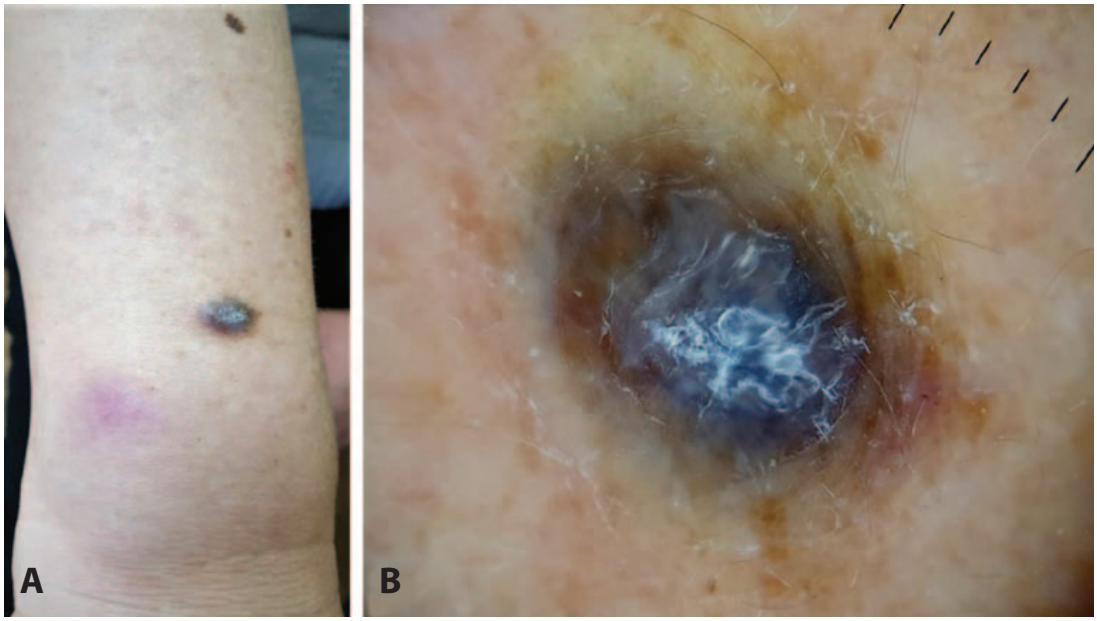

Figure 1. A. Dark-blue to partially brown nodule presented on the right forearm; **B.** Dermoscopic examination revealed a multicomponent pattern composed of homogeneous blue-gray pigmentation, shiny white lines, structureless light-brown pigmented areas and peripheral patchy pigment network

containing dendritic cells **(Figure 2 A, B)**. The additional immunohistochemical examination showed expression of CD 34 by the spindle-shaped cells **(Figure 2 C),** while pigmented cells were positive for S100 **(Figure 2 D),** corresponding to a diagnosis of the pigmented DFSP or Bednar tumor. Consequently, the patient underwent a surgical re-excision with 3 cm safety margins. During the period of 2 years of regular follow-up, there has been no evidence of recurrence.

Discussion

DFSP is a rare cutaneous neoplasm with the reported prevalence of 0.1-1% among all cutaneous malignant tumors (3). Besides conventional DFSF, more than 10 clinicopathological subtypes have been reported including myxoid, giant cell fibroblastoma or juvenile, granular cell, atrophic, palisading, as well as pigmented subtype. The pigmented subtype of DFSF or Bednar tumor shares similar pathohistological, immunohistochemical and cytogenetical features with the conventional DFSF, except for the presence of the melanin-containing dendritic cells (1). The origin of the melanin-containing dendritic cells in this tumor remains unclear: whether it originates from the neoplastic neuroectodermal differentiation, or represents an incorporated and/or colonized epidermal or hair follicle melanocytes (2-4).

A typical clinical appearance of Bednar tumor includes a solitary or multiple papules or nodules, mostly arising in the indurated plaque of tumor (typical protuberant morphology), exhibiting brown-red, blue or bluish-black coloration (1, 5). Usually, patients report a longstanding history of a slow-growing and asymptomatic lesion until it infiltrates the underlying muscle, fascia, or bones, causing discomfort. Initially, lesions may lack a protuberant clinical appearance only revealing a visible pigmentation (5, 6). At this early stage, Bednar tumor should be differentiated from dermatofibroma, blue nevus, melanoma and cutaneous metastases of various tumors. Moreover, Bednar tumor has been described in association with the history of a preceding local trauma, insect bite and vaccine scars (6, 7).

Given the rarity of DFSP, dermoscopic features of these lesions, especially in the context of Bednar tumor, have been insufficiently defined. In the largest study so far, Bernard et al. (8) performed a dermoscopic evaluation of 15 biopsy proven cases of DFSP whereas six der-

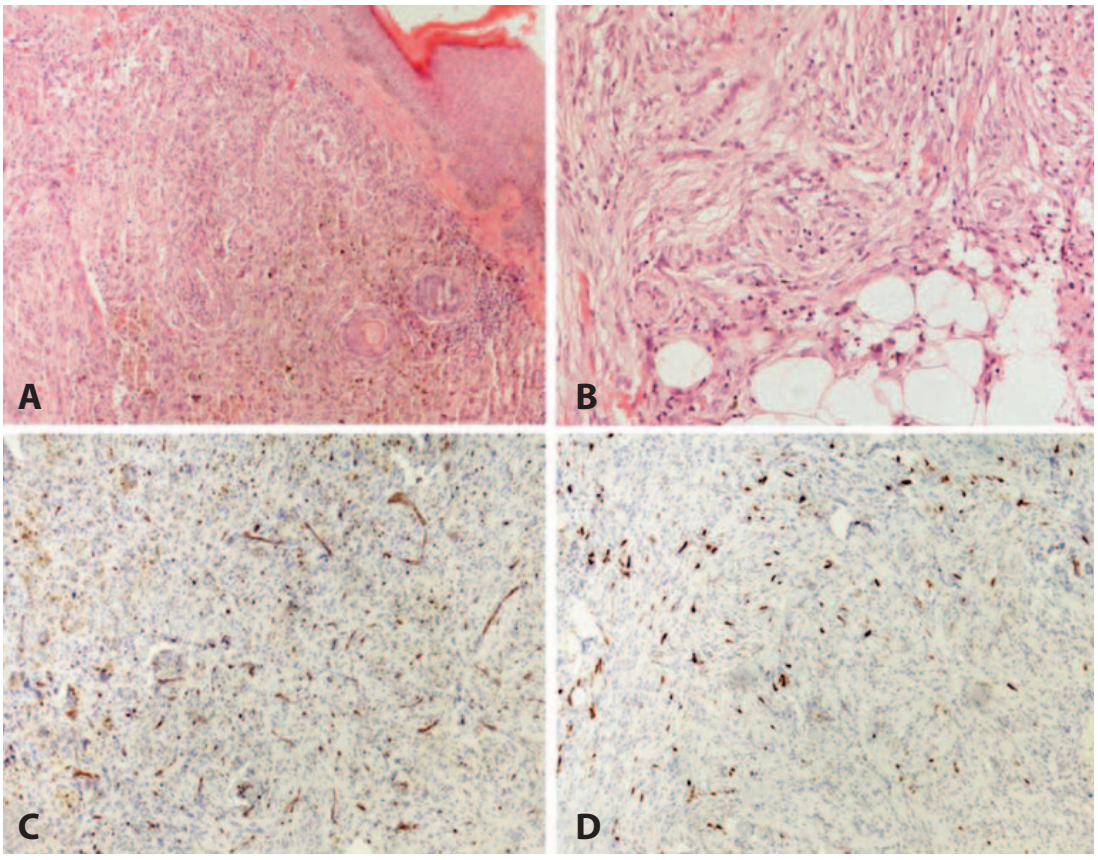

Figure 2. A. Spindle cells arranged in tight storiform pattern admixed with a small population of dendritic cells with melanin (hematoxylin and eosin; H&E x 20); **B.** Infiltration of the subcutaneous tissue (hematoxylin and eosin; H&E x 40); **C.** CD34 positive expression of spindle cells; **D.** Melanin-containing dendritic cells positive for S100

moscopic features of DFSP were observed, including: pigmented network, vessels, structureless light-brown areas, shiny white streaks, pink background coloration and structureless hypo- or non-pigmented areas. The previous study included a dermoscopic description of one Bednar tumor which revealed all 6 dermosocopic features mentioned above. Notably, the majority of the lesions analyzed in this study revealed a multicomponent pattern, which is highly suspicious of malignancy (8). In addition, Maeda et al. (9) reported another case of Bednar tumor which displayed similar dermoscopic features that had been observed by Bernard et al., except for a delicate pigmented network and vessels. In that article, authors stated that combination of "color variegation" and "blue-whitish veil lesions without a peripheral pigment network", in addition to the conventional dermoscopic features of DFSP, should suggest a diagnosis of Bednar tumor (9). Furthermore, Bednar tumor can mimic blue nevus both clinically and dermoscopically, revealing a homogeneous black-bluish pigmentation with white-veil structures (10).

The dermoscopic features observed in the present case are consistent with the reported dermoscopic descriptions of Bednar tumor (8-10). In this report, the blue-gray pigmentation was a prominent dermoscopic feature and it may reflect the histopathological finding of the melanin deposition in the dermis, while shiny white streaks may correlate to collagen alterations in the underlying stroma. Those dermoscopic features are commonly reported in the melanoma and blue nevus. The structureless light-brown pigmented areas and peripheral patchy pigment network may correspond to a distribution of melanin in the upper dermis and in the basal layer of the epidermis, respectively.

In conclusion, we presented a rare case of Bednar tumor with a dermoscopic description which is in line with previous reports. Although dermoscopy may be suggestive of the diagnosis of Bednar tumor, the pathohistological examination remains a gold standard for diagnosis.

Abbreviations

DFSP-dermatofibrosarcomaprotuberans

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Bednar tumor – prikaz slučaja

Sažetak

Bednarov tumor je retka pigmentna varijanta dermatofibrosarkoma protuberans koji histopatološki karakterišu istovremeno dve različite ćelijske populacije, uključujući vretenaste ćelije i dendritične ćelije koje sadrže melanin. Prikazujemo dermoskopske karakteristike Bednarovog tumora sagledane kod pacijentkinje starosti 54 godine. Dermoskopskim pregledom uočen je multikomponentni obazac sačinjen od homogene plavosive pigmentacije sa sjajnim beličastim linijama, bez strukturnih svetlobraon pigmentnih područija i periferne pigmentne mreže. Dermoskopske karakteristike uočene u ovom slučaju u skladu su sa objavljenim dermoskopskim opisima Bednarovog tumora. Iako dermoskopija može sugerisati dijagnozu Bednarovog tumora, histopatološki pregled predstavlja zlatni standard za dijagnozu.

Ključne reči: Dermatofibrosarkom; Dijagnoza; Dermoskopija; Kožne neoplazme; Prikazi slučajeva; Ishod Terapije

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AUTHOR GUIDELINES

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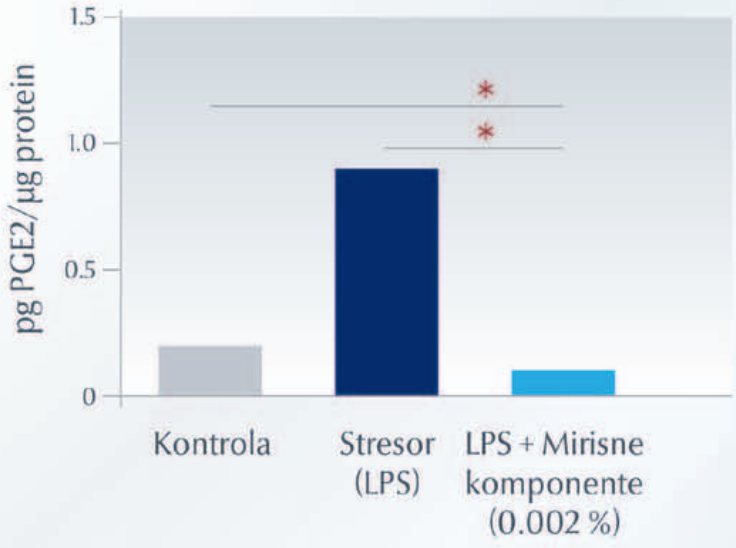

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