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Editorial

Lichen planus: The newer treatment trends

Lichen planus(LP) is a pruritic inflammatory disorder affecting skin, mucous membranes, skin appendages, and other organ systems.¹ It has internal associations, including autoimmune conditions, glucose intolerance, dyslipidemia, and cardiovascular disorders.² In skin classically LP is presented as small, sharply demarcated, flat and polygonal erythematous-livid papules, that may progress to form plaques which is often described by “six-P”; planar, purple, polygonal, pruritic, papule and plaque.³ In classic oral lichen planus (OLP), the mucosa is involved bilaterally and symmetrically with six clinical patterns: reticular (most common), erosive/ulcerative, plaque-like, papular, bullous, and atrophic.⁴ The classic cutaneous LP is typically a self-limiting disease with a good prognosis. Most patients with cutaneous lesions spontaneously clear within 12–24 months.⁵

Lichen planus is thought to be a T-cell-mediated autoimmune disease of unknown aetiology. It is believed to be influenced by genetic and environmental factors, where certain exogenous antigens alters epidermal self-antigens, leading to the activation of cytotoxic T(Tc) cells. The altered self-antigens cross-react with normal self-antigens on basal keratinocytes, resulting in T-cell targeting and apoptosis.⁶ A complex inflammatory network comprising Tc, Th1, IL-23/Th-17 axis, dendritic cells, keratinocytes, NK cells, macrophages, mast cells, and Tregs are involved in its initiation and maintenance.³ Treating LP is practically challenging, tricky and variable for different subtypes. The apex treatment objective is the clearing of the cutaneous lesions and accompanying symptoms including painful oral erosions which significantly hampers food intake.⁷

A gold standard treatment for LP is lacking. However, potent topical, intralesional or systemic corticosteroids, systemic retinoids or cyclosporine are proven first-line treatments.⁷ Phototherapy using ultraviolet B light, psoralen plus ultraviolet A light, the combination of UV/PUVA with retinoids, photodynamic therapy, oral sulphasalazine and topical calcineurin inhibitors are approved as second-line modalities. Hydroxychloroquine, azathioprine, methotrexate, mycophenolate mofetil, or biologics targeting IL-12/23 are listed as third-line modalities.⁷ Though therapeutic options for LP have remained largely stagnant, with advances in drug development and understanding of the pathophysiology of, novel therapies targeting cytokines (biologics) and small molecules blocking intracellular signalling are included in the list. In refractory erosive/ulcerative

OLP anti-IL-17, anti-IL-12/IL-23, and anti-IL-23 monoclonal antibodies represent an effective and safe alternative therapy.⁸ Janus kinase–signal transducer and activator of transcription (JAK-STAT)-dependent cytokines like IFN- γ can play a significant role in the molecular pathogenesis of LP.⁹ JAKs are one of the therapeutic targets to control overreactive immune responses. Tofacitinib is the most reported JAK inhibitor, and it is effective in treating oral, nail, hypertrophic, and scalp LP.¹⁰⁻¹² The success of oral JAK1 inhibitor, upadacitinib in the treatment of refractory, biopsy-proven lichen planus has been recently published.¹³ Considering the wide spectrum anti-inflammatory role of the PDE4 inhibitor, apremilast has been evaluated and found effective in LP refractory to topical steroids.¹⁴ Mycophenolate mofetil can also be considered as another off-label option for recalcitrant cases not responding to first and second-line treatments.¹⁵

With the innovations of newer molecules, it appears that diseases like LP are going to be within the reach of physicians control and patients suffering will be significantly reduced down.

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Original Article:

Association of serum IL-23 and IL-17A level with lichen planus: A case-control study

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Abstract

Background: Cellular involvement in the pathogenesis of lichen planus is well established. Initially it is mediated by T-helper 1 (Th1) response and in the later part it turns into a T-helper 2 (Th2) response. In the etiopathogenesis of lichen planus IL-17A and IL-23 may exert a crucial effect and discovering their role may help to emerge new therapeutic options to ameliorate disease symptoms and also complications like metabolic syndrome and malignancy. **Objectives:** To assess serum level of IL-17A and IL-23 in patients with lichen planus and healthy individuals by ELISA and to observe their association with disease severity. **Methods:** Patient of lichen planus was included as case and age and sex matched healthy individual as control were selected. 3 ml of blood sample was collected from both case & control for ELISA. Disease severity was assessed using LPSI (Lichen Planus Severity Index). **Result:** Serum levels of IL-23 and IL-17A were higher in cases (IL-23=414.0±510.7; IL-17A=139.4±192.1) than the controls (IL-23=22.9±33.5; IL-17A=2.90±2.06) and p value was <0.001, which was significant. These cytokines decline over time with a statistical significance. Male has a higher level (195.71±236.53) of serum IL-17A than female (72.84±86.38) with a p value=0.026). **Conclusions:** Serum levels of IL-23 and IL-17A were significantly elevated in patients with lichen planus and level of these cytokines decrease with increasing disease duration. IL-17A level in serum was higher in male than female indicating a possible sex specific way of IL-17A secretion. No relation of IL-17A and IL-23 with disease severity was observed.

Keywords: Lichen Planus, Association, IL-23, IL-17A

Introduction

Lichen planus is an autoimmune mucocutaneous disease that affects skin, mucous membranes, hair and nails. The incidence of lichen planus ranges from 0.14 to 1.27% of the general population. Two-third of the cases occur between the ages of 30-60 years. The disease can occur at any age though uncommon in children.¹

The aetiology of lichen planus is unknown. Theories of infection including viral, bacterial, autoimmune, metabolic, psychosomatic and genetic causes have all had their proponents.²

In 2011, for the first time it was demonstrated that serum level of IL-17 in patient with lichen planus used to rise significantly and the issue that IL-17 may play a pivotal role in lichen planus pathogenesis was brought into the light.³

IL-17 renders to a family of six- members including IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F.⁴ and among them IL-17A is the prototype of the IL-17 family and often referred to as IL-17.⁵

Secretion of IL-17 through Th-17 cells is influenced by dendritic cell-derived IL-23.⁶ A selectively pivotal role of the IL-23/IL-17 axis in the immune network of oral lichen planus lesions has been established.⁷

In cutaneous lichen planus IL-17 can induce associated pro inflammatory cytokines and antimicrobial peptide release.⁸ For lichen planus the first two drugs in current treatment modalities are- steroid and acitretin which have potential side effects like HPA axis suppression, teratogenicity etc.¹ Despite treatment with various modalities lichen planus remains a therapeutic challenge

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and recurrence is common.⁹

Therapeutic targeting of T17 cells with agents that are antagonist to IL-23/IL-17 axis (secukinumab, ustekinumab, guselkumab) has been very effective in the clinical improvement of mucocutaneous lichen planus.¹⁰ This case control study was conducted to find out the association of serum IL-23/IL17 level with lichen planus and its severity by measuring serum IL-17 and IL-23 level in patients with lichen planus and healthy individuals which may help to add or modify the current treatment modalities or may lead to new immunomodulatory therapy that would be beneficial in lessening patients' sufferings.

Methods:

2.1. Sample size calculation

This was a Case-control study from August, 2021 to June, 2022 conducted in the Department of Dermatology & Venereology at Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka, Bangladesh. Sample size was calculated to be 48 for each group using, $n = ((\sigma_1^2 + \sigma_2^2) (z_{(1-\alpha/2)} + z_{(1-\beta)})^2) / (\mu_2 - \mu_1)^2$

Here,

n = Sample size,

μ_1 = mean value of case

μ_2 = mean value of control

σ_1 = standard deviation for case

σ_2 = standard deviation for control

$z_{(1-\alpha/2)} = 1.96$ for 5% level of significance and

$z_{(1-\beta)} = 0.842$ (From Z table) at 80% power.

2.2. Inclusion criteria:

For case:

Patients with lichen planus diagnosed clinically and/or histopathologically

Lichen planus patients not undergoing any treatment for LP before the study

Age: ≥ 18 years

Both gender

Able to understand questions and communicate well.

For control:

Healthy attendants of patients, laboratory staff, postgraduate medical students, and general people of the same geographical area.

Age: ≥ 18 years

Both gender

2.3. Exclusion Criteria:

Patients suffering from chronic infection or inflammation (e.g. tuberculosis, SpA, rheumatoid arthritis), cardiovascular disease, hypertension, diabetes mellitus, allergic disease, malignancy, haematological diseases, pregnancy etc. Drug therapy may cause LP-like lesions such as NSAIDs, aspirin, ACE inhibitors, beta-blockers etc.

or alter laboratory parameters (eg. corticosteroids), inflammatory skin (eg. Psoriasis, atopic dermatitis) or systemic disease (eg. Rheumatoid arthritis) or overt infections in patients and control.

2.4. Source of the sample:

Case: Patients with lichen planus attending the Department of Dermatology and Venereology BSMMU. They were diagnosed clinically by an expert dermatologist, with or without histopathological confirmation.

Control: Age and sex-matched healthy attendants of patients, laboratory staff, postgraduate students, and general people of the same geographical area.

2.5. Sampling method:

Consecutive type of sampling.

2.6. Severity assessment: The severity of cutaneous lichen planus was assessed following Kaur (11), oral lichen planus following Malhotra (12) and nail lichen planus following Iorizzo (13).

2.7. Data collection technique: Data were collected in a predesigned data collection sheet and results obtained from laboratory methods were recorded.

2.8. Type of specimen: Blood samples from patient and control groups.

2.9. Sample collection: 3 ml blood was collected from each participant by venipuncture after proper disinfection, then centrifuged at 4000rpm for 5 minutes. Separated serum was stored at -25°C till analysis of cytokines. Collected data were checked, edited and analyzed with SPSS software package version-26.

Result

This case-control study was carried out with the aim of demonstrating the association of serum IL-23 and IL-17A levels with lichen planus and to find out the relation of these cytokines in disease severity. A total of 48 clinically and/or histopathologically confirmed patients of lichen planus and 48 healthy and age-sex-matched controls were enrolled in this study. Blood samples were analyzed by ELISA method to assess serum IL-17A and IL-23 levels in the Department of Microbiology and Immunology, BSMMU, Dhaka, Bangladesh.

Table I: Sociodemographic characteristics of the study populations (n=96)

Variables	Case (n=48)	Control (n=48)	p-value
Age group (years)			
<30	21(43.8%)	15(31.3%)	
31-40	13(27.1%)	22(45.8%)	
41-50	9(18.8%)	7(14.6%)	
>50	5(10.4%)	4(8.3%)	
Mean \pm SD	35.4 \pm 11.6	35.5 \pm 9.79	1.000 ^{ns}
Gender			
Male	26(54.2%)	29(60.4%)	0.536 ^{ns}
Female	22(45.8%)	19(39.6%)	

Data were expressed as frequency and percentage and mean \pm SD Unpaired student t-test and Chi-square test were performed to compare the two groups ns = not significant The sociodemographic characteristics of study populations are shown in table-I. The mean age of respondents among cases (35.4 \pm 11.6) was slightly lower than the controls (35.5 \pm 9.79). Among study patients male candidates constitute 54.2% and female candidates constitute 45.8% and among controls 60.4% were male and 39.6% were female. To see the statistical significance of this difference, an Unpaired student t-test and Chi-square test was performed. Observed differences were not statistically significant. Other observed sociodemographic characteristics (marriage, occupation) also denote no statistical significance among cases and controls.

Table II: Distribution of the study patients (case) by location and severity of lichen planus (n=48)

Location and severity of Lichen planus	Frequency	Percentage (%)
Oral	14	29.2
Mild	2	14.3
Moderate	11	78.6
Severe	1	7.1
Nail	5	10.4
Mild	4	80.0
Moderate	0	0.0
Severe	1	20.0
Cutaneous	37	77.1
Mild/moderate	31	83.8
Severe	6	16.2

The percentage of distribution of study patients according to their site of involvement and clinical severity is shown in Table-II.

Total 37 patients had cutaneous involvement and 83.8% of them had mild/moderate severity according to LPSI (Lichen Planus Severity Index) of Kaur H et al 2019. Total 14 patients had oral lichen planus and most of them (78.6%) had moderate severity according to Malhotra AK et al,2007. Only 5 patients had nail involvement and all of them had mild disease except only one, who had severe nail lichen planus according to Iorizzo et al. 2020.

Table III: Comparison of serum IL-17A level and serum IL-23 level between case and control group (n=96)

Laboratory parameters	Case (n=48)	Control (n=48)	p-value
Serum IL-17A level (pg/ml)	139.4 \pm 192.1	2.90 \pm 2.06	<0.001 *
Mean \pm SD	93.2	2.28	
Median Range (min-max)	4.26-865.9	1.0-10.5	
Serum IL-23 level (pg/ml)	414.0 \pm 510.7	22.9 \pm 33.5	<0.001 *
Mean \pm SD	195.6	12.6	
Median Range (min-max)	5.10-2221.6	7.10-192.0	

p-value obtained by Mann-Whitney test, *significant Table- shows the serum cytokine level of study populations. A significant difference was observed between cases and healthy controls, for IL-17A it was 139.4 \pm 192.1 vs 2.90 \pm 2.06, p <0.001 and for IL-23 it was 414 \pm 510.7 vs 22.9 \pm 33.5, p < 0.001.

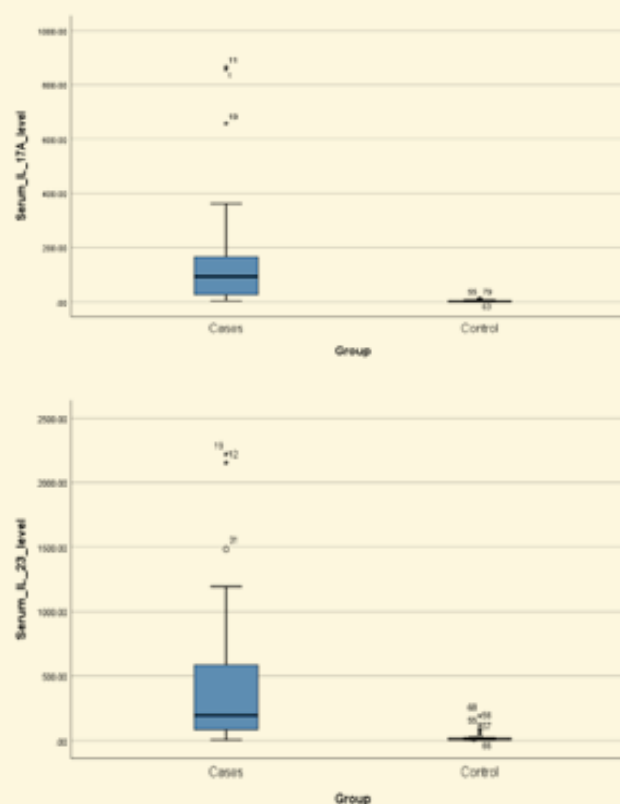


fig 1. Box plot showing the central tendency of serum IL-17A and serum IL-23 level

Here in Figure- the difference in the median value of serum cytokines (IL-17A and IL-23) between patients with lichen planus and healthy controls is shown. The dark line within each box indicates the median value. Fifty percent of the data lay inside the box. The line/ whisker extended from the box indicates the distribution of data. Indicators along this line with numbers indicates outliers (abnormally distributed data). Distribution is skewed to the longer whisker.

Table IV: Comparison of serum IL-17A level and serum IL-23A level among different demographic variables of case group (n=96)

Variables	N	Serum IL-17A Mean±SD	Serum IL-23A Mean±SD
Age group (years) ^a			
<30	21	137.46±194.78	321.34±329.45
31-40	13	153.58±172.64	425.84±576.48
41-50	9	175.06±259.83	654.64±683.04
>50	5	46.44±73.25	339.34±639.80
p-value		0.683 ^{ns}	0.434 ^{ns}
Gender ^b			
Male	26	195.71±236.53	516.47±583.68
Female	22	72.84±86.38	292.92±387.11
p-value		0.026 ^s	0.132 ^{ns}

p-value obtained by a ANOVA test and b Unpaired t-test, ssignificant, ns= not significant

Here in Table-IV serum level of cytokines (IL-17A and IL-23) among study patients were compared with different demographic variables. Age and occupation were compared with ANOVA test and no significance was found. Mean value of cytokines were compared with both gender and there was significant association of serum IL-17A level with gender of patients, p=0.026.

Table V: Comparison between disease severity and laboratory parameters (n=48)

Location and severity of Lichen planus	n	Serum IL-17A Mean±SD	Serum IL-23 Mean±SD
Oral			
Mild	2	98.1±101.4	343.2±433.2
Moderate	11	107.5±108.4	334.2±433.2
Severe	1	28.7	91.0
p-value		0.786 ^{ns}	0.806 ^{ns}
Nail			
Mild	4	39.2±37.8	133.6±43.2
Severe	1	309.6	666.7
p-value		0.008*	0.002*
Cutaneous			
Mild/moderate	31	153.2±226.2	476.2±583
Severe	6	113.2±62.2	246.6±221.0
p-value		0.673 ^{ns}	0.353 ^{ns}

p-value obtained by Mann-Whitney test, *significant, ns=not significant

Here both IL-17A (p=0.008) and IL-23 (p=0.002) showed significant relation with disease severity in case of nail lichen planus. No significance was found with serum level of IL-17A and IL-23 level with severity in other variants of the disease.

Table VI: Distribution of the study patients (case) by disease duration (n=48)

Disease duration (months)	Frequency	Percentage (%)
< 24 months	36	75.0
≥24 months	12	25.0
Total	48	100.0
Mean ± SD	14.93±19.41	
Range (min-max)	(1.50 – 94.5) months	
Median	6.25	

Study patients were distributed according to disease duration in Table-. It shows that 75% of cases had the disease for < 24 months. The mean duration of the disease was 14.93±19.41.

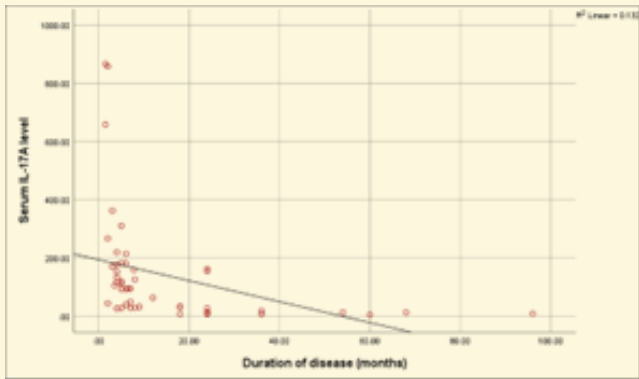


fig 2. Correlation of duration of disease with serum IL-17A level

p-value obtained by Pearson’s correlation. Pearson’s correlation coefficient (r) test was done to see the relationship between disease duration and serum IL-17A level. Here, a negative (-) r value indicates an inverse correlation of IL-17A level with disease duration in lichen planus patients.

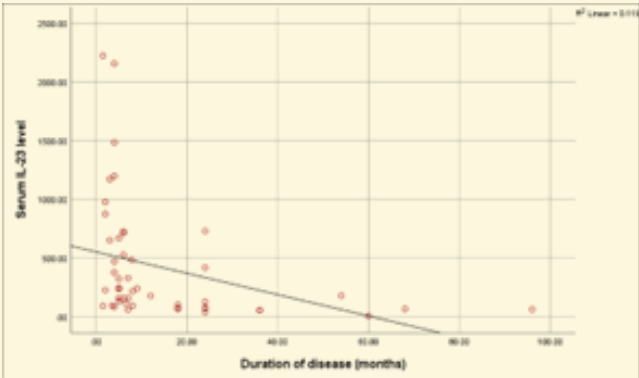


fig 3. Correlation of duration of disease with serum IL-23 level

p-value obtained by Pearson’s correlation. Pearson’s correlation coefficient (r) test was done to see the relationship between disease duration and serum IL-23 level. Here negative (-) r value indicates an inverse correlation of IL-23 level with disease duration in lichen planus patients.

Table VII: Comparison of IL-17A and IL-23 between disease duration below 24 months and above 24 months (n=48)

	Disease duration				p-value
	<24 months (n=36)		>24 months (n=12)		
	Mean±SD	Median	Mean±SD	Median	
Serum IL-17A level	173.8±209.0	113.5	36.26±57.12	12.4	<0.001*
Serum IL-23 level	500.3±555.3	242.2	155.3±209	66.4	0.001*

p-value obtained by Mann-Whitney test, *significant, ns=not significant Here in Table-VIII serum levels of IL-17A and IL-23 in between two groups of people (one having the disease for less than 24 months and another group for more than 24 months) are shown. For both cytokines, a significant decline in serum level over time was observed (for IL-17A, p<0.001 and for IL-23, p=0.001)

Discussion

Lichen planus is an autoinflammatory mucocutaneous disease that often follows a chronic course. Multifactorial aetiology and a complex interplay between innate and adaptive immune response have made the etiopathogenesis of the disease an unsolved mystery to date. A possible role of IL-17, the signature cytokine of Th17 cells and IL-23 as an important backbone material of effector Th17 cells have been suggested in many recent studies as an important immune-related pathogenetic mechanism behind the disease (7,14,15). Genetic predisposition has also been suggested as a responsible factor for lichen planus pathogenesis (16). Data focusing aetiopathogenesis of this geographic area is scarce to date. This case-control study was designed to see the association of serum IL-23 and IL-17A levels with lichen planus and to find out the relation of these cytokines with disease severity. Forty-eight clinically and/or histopathologically confirmed patients of lichen planus and forty-eight healthy and age-sex-matched controls were included in this study. Clinical disease severity was assessed with various scales (11-13) according to the site of involvement in the Department of Dermatology and

Venereology, BSMMU, Dhaka, Bangladesh. Blood samples were analyzed by ELISA method to assess serum IL-17A and IL-23 levels in the Department of Microbiology and Immunology, BSMMU, Dhaka, Bangladesh.

In this study, the mean age of the patients was 35.4 ± 11.6 years and the mean age of the controls was 35.5 ± 9.79 years. This result is consistent with an epidemiological study done in India where the mean age of patients was 36.38 years (17). As the controls were selected according to matched age and sex, the value was not significant ($=1.000$), indicating that age will not affect other measuring variables. A major percentage of patients (70%) in this study aged below forty. Age is a primary risk factor for a number of chronic diseases. Type 2 diabetes mellitus, hypertension and other cardiovascular diseases are among the most serious ones (18). These diseases require regular consumption of some drugs (eg. Oral hypoglycemic drugs, thiazide diuretics, ACEIs) which may induce lichenoid eruption and may be indistinguishable from classic lichen planus (16). So the study population of this study was designed to avoid dilemmas regarding drug induction.

Slight male dominance (54.2%) was present among patients in comparison to females (45.8%). The oral disease was present among 14 patients and females constitute the majority (57.14%) though statistically insignificant ($p=0.165$). In lichen planus, no definite sex variation is seen but some studies claim the adults with oral presentation have female dominance whereas the childhood lichen planus has a male preponderance (19). As the exclusion criteria of this study exclude children (<18 years), male dominance in this group couldn't be assessed.

The concentrations of IL-17A and IL-23 in the serum of patients with lichen planus were significantly higher than those in the controls (IL-17A, $p<0.001$ and IL-23, $p<0.001$). IL-17A level was also found higher in the male gender. The high levels of IL-17A and IL-23 in the sera of patients of lichen planus have been reported in several studies but they reported no relation with sex. (3,15, 20).

All (21) also found the same observation in a comparative study between Psoriasis, lichen planus and atopic dermatitis. Serum levels of IL-17A and IL-23 were significantly higher among these three groups than the controls though he reported no relation between extent of disease, disease duration or gender. On the contrary, Mahmoud (14) reported a positive correlation between serum

IL-17A level and extent of disease suggesting a possible relationship between serum IL-17A level and disease severity. He also reported no difference between serum levels of IL-17A between males and females.

On the point of sex-specific IL-17 levels, our study found a significant difference in serum IL-17A levels between males and females. In our study, the mean serum IL-17A level in males was 195.71 ± 236.53 and in females, it was 72.84 ± 86.38 , $p=0.026$; which was significant. Studies in animal models have suggested that men are more prone to Th17 and Th2 dominance and women are thought to be more prone to Th1 dominance. TCR and CD28 signals coupled with male androgen have a direct effect in upregulating peroxisome proliferator-activated receptor α (PPAR α) mRNAs in T cells of men and finally cause Th-17 cells to secrete more IL-17A (22). Another recent study regarding the Th17 cellular effect in CNS autoimmunity showed that the male sex chromosomal component augments Th17 pathogenicity and promotes Th17 responses rather than androgens (23). Here, Zhang (22) claims that, though underlying influence may be different, there is male Th17 dominance in autoimmune disease which is consistent with our finding.

Regarding the relation of disease severity with serum cytokines levels, we found no relation except in nail lichen planus. Here nail lichen planus shows a significant relation between disease severity and serum level of cytokines, but the case number is too small (only five) to draw a conclusion. In his study, Mahmoud (14) measured severity in terms of the extent of body surface involvement expressed in percentage. There was no documentation of lesional description like, whether it was hyperpigmented, hypertrophic papule/ plaque, or only violaceous papule etc. On the other hand, this current study denotes different points for different morphology according to Kaur (11). On the other hand, considering these, it could be said that establishing the relation of disease severity with serum cytokines needs further exploration because lesional description along with different severity scaling for different lichen planus variants may make it difficult to interpret and align the results of different studies into an assimilated one.

The mean disease duration in this study was 14.93 ± 19.41 months. & 75% of patients' disease duration is < 2 years (24 months). Cutaneous lichen planus spontaneously resolves within 1-2 years, but oral lichen planus may take 5 years or more or

may adopt further chronic course. Lichen planopilaris causes permanent scarring alopecia (24).

In our study we found an inverse relation between IL-23 and IL-17A level with disease duration. Lu (7) mentioned positive correlations between the expressions of IL-23 and IL-17 at both protein and mRNA levels in the reticular oral lichen planus subgroup indicating upregulation of the IL-23/IL-17 axis in the early stage of disease. He found a lack of correlation between IL-23 and IL-17 in erosive lichen planus, which is the later stage of the disease. They mentioned persistent exposure to high levels of IL-23 might be a factor behind this and indicated potential regulator mechanisms other than IL-23/IL-17A might be responsible.

The plasticity of Th17 cells toward Th1 cells is linked to the prolonged exposure of Th17 cells to IL-23. There is a complex relationship between the Th1 and Th17 lineage's plasticity. The pathogenic Th17 cells engender the IL-17+IFN γ + double-positive T cell subsets, termed as Th1 like Th17 or Th1/Th17. These cells secrete both IFN γ and IL-17 and contribute to the pathogenesis of autoimmune disease but their production of IL-17 is much less than the Th17 cells before converting into Th1-like Th17 cells. Th-1 like Th-17 cells are also much resistant to Treg mediated suppression via IL-10. Thus autoimmunity is carried out (25).

The goal of this study was to demonstrate the association of serum IL-23 and IL-17A levels with lichen planus. Though the study sample was not sufficient enough to give the actual scenario of the total Bangladeshi population it will definitely give an overview about the association of these cytokines with different other variables in lichen planus. From the findings of this study, it is evident that serum IL-23 and IL-17A levels in patients with lichen planus are way too higher than the controls and there is a significant variation of cytokine levels in serum between males and females. No relation between generalized and localized disease with IL-23 and IL-17A levels has been found. The same goes for the relation between disease severity and serum cytokine levels. Regarding the course of the disease, this study found a significant diminish in serum cytokines in relation to disease progression, though no conclusion could be drawn about the obvious point of diminution of their serum level in the course of the disease, leaving scope for future studies.

Conclusion

This current study revealed serum IL-23 and IL-17A levels are significantly higher in patients with lichen planus. The serum level of IL-17A is much higher in male patients than the female. No relation between serum cytokine levels with disease severity. There lies an inverse relation between disease duration and serum cytokine levels in patients with lichen planus.

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Original Article:

Effect of Intralesional Triamcinolone Acetonide on Alopecia Areata

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Abstract

Background: Alopecia areata (AA) is a chronic, non-scarring autoimmune disorder characterized by patchy hair loss, significantly impacting patient quality of life. The lifetime prevalence of AA is approximately 1.7%, with substantial emotional and psychological implications. **Objective:** This study primarily sought to investigate the efficacy of two different concentrations of intralesional triamcinolone acetonide (ILT) in managing patchy scalp alopecia areata. **Methodology:** An open clinical trial was conducted at the National Institute of Diseases of the Chest and Hospital, Dhaka Bangladesh, from January 2023 to June 2024. The study enrolled 55 patients with patchy alopecia areata involving less than 50% of scalp surface area. Participants were systematically divided into two treatment groups: Group A (n=27) received intralesional triamcinolone acetonide at 5 mg/mL, while Group B (n=28) received 10 mg/mL concentration. Patients underwent monthly intralesional injections, with comprehensive assessments performed at 12 weeks and a one-year follow-up to evaluate treatment response and potential recurrence. **Results:** The two concentration groups' treatment outcomes were identical. After 12 weeks, 44.4% of patients in the 5 mg/mL group and 42.9% in the 10 mg/mL group experienced complete hair regrowth, with 63.0% and 64.3% of patients reporting satisfactory overall results, respectively. With no documented cases of hypopigmentation, the side effect profiles were mild and similar, mainly manifesting as folliculitis (3.7% vs. 3.6%), telangiectasia with atrophy (3.7% vs. 10.7%), and localized atrophy (11.1% in the 5 mg/mL group vs. 10.7% in the 10 mg/mL group). The chronic nature of alopecia areata was demonstrated by the recurrence rates during follow-up, which were 50.4% for the 10 mg/mL group and 44.4% for the 5 mg/mL group. This study emphasizes the similar effectiveness of intralesional triamcinolone acetonide at both concentrations, giving physicians options for treatment choices. It also emphasizes the significance of early intervention and all-encompassing patient care. **Conclusions:** Intralesional triamcinolone acetonide represents a valuable treatment modality for localized alopecia areata. While demonstrating significant potential for hair regrowth, the study also revealed the challenges associated with long-term management, characterized by relatively high recurrence rates.

Keywords: Intralesional triamcinolone acetonide, Alopecia areata, Scalp hair regrowth, Steroid injection therapy, Autoimmune hair loss, Treatment concentration efficacy.

Introduction

Alopecia areata (AA), is a chronic, remitting, non-scarring, presumed autoimmune disease of the hair follicles leading to hair loss. AA is commonly linked to severe emotional discomfort and has a 1.7% lifetime frequency. A very diagnostic feature is the appearance of distinct,

hairless areas with yellow spots and short, broken hairs (exclamation mark hairs) surrounding the edges.¹⁻⁴ There are various methods of treatment approaches that should be customized based on the depth and severity of the sickness as well as the

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patient's psychological state. Regretfully, there is no cure or preventative therapy.⁵⁻⁷

One of the initial therapeutic choices for AA in adults is often intralesional steroids, typically triamcinolone acetonide (TA) in dosages of 2.5–10 mg/mL. The patient's age, the degree of hair loss, and the results of prior treatments all influence the treatment option. The best options for treating localized AA in adults with less than 50% scalp involvement are topical calcineurin inhibitors, oral corticosteroids, intralesional (IL) corticosteroid injections, and local immunotherapy (diphencyprone, anthralin).^{1,8,9} The first-line IL corticosteroid treatment for people with patchy, limited AA is still triamcinolone acetonide (TA). Different clinics employ different IL corticosteroid dosages and dilutions for AA therapy, and doctor expertise influences the IL injection dosages.^{1,10} Generally, TA doses of 2.5 mg/mL are advised for the face (beard, eyebrows) and 5 mg/mL for the scalp.¹¹ However, case series with small sample numbers and diverse patient groups make up the majority of the present research.³ Alopecia areata has long been treated with intradermal corticosteroid injections. A series employing hydrocortisone was originally reported by Kalkoff & Macher in 1958. Later, Gombiner & Malkinson (1961) reported the use of triamcinolone 10 mg/mL, while Orentreich et al. (1960) presented injections of insoluble forms of prednisolone, hydrocortisone, and fludrocortisone as a viable technique to treat AA.^{12,13,14} The advantages of IL injections of 5 mg/mL triamcinolone hexacetonide and 10 mg/mL TA were reported by Porter and Burton (1971).^{15,16} Hair regrowth after 12 weeks was best accomplished in the ITA group, according to prior open-label randomized research evaluating the effectiveness of topical bethametasone valerate foam, tacrolimus ointment, and intralesional triamcinolone acetonide (ITA) (10 mg/mL) for the treatment of localized AA.¹⁷

Methodology:

It was a study with open clinical trial. Within the data collection period, in this study 55 patients were enrolled if they were diagnosed histologically and clinically with AA. From January 2023 to June 2024, this study was conducted in a private chamber and as an outpatient at the National Institute of Diseases of the Chest and Hospital in Bangladesh. Patients of all ages who had patchy alopecia areata (AA) on their scalps that covered less than 50% of their scalp

surface area and were receiving treatment with monthly injections of triamcinolone acetonide at a dose of 5 mg/mL or 10 mg/mL were specifically eligible to participate. Patients undergoing combination therapy and those with alopecia totalis or universalis, as well as those with extensive scalp involvement (surface area >50%), were excluded from the study. Only the scalp patches were evaluated, although individuals with AA patches on both the scalp and other areas (such as the beard, moustache, or eyebrows) were included. Informed consent was given by each patient or their legal guardian to participate in the study. We took serial photos of the patients, if any were available, and their medical records. Demographic information (age, gender), AA characteristics (affected scalp surface area, duration, number of patches, nail and extra scalp involvement), and medical history (history of AA, comorbidities, atopy, and intralesional triamcinolone acetonide family history of AA on alopecia areata) were among the data extracted from medical records. Because there is no leakage between the syringe and needle, BD insulin (1 cc) syringes are a good option. As a diluent, sterile saline is better than xylocaine because the latter stings more. When treating eyebrows, it can be helpful to apply a topical anesthetic 30 to 60 minutes before the treatment in order to reduce injection pain. Additionally, a needleless device (such as Dermajet™) can be used to administer ILCs. Between patients, the device needs to be sterilized. Every four to six weeks, the treatments are repeated. In four to eight weeks, initial regrowth is frequently observed. The ILCs should be discontinued if, after six months of treatment, there is no improvement. Some AA patients may have glucocorticoid resistance due to thioredoxin reductase 1 expression being downregulated in the outer root sheath. ILCs are typically not administered to children under the age of ten due to injection site pain. ILT was performed monthly for all patients. Using a 30-gauge needle, the steroids diluted with lidocaine or regular saline were injected at 1-cm intervals, beginning from the patch's edge and working toward its centre; roughly 0.1–0.2 mL was injected per site.

Prior to the second and third treatments, response of the treatment and side effects were documented. At the follow-up visit, one year following the last injection, a recurrence assessment was conducted.

Result

A thorough comparison of Group A (ILT 5 mg/mL) and Group B (ILT 10 mg/mL) is given by the results from the four tables (Tables 1-4). Table 1 demonstrates that the groups' demographics are similar, with a similar mean age (20.9 years in Group A vs. 20.0 years in Group B, $p=0.333$) and gender distribution (44.4% female in Group A vs. 46.4% in Group B, $p=0.323$). Alopecia areata (AA) patches treatment duration, number, and affected scalp surface area did not differ significantly ($p>0.05$), according to Table 2, which highlights clinical characteristics. Additionally, there were comparable rates of atopy, comorbidities, nail involvement, family history of AA, and prior AA history in both groups. Table 3 presents the results of treatment for Group A. At 12 weeks, 44.4% of the group experienced complete hair regrowth, 63.0% reported satisfactory results, and 18.5% experienced side effects, with atrophy being the most common (11.1%), followed by folliculitis (3.7%) and telangiectasia with atrophy (3.7%), with no hypopigmentation cases. Group B's treatment results are shown in Table 4; at 12 weeks, 42.9% of the group experienced full hair regrowth, 64.3% reported satisfactory results, and 17.9% experienced side effects, such as atrophy (10.7%), telangiectasia with atrophy (3.6%), and folliculitis (3.6%), with no hypopigmentation. Group B had a marginally higher recurrence rate (50.4%) than Group A (44.4%).

Table I: Distribution of the respondents' according to socio-demographic characteristics (n=55)

Parameter	Group A ILT: 5 mg/mL (N = 27)		Group B ILT: 10 mg/mL (N = 28)		P-value
	n	%	n	%	
Gender					
Female	12	44.4	13	46.4	0.323
Male	15	55.6	15	53.6	
Age					
Mean(SD) (years)	20.9 (11)		20.0 (12)		
≤18	10	37.0	10	35.7	0.333
19-30	12	44.4	13	46.4	
>30	5	18.5	5	17.9	

Table II: Distribution of the respondents' according to clinical features and medical history (n=55)

Parameter	Group A ILT: 5 mg/mL (N = 27)		Group B ILT: 10 mg/mL (N = 28)		P-value
	n	%	n	%	
Duration of treated AA patches					
Mean(SD)(months)	13.6 (27)		12.8 (26)		0.835
≤2	9	33.3	10	35.7	
3-6	8	29.6	8	28.6	
>6	10	37.0	10	35.7	
Number of patches					
Mean (SD)	3.4 (4.2)		3.5 (4.0)		0.452
1	9	33.3	10	35.7	
2	8	29.6	8	28.6	
≥3	10	37.0	10	35.7	
Scalpsurfaceareaaffected					
	5.4 (5.2)		5.0 (4.8)		0.658
≤3	8	29.6	9	32.1	
3-5	9	33.3	10	35.7	
6+	10	37.0	9	32.1	
AA's past history	6	22.2	7	25	0.553
Personal history of atopy (allergic rhinitis, atopic dermatitis, asthma,)	8	29.6	8	28.6	0.587
Comorbidities (diabetes mellitus, hypothyroidism, hypertension, low ferritin)	8	29.6	8	28.6	0.587
Juvenile rheumatoid arthritis, psoriasis, anxiety, vitiligo, depression					
Nail involvement (leukonychia, fine pitting, trachyonychia,)	2	7.4	3	10.7	0.522
Extracscalp sites (legs, eyebrow, beard, moustache)	6	22.2	6	21.4	0.663
AA's Family history	4	14.8	4	14.3	0.536



fig 1. A patient with temporal and occipital patches showed complete hair regrowth after single injection of ILT 10mg/mL



fig 2. Skin atrophy observed at the location of the ILT injection (arrows)

Table III: Distribution of the respondents' according to response of treatment group A ILT: 5 mg/mL (N=27)

Variables	ILT 5mg/mL (N=27)	
	n/N	%
Patients whose hair completely regrow after 12 weeks	12/27	44.4
Patients who showed satisfactory outcome at 12 weeks	17/27	63.0
Overall side-effects	5/27	18.5
Atrophy	3/27	11.1
Telangiectasia and Atrophy	1/27	3.7
Folliculitis	1/27	3.7
Hypopigmentation	0/27	0.0
Recurrence of Folliculitis Hyperpigmentation following a year of monitoring	12/27	44.4

Table IV. Distribution of the respondents' according to response of treatment group B ILT: 10 mg/mL (N=28)

Variables	ILT 10 mg/mL (N=28)	
	n/N	%
Patients whose hair completely regrow after 12 weeks	12/28	42.9%
Patients who showed satisfactory outcome at 12 weeks	18/28	64.3%
Overall side-effects	5/28	17.9%
Atrophy	3/28	10.7%
Atrophy and telangiectasia	1/28	3.6%
Folliculitis	1/28	3.6%
Hypopigmentation	0/28	0.0%
Recurrence after 6 months of follow-up	13/28	50.4%

Discussion

We included two patient groups in this study that had similar clinical and demographic traits. According to the results, most often used two ILT doses (5 and 10 mg/mL) for treating patchy AA on the scalp may be similarly effective after 12 weeks. ILT 10 mg/mL, however, had somewhat quicker outcomes and was better after four weeks. Only a small number of studies that primarily examined the effectiveness of varying ILT concentrations in the treatment of patchy AA were found in the literature review; these studies used disparate approaches and had inconsistent findings. Three ILT concentrations (2.5 mg/mL, 5 mg/mL, and 10 mg/mL) were shown to be similarly efficacious and superior to normal saline in intra-pilot research with four patients.¹⁸ ILT response is concentration dependent, according to the findings of another trial with 15 patients, but these findings were not statistically significant.¹⁹ More recent studies found that 5 mg/mL and 10 mg/mL were equally beneficial, based on a systematic review and meta-analysis of seven earlier investigations. However, the authors pointed out discrepancies among the studies that were part of the review about the main outcome that was examined, the method, the frequency, and the length of therapy and the accessibility of clinical characteristics and demographic data.³

However, ILT 10 mg/mL was shown to be more effective than ILT 5 mg/mL, which in turn was more

effective than ILT 2.5 mg/mL in a randomized controlled study. ILT 10 mg/mL was linked to a greater frequency of adverse cutaneous effects. However, there were just a few patches on the scalp in this study—28 patches received ILT 10 mg/mL treatment, compared to 27 patches receiving ILT 5 mg/mL—and patients were not observed for more than six months.¹ Since only mild and local side effects (atrophy, telangiectasia, folliculitis, and dyspigmentation) were noted, ILT safety was clearly proven in this research. Although they were somewhat more common in the ILT 10 mg/mL group, the difference was statistically noteworthy. With 48% of patients in both groups achieving total hair regrowth and 70% experiencing excellent outcomes after 1–3 injections, the current study's results show a strong response to ILT therapy. Longer disease duration (>6 months) was shown to have negative effects, indicating that early treatment may improve the likelihood of a positive outcome. According to a prior study, a longer duration of alcohol use was linked to a lack of response to topical and intralesional corticosteroid regimens.²⁰

Our results also show that, regardless of the ILT dosage, over half of AA patients will relapse. This study revealed common correlations between AA and autoimmune diseases. Some of these illnesses were only discovered through examinations or follow-up, even though the majority of patients had them known upon presentation. For instance, three of the seven individuals with hypothyroidism were identified by baseline screening. Furthermore, a young woman who had received efficient therapy for patchy AA was later diagnosed with juvenile rheumatoid arthritis, and same sequential relationships were documented.^{21,22} Patients' exposure to the local and systemic adverse effects of steroids. This corpus of research would greatly benefit from a comparison of even lower ILT concentrations (e.g., 2.5 mg/mL vs. 5 mg/mL). Several corticosteroid regimens (intralesional, topical, or their combination) are actually equally effective in treating focal AA, according to a current study.²⁰

Conclusion

This study provides worthwhile insights into the management of alopecia areata using intralesional triamcinolone acetonide. The findings demonstrate that both 5 mg/mL and 10 mg/mL concentrations offer comparable efficacy in treating patchy scalp

AA, with the 10 mg/mL concentration showing marginally faster initial response. The relatively high rate of satisfactory outcomes and complete hair regrowth underscores the potential of ILT as a treatment option. However, the significant recurrence rate suggests that AA remains a challenging condition with a tendency for relapse. The study also highlighted important clinical observations, such as the potential association with AA of other autoimmune conditions like hypothyroidism and juvenile rheumatoid arthritis, highlighting the importance of thorough patient assessment and monitoring.

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Original Article:

Relationship of Serum High Sensitivity C - reactive Protein Level with Severity of the Disease in Patients with Psoriasis According to Psoriasis Area and Severity Index

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Abstract

Background: Psoriasis is an inflammatory disease of the skin of multifactorial aetiology. Psoriasis has been considered mainly to be a Th1-driven autoimmune disease defined by a cytokine pattern consisting of IFN- β , tumour necrosis factor-alpha (TNF- α), IL-1, IL-2, IL-3, IL-6, IL-8, epidermal growth factor and transforming growth factor-alpha (TGF- α). However recent findings have revealed a potential role for IL-23 and Th17 responses in the pathogenesis of psoriasis. C-reactive protein (CRP) is important for psoriasis due to its relation with cytokines that are responsible for skin inflammation. **Objectives:** This study measured the serum hsCRP level in patients with psoriasis and assessed its relationship with the severity of the disease. **Materials and Method:** This cross-sectional study included 52 psoriatic patients, diagnosed in the Department of Dermatology & Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. The study was conducted in two years period, from July 2018 to June 2020 and purposive type of sampling technique was applied to collect the sample from the study population. Disease severity was measured by the Psoriasis Area Severity Index (PASI). **Results:** The mean serum hsCRP level was 6.29 ± 6.8 and the mean Psoriasis Area and Severity Index (PASI) was 10.07 ± 5.88 . The mean hsCRP in mild psoriasis ($PASI \leq 10$) was 1.82 ± 1.32 and in moderate to severe psoriasis ($PASI > 10$) was 11.51 ± 6.93 . There was a significant positive correlation between serum hsCRP level and PASI ($r=0.795$, $p<0.001$). **Conclusion:** The present study revealed a positive correlation between the disease activity of psoriasis and with patient's serum hsCRP concentration. So, serum hsCRP can be considered a marker of disease activity. **Keywords:** C reactive protein, Psoriasis, BSMMU, PASI

Introduction

Psoriasis is a complex chronic inflammatory systemic disease, with environmental and genetic components, that affects the skin, nails and occasionally the joints, with periods of exacerbation and remission.¹ Psoriasis is considered a global problem with a prevalence ranging from 0.5 to 11.4 percent.² It poses a significant physical, mental and social burden.³ Quality of life of the patient, in general, is often significantly impaired.⁴ Significant disfigurement, discomfort, disability and loss of productivity are important challenges for the patients. There is also a significant cost to mental well-being, such

as higher rates of depression, leading to a negative impact on individuals and society.⁵ Social exclusion, discrimination and stigma are psychologically devastating for individuals suffering from psoriasis and their families.⁶ Psoriasis can occur at any age, and is most common in the age group 50–69.⁷ Psoriasis involves the skin and nails and is associated with several comorbidities. Skin lesions are localized or generalized, mostly symmetrical, sharply demarcated, red papules and plaques, and usually covered with white or silver scales. Between 1.3% and 34.7% of individuals with psoriasis develop chronic,

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inflammatory arthritis (psoriatic arthritis) that leads to joint deformations and disability.⁸ Between 4.2% and 69% of all patients suffering from psoriasis develop nail changes.⁹ Individuals with psoriasis are reported to be at increased risk of developing other serious clinical conditions such as cardiovascular and other non-communicable diseases (NCDs).¹⁰ Psoriasis was first described as a disease that primarily affects epidermal keratinocyte proliferation and secondary cutaneous inflammatory infiltration. In the last decade, it has been evident that psoriasis is a systemic, immune-mediated, inflammatory disease primarily involving Th1 cells. Cytokines of the Th1 pathway (interferon-Gamma, interleukin 2, interleukin 12, and TNF-alpha) predominate in psoriatic plaques. It is widely accepted that an unknown stimulus activates dendritic antigen-presenting cells. The activated antigen-presenting cells then activate helper T cells which lead to the subsequent release of a cascade of inflammatory cytokines. This cascade results in the recruitment and activation of other cell types such as endothelial cells and neutrophils, and the production of chemokines and growth factors. Eventually, that leads to hyperproliferation of keratinocytes. A chronic inflammatory state that ensures and leads to the formation of psoriatic skin lesions.¹¹ There is increased mitotic activity of the basal cell layer which results in rapid epidermal cell turnover with the 28-day normal epidermal cell cycle reduced by 3 to 5 days. The stimulus for the increased rate of keratinization and even the site of the initial pathologic changes remains controversial.¹² This is reflected clinically by profuse scaling, histologically by a greatly thickened epidermis with increased mitotic activity and by the presence of immature nucleated cells in the horny layer and under the electron microscope by reduced production of intracellular filaments and granules seen within normal keratinization and biochemically by increased synthesis and degradation of nucleoproteins.¹³ While analyzing the triggering factors, it was seen that mental stress was the most important triggering factor seen in 48% of patients.¹⁴ Psychological factors can trigger the onset or exacerbation of disease.¹⁵ The stress reaction in the patients is mediated by a hypothalamic, pituitary-adrenal relationship with immunologic effects. The commonest factor for the onset of the disease is the environment in which a person has been living and working for a longer period of time and the attitude of a person towards such environment. The other commonest triggering factor was found to be drug intake, which was seen in 36% of patients. The sore throat was found to be a triggering factor in 36% of cases. Trauma as a trigger was found in 22% of cases.¹⁴ Any form of trauma results in psoriasis appearing in the

traumatized areas known as koebner's phenomenon¹⁶ Outbreaks often correlate with environmental triggers, often linked to nutritional deficiencies and poor eating habits.¹⁷ It is of important and prevalent skin disease developing due to increasing epidermal cell multiplication. The disease may be intensified by different factors such that the lesions may extend, erythroderma(affecting more than 90% of body skin) may develop and the patient may be hospitalized.¹⁸ Considering available reasons for psoriasis, the main reason is not known but several factors such as family records and accompanying some Human Leukocytes Antigens (HLA) have been mentioned.¹⁹

C-reactive protein (CRP) was first described in 1930 by Tillett and Francis, named after its ability to precipitate and interact with phosphorylcholine residues of the C polysaccharide derived from teichoic acid within the cellular wall of *Streptococcus pneumoniae*, as well as its ability to precipitate with calcium ions.²⁰ CRP is a highly sensitive systemic marker of inflammation and tissue damage. The acute-phase response involves the nonspecific physiological and biochemical responses of endothermic animals to most forms of tissue damage, infection, inflammation, and malignant neoplasia. Plasma CRP is produced exclusively by hepatocytes, predominantly under transcriptional control by the cytokine IL-6, although other sites of local CRP synthesis and possibly secretion have been suggested. De novo hepatic synthesis starts very rapidly after a single stimulus, with serum concentrations rising above 5 mg/l by about 6 hours and peaking around 48 hours. The plasma half-life of CRP is about 19 hours and is constant under all conditions of health and disease, so the sole determinant of circulating CRP concentration is the synthesis rate which thus directly reflects the intensity of the pathological processes stimulating CRP production. When the stimulus for increased production completely ceases, the circulating CRP concentration falls rapidly, at almost the rate of plasma CRP clearance. The circulating value of CRP reflects ongoing inflammation and/or tissue damage much more accurately than other laboratory parameters of the acute-phase response, such as plasma viscosity and the erythrocyte sedimentation rate. The CRP concentration is thus a very useful nonspecific biochemical marker of inflammation, measurement of which contributes importantly to screening for organic disease, monitoring of the response to treatment of inflammation and infection, and detection of intercurrent infection in immunocompromised individuals, and in the few specific diseases characterized by modest or absent acute-phase responses.²¹ Psoriasis development depends on skin infiltration of Th1/Th17 cells that stimulate

macrophages and dermal dendritic cells to release mediators that sustain inflammation and cause abnormal keratinocyte proliferation. The mediators of the Th17 immune system include IL-1, IL-6, IL-23 and transforming growth factor (TGF)- β . Elevated C-reactive protein levels result from the interaction between pro-inflammatory cytokines, namely IL-6, TNF-alpha and IL-1. The increased magnitude of CRP seems to be related to the extent of tissue injury and inflammation severity in the active stage of psoriasis.²² C-reactive protein has special importance for psoriasis due to its relation with cytokines responsible for skin inflammation.²³ Conventional CRP assays can not detect low levels of rise in CRP. The high-sensitivity C-reactive protein (hsCRP) assay is a quantitative analysis of very low levels of CRP in blood (<10mg/L). The high-sensitivity CRP (hsCRP) test accurately measures low levels of C-reactive protein to identify low but persistent levels of inflammation. Though several clinical tools for assessing the severity of psoriasis are available, no relevant biochemical marker is commonly recommended for patients with psoriasis. Thus in recent years, a biochemical marker was always thought to be important to find out, which could be the representative of severity of the disease. Analyzing the importance of C-reactive protein in psoriasis, the latter can offer new hope for the physician both in assessing the severity of the disease and also in the global treatment of psoriasis.

Materials & Methods

It was a Cross-Sectional type of observational study. The study was conducted in the Department of Dermatology & Venereology and the Department of Microbiology at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, conducted two years period, from July 2018 To June 2020. Study subjects were the individuals, who were diagnosed with psoriasis vulgaris clinically, with or without the supporting evidence of histopathology. A purposive type of sampling technique was applied to collect the sample from the study population during the study period.

Study Procedure

This present study included 52 psoriatic patients. Patients attending the outpatient and inpatient Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University; who were diagnosed with cases of psoriasis vulgaris by clinical with or without histopathological confirmation by an expert dermatologist, were informed about the objectives of this study. Related information was collected Disease severity of every patient was measured by using the severity assessment tool namely, the Psoriasis Area and Severity

Index (PASI). The score of PASI usually varies between 0 and 72. A PASI score ≤ 10 was classified as mild disease, whilst a score of >10 was considered to be moderate to severe disease. Patient's own palm was used according to the checklist based on inclusion and exclusion criteria from them. All aseptic precautions five (5) ml of venous blood were drawn into a vacutainer tube containing no anticoagulant from the median antecubital vein of each patient. Serum concentrations of hsCRP were measured in the Department of Microbiology, Bangabandhu Sheikh Mujib Medical University, Dhaka. Serum hsCRP was analyzed by a nephelometric method using an automated analyzer: BN ProSpec, SIEMENS. After getting the report, the values of the biochemical variable were documented in the data collection sheet.

Result

The mean serum hsCRP level was 6.29 ± 6.8 and the mean Psoriasis Area and Severity Index (PASI) was 10.07 ± 5.88 . The mean hsCRP in mild psoriasis (PASI ≤ 10) was 1.82 ± 1.32 and in moderate to severe psoriasis (PASI >10) was 11.51 ± 6.93 . There was a significant positive correlation between serum hsCRP level and PASI ($r=0.795$, $p<0.001$).

Table: I Distribution of the study population by PASI score (n=52)

PASI score	Frequency	Percentage (%)	PASI Mean \pm SD
≤ 10 (Mild disease)	28	53.8	5.41 ± 2.07
>10 (Moderate to severe disease)	24	46.2	$15.51 \pm 3.7.7$
Total	52	100.0	10.07 ± 5.88

Table-I It was observed that the majority (53.8%) of patients belonged to PASI score ≤ 10 (Mild disease) and nearly half (46.2%) of patients belonged to PASI score >10 (Moderate to severe disease). The mean PASI score was found 10.07 ± 5.88

Table-II: Association of age with severity of psoriasis (n=52)

Age group (years)	Severity of psoriasis		p-value
	Mild disease (n=28) No. (%)	Moderate to severe disease (n=24) No. (%)	
18-20	3(10.7)	1(4.2)	0.341 ^{ns}
21-30	12(42.9)	8(33.3)	
31-40	8(28.6)	4(16.7)	
41-50	2(7.1)	3(12.5)	
51-60	3(10.7)	7(29.2)	
>60	0(0.0)	1(4.2)	
Total	28(100.0)	24(100.0)	

Data were expressed as frequency and percentage (%) Chi-square test was done, ns= not significant Table-II shows the association of age with the severity of psoriasis in study populations. It was observed that statistically insignificant ($p=0.341$) association between the age of patients with the severity of the disease.

Table III : Association of serum hsCRP with severity of disease according to PASI (n=52)

hsCRP (mg/L)	Severity of psoriasis		Total (n=52) Mean±SD	p-value
	Mild disease (PASI≤10) (n=28) No. (%)	Moderate to severe disease (PASI>10) (n=24) No. (%)		
Normal (3.0 mg/L)	22(78.6)	0(0.0)		
Elevated (>3.0 mg/L)	6(21.4)	24(100.0)		
Mean±SD	1.82±1.32	11.51±6.93	6.29±6.81	<0.001*
Range (min- max)	(0.20– 4.65)	(4.62 –25.5)	(0.20-25.5)	
Data were expressed as mean±SD Unpaired student-t test was done, *significant				

Table III, shows that hsCRP was strongly associated with the severity of psoriasis according to PASI (P10) was 11.51±6.93 ranging from 4.62 mg/L –25.5 mg/L

Table-IV: Relation of demographic variables with severity of psoriasis. (n=52)

Variables	Severity of psoriasis		p-value
	Mild disease (n=28) No. (%)	Moderate to severe disease (n=24) No. (%)	
Age (years)	32.71±10.60	39.58±14.64	0.056 ^{ns}
Age of onset (years)	29.64±10.29	36.38±13.96	0.051 ^{ns}
Duration of disease (years)	3.42±3.06	3.70±3.34	0.748 ^{ns}

Data were expressed as mean±SD
Unpaired student t-test was done, ns= not significant

Table-IV shows the relationship between demographic variables and with severity of psoriasis and found no significant relationship among these demographic variables.

Table : V Correlation coefficients of severity of psoriasis (PASI) with age, onset of disease, duration of disease and hsCR

Variables	PASI	
	Correlation coefficient (r)	p-value
Age (years)	+0.306	0.027*
Age of onset	+0.296	0.033*
Duration of disease	+0.107	0.451
hsCRP	+0.795	<0.001*
Pearson's correlation coefficient test was done, *significant		

Table V: It was observed that PASI, the most commonly used clinical assessment tool for disease severity, showed a significant strong positive correlation with hsCRP ($r=0.795$, $p<0.001$) and a significant weak positive correlation with age ($r=0.306$, $p=0.027$), age of onset ($r=0.296$, $p=0.033$). However, PASI showed a weak insignificant positive correlation with duration of disease ($r=+0.107$, $p=0.451$).

Discussion

This cross-sectional study was carried out to measure serum hsCRP levels in patients with psoriasis and to find out its relationship with the severity of the disease. In this study, the majority (38.5%) of patients belonged to 21-30 years. The mean age was found 35.9±12.9 years with a range from 18 to 70 years. Adrian et al. (2005)²⁵ reported a mean age of 35±15.5 years in their study population. Male predominance was observed in this study with a male-female ratio of 3.1: 1. Globally this ratio is considered to be 1:1 (WHO global report on psoriasis, 2016)²⁶. A study done by Sikder et al. (2017)²⁷, on psoriatic patients at Bangabandhu Sheikh Mujib Medical University, Dhaka, included 30 patients whose age range was 15-67 years, with a mean of 35.8±16.9 years.²⁷ Male-female ratio in that study was 2:1. Jain k et al. (2017) observed a male-to-female ratio of 1.92:1 in their study.¹ The current study showed a slightly higher male-female ratio in comparison to other studies. Various factors can be considered reasonable for this difference in the sex ratio in this current 52 study. Social aspects such as the way men and women perceive their health, their different social roles and levels of tolerability could be considered as some of the important determinants for accessibility to health care facilities. Sometimes cultural and religious barriers impose major stigma explaining why in Bangladesh, women are not privileged enough to seek medical help whenever needed. For these issues, males were thought to be enrolled more in number in this study in comparison to the female patients. The mean age of onset of psoriasis was 32.75±12.46 years with a range from 13 to 57 years. The mean duration of the disease was 3.55±3.16 years with a range from 0.20 to 11.0 years. Jain K et al. (2017)¹ reported the mean age of onset of their study subjects as 32±14.10 years.¹ This finding is almost similar to the current study. In the current study, it was observed that PASI, the most commonly used

clinical assessment tool for disease severity, showed a significant weak positive correlation with age ($r=0.306$, $p=0.027$), insignificant weak positive correlation with duration of disease ($r=+0.107$, $p=0.451$). El-Komy et al. (2020) in their study found that PASI correlated positively with patients' age and duration of psoriasis. 27 In another study by Cakmur&Dervis, (2015) found a positive correlation between disease duration and the severity of psoriasis (PASI). These findings are similar to the current study. In this study, it was observed that the majority (53.8%) of the patients had mild psoriasis ($PASI \leq 10$) and nearly half (46.2%) of the patients had moderate to severe psoriasis ($PASI > 10$). The severity of psoriasis was determined by the PASI score. A PASI score ≤ 10 was considered mild psoriasis and >10 was considered a moderate to severe form of psoriasis 29. The mean PASI score was found 10.07 ± 5.88 . Vadakayil et al. (2018) observed that the mean PASI score in 53 their study patients was 18.15 ± 12.208 . Kumari and Kumar, (2018) found the mean PASI score of psoriatic patients was 15.58 ± 6.51 . 30-31 The mean PASI in patients with psoriasis was 10.36 ± 10.36 . 32 In another study, Gisondi et al. (2012) found the mean PASI in patients with psoriasis was 11.1 ± 10.43 . So, most of the study showed that mean PASI corresponds to the current study. In this study, the mean hsCRP in mild disease ($PASI \leq 10$) was 1.82 ± 1.32 ranging from 0.20 to 4.65 and in moderate to severe disease ($PASI > 10$) was 11.51 ± 6.93 ranging from 4.62 to 25.5. Out of 52 patients, the disease was mild ($PASI \leq 10$) in 28 patients and moderate to severe ($PASI > 10$) in 24 patients. When comparing the mean PASI in each severity group (mild, moderate to severe) to the mean hsCRP in that group, the results were statistically highly significant. It was also observed that the mean hsCRP was higher in the group with maximum severity of psoriasis. Mean hsCRP levels of patients with moderate to severe psoriasis in studies by Keerthana et al. (2016) and Agravatt et al. (2013) were 7.42 ± 3.26 mg/l and 6.26 ± 3.84 mg/l, respectively, with a highly significant correlation with PASI. 23, 34 In another study conducted by Murari (2017) found that the mean hsCRP levels of patients with moderate to severe psoriasis were 10.64 ± 2.23 with a highly significant correlation with PASI. 22 These findings are nearly similar to the current study. The present study found a significant strong positive correlation between hsCRP and PASI ($r=0.795$, $p < 0.003$). Uaratanawong et al. (2016) in

their study observed findings similar to the current 54 studies. 35 Gupta et al. (2019) in their study also found a significant correlation of hsCRP with PASI score ($r=0.48$, $p < 0.001$). 36 This present study considered this fact as the explanation of this observation.

Conclusion

A statistically significant positive correlation was found between the PASI score and serum hs-CRP level. A statistically significant weak positive correlation was found between PASI score and age. A statistically significant weak positive correlation was found between PASI score and age of onset. A statistically insignificant weak positive correlation was found between the PASI score and the duration of the disease.

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Original Article:

Skin Clues to Hidden Cancers: Recognizing Cutaneous Manifestations of Internal Malignancies

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Abstract

Introduction: Cutaneous metastases, though relatively uncommon, are significant clinical markers that can indicate the presence of underlying malignancies. Recognizing cutaneous lesions as signs of internal malignancies is crucial, as timely intervention can enhance survival rates. This study aimed to investigate the cutaneous manifestations of internal malignancies.

Methods: This descriptive longitudinal study was conducted in the Dermatology Outpatient Department and Oncology Department of Bangladesh Medical College Hospital (BMCH), from July 2023 to December 2023. A total of 30 patients were selected as study subjects by purposive sampling technique as per inclusion and exclusion criteria. Collected data were entered, checked and analyzed with the aid of computer software SPSS version-19. **Result:** The study found that cutaneous metastases were most common in patients aged 51-60 years, with a male predominance (60%). Skin involvement was the most frequent (46.7%), followed by nails (26.7%) and hair (16.7%). The scalp was the most common site for skin lesions (26.7%), and ulceration was the most prevalent lesion type (33.3%). There was a significant reduction in symptoms such as itching, burning pain, and wetness between the first and second visits, suggesting positive treatment outcomes. The most common malignancies linked to cutaneous metastases were breast cancer (30%), colon cancer (20%), and lung cancer (23.3%). These findings highlight the importance of recognizing skin changes as early indicators of underlying malignancies, which is particularly valuable in resource-limited settings for early detection and treatment. **Conclusion:** The study underscores the critical role of cutaneous manifestations in the early detection of internal malignancies, particularly in regions with limited healthcare resources. Skin signs can provide an important opportunity for early diagnosis before more advanced diagnostic tools are accessible. The findings highlight the potential for these dermatologic clues to prompt timely interventions and referrals, thereby improving prognosis and treatment outcomes, particularly in underserved populations.

Keywords: Cutaneous Lesion, Internal Malignancy, Ulceration, Itching.

Introduction

The skin is a complex organ system endowed with its own distinctive physical, biochemical, and physiological properties. It interacts with other systems of the body in various disorders. The skin can often be a signpost directing the physician to the organ involved and sometimes to the specific disease process present. Sometimes this disease process is a malignancy. A complete skin assessment should be part of every physical examination because it may provide useful

information regarding the patient's overall health. The skin examination can reveal signs of a predisposition toward malignancy and yield valuable early clues suggesting an underlying neoplastic process.¹ Internal malignancies are accompanied by various skin changes which may be specific infiltrates or non-specific changes. Specific infiltrates that show characteristic malignant cells on histopathological examination. This may occur either by direct extension or by tumour metastasis. Indirect

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involvement of the skin by visceral tumours can cause a variety of characteristic inflammatory, proliferative metabolic, and neoplastic changes and changes due to chemotherapy without the actual presence of tumour cells.² Cutaneous metastases are relatively uncommon, but they are important to recognize because cutaneous metastases indicate a sign of recurrence and widespread metastases have a poor prognosis and the survival period is reduced. The mortality rate is usually high with cutaneous metastases though early recognition offers some chance of survival, especially in those that present with cutaneous metastases. Cutaneous metastasis may precursor the recurrence of malignancy after treatment. Cutaneous metastasis can arise at any age but most cutaneous metastases occur during or after the fifth decade.³ The most common tumor to metastasize to the skin is breast cancer and the most common site is the chest. Other skin manifestations due to chemotherapy, radiotherapy, or hormone therapy are also occurring.⁴ Cutaneous metastases are relatively rare, yet they play a significant role in indicating the presence of internal malignancies, often signifying recurrence and widespread disease, which typically correlates with poor prognosis. The recognition of skin changes associated with internal cancer is critical for timely intervention, as skin lesions can be easily biopsied for histopathological examination. While the skin is the 18th most common site for metastasis, it provides accessible tissue that may yield important diagnostic information. In Bangladesh, cancer remains a significant health issue, with an estimated incidence of approximately 167,256 new cases annually. The leading types of cancer include oesophageal, oral cavity, lung, and breast cancers, which are prevalent across the population, particularly affecting individuals over the fifth decade of life. Understanding the epidemiology of cancer in this region highlights the need for heightened awareness and early detection strategies, especially concerning cutaneous manifestations of internal malignancies.⁵ This study aimed to investigate the cutaneous manifestations of internal malignancies.

Methods:

This descriptive longitudinal study was conducted in the Dermatology Outpatient Department and Oncology Department of Bangladesh Medical College Hospital (BMCH), from July 2013 to December 2013. All patients attending the Dermatology outpatient department and Oncology department of BMCH were considered as the study population. A total of 30 patients were selected as study subjects by purposive sampling technique. A detailed history from a face-to-face interview with the patient, clinical examination, record review, and results of

investigations were evaluated. An informed consent was taken from the patient. All the relevant information from the history, clinical examination, and investigation results were recorded in a predefined questionnaire or data collection sheet. Collected data were entered, checked, and analyzed with the aid of computer software SPSS version-19. Descriptive and analytic statistics were applied where needed. Ethical clearance was taken from the Hospital's ethical committee.

Inclusion criteria: a. Patients with clinically suspected skin manifestations of cancer patients and b. Patients with skin metastases in the internal malignancy confirmed by histopathology. Exclusion criteria: a. Patients below 18 years of age, b. Non-cooperative patient and c. The patient dropped out/expired before investigations were completed.

Result

Table I: Distribution of the respondents' according to socio-demographic characteristics (n=55)

Age (years)	n	%
< 40	04	13.3
41-50	08	26.7
51-60	12	40.0
> 60	06	20.0
Mean \pm SD	51.66 (\pm 7.68)	
Sex		
Male	18	60.0
Female	12	40.0

It was observed that the mean age was 51.7 (\pm 7.7) years, maximum age group was 51-60 years which was 12(40%). The majority 60% were male and 40% were female. Male female ratio 1.5:1. (Table I)

Table II: Affected areas of the disease (N=30)

Affected area	n	%
Skin	14	46.7
Mucous membrane	03	10.0
Nail	08	26.7
Hair	05	16.7

Regarding affected areas, skin involvement was most prevalent, affecting 46.7% of cases. Nails were the second most affected area, observed in 26.7%, followed by hair in 16.7%. Mucous membranes were less frequently affected, involved in only 10.00% of cases. (Table II)

Table III: Areas of onset of the skin lesion (N=30)

Onset	n	%
Scalp	08	26.7
Face	02	6.7
Neck	06	20.0
Upper extremity	02	6.7
Lower extremity	02	6.7
Chest	04	13.3
Abdomen	04	13.3
Back	02	6.7
Perineum	03	09.6

The scalp was the most common site, seen in 26.7% of cases, followed by the neck (20.0%). Chest and abdomen were each affected in 13.3% of cases. Less common areas included the perineum (9.6%), and face, upper and lower extremities, and back (each 6.7%). (Table III)

Table IV: Details spread of the skin lesion (N=30)

Details of spread	n	%
Ulceration	10	33.3
Scale	08	26.7
Papule	04	13.3
Rash	02	06.7
Maculae	04	13.3
Nodule	02	06.7

Ulceration was the most frequent, occurring in 33.3% of cases, followed by scaling in 26.7%, indicative of surface changes often linked to aggressive pathology. Smaller, raised papules were observed in 13.3% of cases, while maculae, flat discolored spots, were also noted in 13.3%, both of which can signal an underlying disease. Less common were nodules and rashes, each in 6.7% of cases. (Table IV)

Table V: Comparison of the skin lesion between the first visit and second visit (N=30)

Skin lesion	First Visit (N=30)	2nd Visit (N=30)	p-value
Itching			
• Yes	14(46.7)	08(26.7)	0.001
• No	16(53.3)	22(73.3)	
Burning pain			
• Present	22(73.3)	08(26.7)	0.04
• Absent	08(26.7)	22(73.3)	
Wet			
• Present	10(33.3)	06(20.0)	<0.001
• Absent	20(66.7)	24(80.0)	
Dry			
• Present	20(66.7)	10(33.3)	0.01
• Absent	10(33.3)	20(66.7)	
Blisters			
• Present	06(20)	06(20)	1.0
• Absent	24(80)	24(80)	
Growth bleeding			
• Present	08(26.7)	02(6.7)	0.06
• Absent	22(73.3)	28(93.3)	

Itching decreased from 46.7% to 26.7% of cases ($p = 0.001$), and burning pain reduced markedly from 73.3% to 26.7% ($p = 0.04$). Wetness also showed a significant decline from 33.3% to 20.0% ($p < 0.001$), while dryness dropped from 66.7% to 33.3% ($p = 0.01$). Blisters remained unchanged, present in 20% of cases at both visits ($p = 1.0$). Growth bleeding decreased from 26.7% to 6.7%, though not statistically significant ($p = 0.06$). Overall, symptom severity appears to lessen by the second visit. (Table V)

Table VI: Clinical type of cancer of the study population (N=30)

Type of cancer	n	%
Ca colon	06	20.00
Ca breast	09	30.00
Ca lung	07	23.33
Lymphoma cutis	03	10.00
Carcinoma of the cervix	02	6.67
Carcinoma of the ovary	03	10.00

The commonest malignancy encountered in Ca colon 06(20%), Ca breast 09(30%), Ca lung 07 (23.33%), Lymphoma cutis 03 (10.0%), Carcinoma of the cervix 02 (6.7%) and Carcinoma of the ovary were 03(10%). (Table VI)

Discussion

An association between systemic malignancy and cutaneous manifestations has long been recognized. The cutaneous features that can occur are numerous and heterogeneous, and many different etiologic mechanisms are represented.⁶ These skin metastases reveal the presence of disseminated malignant disease and can lead to the diagnosis of unsuspected internal tumours or the spread or recurrence of an already diagnosed tumour.⁷ In this study, the mean age of patients with cutaneous metastases was 51.66 (± 7.68) years, with a notable concentration in the 51-60-year age group, which accounted for 40% of cases. The study found a male predominance, with a male-to-female ratio of 1.5:1, mirroring findings by Rajagopal et al., who reported a similar male predominance among their cohort of 300 patients, where 52% were male and 48% were female.⁸ In the study of Ayyamperumal et al. 65% were males and 35% were females, the most common age group affected was in the fifth and sixth decades of life.⁹ The onset of skin lesions varied, with the scalp being the most commonly affected area (26.7%), followed by the chest, abdomen, and back. These results align with a previous study that detailed a slightly different distribution of skin lesion onset but confirmed the scalp and trunk as prevalent sites for metastases.¹⁰ Another study by Krathen et al. has similarly noted variations in the distribution of metastases across different body regions, emphasizing the skin's role as a metastatic site, albeit infrequently.¹¹

Skin manifestations can serve as initial signs of internal malignancies. For example, paraneoplastic pemphigus and pruritus have been noted in association with various cancers, including hepatocellular carcinoma and lymphoma. The study also reported generalized pruritus in several patients with different types of internal malignancies, supporting previous findings by Rajagopal et al. that found pruritus is a common symptom in patients with underlying malignancies.⁸ Specific presentations such as flushing associated with pheochromocytoma and purpura in patients with acute myeloid leukaemia were also noted, emphasizing the varied dermatological manifestations that can accompany systemic diseases. Regarding the characteristics of the skin lesions, ulceration (33.3%) was the most common type, followed by scaling and papules. This distribution aligns with previous studies that have highlighted the diversity of skin manifestations in cutaneous metastases. The current study demonstrat-

ed significant improvement in symptoms such as itching, burning pain, and lesion characteristics between the first and second visits, suggesting a positive response to treatment. In terms of malignancies associated with cutaneous metastases, the study found colon cancer (20%) and breast cancer (30%) to be the most prevalent types. The findings align with Rajagopal et al., who noted a similar trend, particularly in males, where lung and colon cancers were prevalent, while breast and cervical cancers were more commonly seen in females.⁸ The overall prevalence of melanomas as a significant source of cutaneous metastases was also highlighted, confirming existing literature that positions them as one of the leading malignancies linked to skin metastasis. Moreover, Kilaru KR et al. showed in their study that cutaneous paraneoplastic syndromes serve as crucial clinical indicators that can appear before, alongside, or after the diagnosis of a specific cancer. Identifying these syndromes is essential, as it can enhance the likelihood of successful treatment and improve the patient's overall prognosis.¹² In low-resource settings, the ability to recognize cutaneous manifestations of internal malignancies holds particular importance, as it allows for the early identification of potentially life-threatening conditions without relying on costly imaging or laboratory diagnostics. Skin signs like acanthosis nigricans, erythema gyratum repens, and paraneoplastic pemphigus can serve as critical, low-cost screening tools. Recognizing these dermatologic clues can prompt further evaluation and referrals, even when more advanced cancer detection resources are limited.^{13,14}

Limitations of the study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

Conclusion

Cutaneous metastases are important indicators of cancer recurrence and widespread disease, often linked to poor prognosis and reduced survival rates. Although the skin is the 18th most common site for metastasis, its lesions are easily accessible for biopsy and histopathological examination. Recognizing these metastases early can help prolong patient survival, as they may appear before internal visceral metastases. Skin lesions can occur in various locations, including the scalp, face, and extremities, presenting as ulcerations, scales, papules, rashes, maculae, or nodules.

Improvements in symptoms like itching and burning pain were noted between the first and second patient visits.

Recommendation

Depending on the study findings following recommendations were made -

- There is a need to increase awareness in the general public regarding the impact of skin healthcare needs for timely treatment.
- Major concern is to be given to increase awareness in the general population regarding cancer signs and how to prevent it.
- Access to healthcare is to be improved and must be provided at the primary and community level.
- Conducting research across multiple hospitals, particularly in diverse geographical or socio-economic areas, could increase sample size and offer a more representative view of the population. This approach would also help capture regional variations in disease presentation and provide insights into how local factors influence outcomes.
- Future studies could use a cross-sectional approach with data from community-based health screenings or general outpatient visits.

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Conflict of interest

None declared

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Review Article:

Management of Prurigo Nodularis: a review

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Abstract

Prurigo nodularis is a chronic condition of the skin that presents with highly pruritic inflammatory nodules. It may occur alone, or with other skin & systemic diseases. Persistent itching in prurigo nodularis interfere with daily activities and leads a burden on patients well beings. Disruption of neurologic and immunologic function with upregulation of IL-4, IL-31 and neuropeptides are key factors regarding its pathology. Several topical agents (e.g., local corticosteroid, calcineurin inhibitors, calcipotriene, capsaicin, ketamine) & systemic neuro modulators (e.g., gabapentin, pregabalin, paroxetine, aprepitant, naltrexone) and immune modulators (e.g. Methotrexate, cyclosporine, azathioprine, biologics) have been studied to overcome this distressing condition. In addition, maintenance of skin hydration, stress relief and management of associated condition found promising for sustained response to therapy. Recently FDA has approved dupilumab for prurigo nodularis treatment.

Keywords: Prurigo nodularis, Pruritus, neuro modulator, immune modulator.

Background

Prurigo nodularis (PN) is a chronic inflammatory condition of the skin characterized by presence of intensely itchy nodules. This chronic pruritic condition is further exacerbated by repeated scratching, thus a vicious itch-scratch cycle is developed.¹ Though PN may present as an isolated condition, is frequently associated with other skin and systemic disorders.²⁻⁴ Atopic dermatitis is commonly found with PN.⁵ Other dermatosis that may be associated with PN are xerosis cutis, epidermolysis bullosa, mycosis fungoides, post herpetic neuralgia etc.⁶⁻⁷ In addition, systemic disease, such as renal and hepatic impairment, diabetes, malignancy, psychiatric disease, human immunodeficiency virus (HIV) and other infections may be associated with PN.¹

Diagnosis of PN is usually made clinically. Chronic, paroxysmal or continued pruritus with itchy excoriated nodules, papules and plaques that involve symmetrically the extensor extremities are typical presentations of PN, may also appear on abdomen and upper back.⁷ Patients with PN should carefully evaluate to determine the severity of disease, and its impact on patients' quality of life.⁸ Laboratory work up help to

determine other coexisting systemic disease.⁷ Complete blood count, liver and renal function should be measured in all patients.^{9,10} In addition, laboratory markers for diabetes, thyroid disease, HIV, hepatitis B & C and other infectious etiologies are performed if risk factors are present. Histopathological evaluation of PN helps to support the diagnosis and excludes other dermatoses. Additional screening for malignancy and other diseases is considered if any suggestive features exist.⁸

The pathogenesis of PN is not fully understood. Studies define that, neural & immunologic dysregulation are the causal factors.¹¹ Nerve changes within PN lesions are regulated by some neuropeptides. In PN lesions there is increased expression of Substance P (SP), nerve growth factor and calcitonin gene-related peptides. These neuropeptides play a role in the pruritic cycle through mast cells, eosinophils, effects on kappa- and mu- opioid receptors and endorphins.⁵ Dysregulation of these neuropeptides leads to nerve plasticity and an increased dermal nerve fiber density, even though these changes may occur due to frequent scratching behavior.¹

Histopathological studies of PN lesions reveal within the

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dermis there are dense infiltrates of T lymphocytes, eosinophilic granulocytes and mast cells.¹ In PN there is upregulation of cytokines release from Th2 cells such as IL- 4, IL-13, IL-31 and increase histamine, prostaglandin, tryptase, eosinophil cationic protein and neuropeptides.^{1,11} The IL- 31 axis correspond with marked pruritus (1). IL 31 binds to IL-31 receptor A (IL-31RA) and oncostatin M (OSM) beta receptor located on keratinocytes, eosinophil and nerves. Binding of IL-31 to its receptors facilitates the activation of JAK1, JAK2 and STAT3 pathways.¹² All these increases pruritus perception and scratching habits in PN.⁵

Treatment modalities

Management of PN constitute significant challenges, as there is lack of proper treatment guidelines, as well as due to intractable and chronic nature of the disease (8). Different modalities of treatments are available include local moisturizers, topical & systemic therapy. Both neuro and immune modulators are helpful to treat PN.⁵ Decision of therapy usually influenced by severity of disease, existing underlying cause, comorbidities and risk benefit ratio.¹³ Regarding antihistamine therapy, effect on treatment of PN is not conclusive. Some case series found good response with a combination of non-sedating at day time and sedating at night while other studies dose not recommended.^{6,8}

General measures

Lifestyle modifications and behavioral therapies are cornerstone in the management of PN. Maintaining of proper skin hydration is essential. Frequent application of moisturizer helps to restore the skin barrier. Avoidance of pruritogenic stimuli such as- prolonged bathing and over drying, skin irritant- wool clothing's is necessary.¹⁴ Habit reversal therapy is needed to break the itch-scratch cycle.¹⁵

Local therapeutic agents

Topical capsaicin, ketamine, lidocaine and amitriptyline that target the neural component are effective to relief pruritus.⁸ Though, studies found short term response with this treatment.¹⁶⁻¹⁷

Topical corticosteroids, Vitamin D derivatives-calcipotriene, calcineurin inhibitors (CNI) includes tacrolimus & pimecrolimus, are initially use to treat PN (5). They exert their actions through immunomodulatory effects.⁶ Studies found good response with 0.1% betamethasone valerate.¹⁸ Significant response was found with applications 0.1% pimecrolimus cream twice daily for 8 weeks.¹⁹ CNI may use as an alternative of topical steroid where prolong

therapy is needed.⁶

A small RCT compared efficacy between calcipotriene & betamethasone valerate 0.1%, found greater efficacy with calcipotriene.²⁰

For thicker lesions, IL triamcinolone acetonide (TA) is preferred. Combination of IL steroid & cryotherapy showed improved response.²¹ Telangiectasia, hypo & hyperpigmentation may occur with the application of local steroid.⁸

Phototherapy

Narrow band ultraviolet B (NBUVB), psoralen ultraviolet A (PUVA), and UVA monotherapy have been used to treat PN. Ultraviolet lights decreased itch through anti-inflammatory effects.²² UVB radiations also reduces NGF & IL-31.²³ Phototherapy is particularly helpful in patient with extensive PN with comorbidities.⁶ Studies describes significant relief of itch with NBUVB therapy with an average quantity of 23.88±26.00 J/cm².⁶ The combinations of NBUVB and PUVA showed better response in compared with PUVA alone.²² Excimer LASER is an option for localized PN.⁶ Among topical corticosteroid and excimer laser, excimer laser proved more effective.²³⁻²⁴

Gabapentin and Pregabalin

Patient with PN showed a good response with gabapentin and pregabalin.²⁵⁻²⁶ M Mazza at al. described significant improvement after three months of therapy with pregabalin.²⁶

SSRI and TCA

Paroxetine, Fluvoxamine and Amitriptyline have demonstrated efficacy in the management of PN.²⁶⁻²⁷ A pilot study by Zalaudek et al found good response with Amitriptyline, dose schedule was 60 mg daily for 3 weeks, followed by 30 mg daily for 2 weeks and then 10 mg daily for 1 week. Side effects were tolerable.²⁶ Standeret al described efficacy for Paroxetine 20 mg/day in PN.²⁸

Neurokinin 1 receptor (NK1r) antagonist

Aprepitant and Serlopitant are two NK1r antagonists. Studies found substantial improvement with Aprepitant.⁶ A case control study by K. Agelopoulos at al. revealed reduction of pruritus by four weeks treatment with oral Aprepitant (80 mg/day).²⁹ Some studies also described the use of topical aprepitant 1% gel.³⁰ Stander et al found significant improvement with daily 5 mg Selopitant for 8 weeks.³¹

Methotrexate

The immunomodulatory properties of MTX cause relief of pruritus.⁴ In a study, 13 patients received weekly doses ranging from 7.5 -20 mg of MTX for a duration of 6 months and 10 patients experienced remarkable improvement.³² Mariam Al Zaabi successfully treated a case of refractory PN with MTX for 3 months.³³ MTX induced nausea, fatigue & other adverse effects can be minimized by folic or folinic acid supplementation.⁵ The recommended oral weekly dosage of methotrexate in PN is 7.5 to 15 mg. The starting dose is 7.5 mg for two weeks, followed by weekly increments of 2.5 to 5 mg.⁸

Cyclosporine

Cyclosporine is effective for refractory PN. A clinical trial in 14 patients with a daily dose of 3-5 mg/kg of oral cyclosporine showed significant improvement. Maximum response developed after 2 weeks to 12 months therapy.³⁴ In a study by Wiznia et al., eight patients were treated with 2-4 mg/kg of cyclosporine, six patients experienced a significant reduction of symptoms, indicating a successful remission.³⁵ Despite the possibilities of side effects, the majority of patients tolerate this drug well (34). According to expert panel, recommended dose of cyclosporine is 3 mg/kg daily for 2-4 weeks, followed by escalation of dose by 0.5-1mg/kg daily at every 2-4 weeks.⁸ Recently, cyclosporine is considered as a first line drug for chronic refractory PN.⁵

Azathioprine

Study describes relief of pruritus with azathioprine therapy.⁵ In a case report two patients were treated with azathioprine 50 mg twice daily for severe PN, good improvement was found after 2-3 months.³⁶ However, more studies are required to determine the effects. Adverse effects, such as- gastrointestinal upset, altered liver function, infection and myelosuppression are common with Azathioprine.⁵ Regular monitoring and dose adjustment are helpful to minimize toxicity. Dose of azathioprine for management of PN is 50-200 mg/day.⁸

Opioid receptor modulating drugs

Pruritus perception is partly regulated by opioid receptors. Activation of kappa- opioid receptor leads to attenuation of pruritus, while activated mu-opioid receptor intensify itch perception.³⁷ Naltrexone, a mu-opioid receptor antagonist, showed significant antipruritic effect in PN patients.¹ In one study 18 patients with chronic pruritus were treated with naltrexone. The drug dose was oral 50 mg/day and mean duration was 66

days. Though these patients were unresponsive to other treatments, 89% patients showed symptomatic improvement, marked improvement was seen in 50%, while 33% patients were nearly cured.³⁸ Another trial conducted on 65 patients found similar improvement.¹ Although gastrointestinal and neurological adverse effects were observed in some patient, was resolved within 2 weeks.³⁸ Trial with Nalfurafine, a kappa- receptor agonist, in patients with uremic pruritus, with an oral dose of 2.5 and 5 microgram/day for 14 days and intravenous infusion of 5 microgram thrice weekly for 2 weeks showed good response.³⁷ Nalbuphine and Butorphanol are dual kappa- receptor agonist and mu-receptor antagonist, showed efficacy for treatment of PN in few case reports.⁶

Thalidomide and Lenalidomide

In PN, thalidomide and lenalidomide exert their action through neurotoxic effect. In refractory prurigo nodularis, studies found significant improvement with Thalidomide. Although, these medicines are very effective, various side effects limits their use in PN.^{6,39}

Biologics

Nemolizumab: Nemolizumab, an IL-31 RA monoclonal antibody, that binds with IL-31 RA and inhibit IL-31 induced inflammatory cascades and pruritus.¹ In a double-blind clinical trial by Ständer et al., nemolizumab was administered subcutaneously at 0.5 mg/kg every 4 weeks for 12 weeks. Within 48 hours of first dose, there was significant reduction of symptoms. Side effects related to nemolizumab was mild and tolerable.⁴⁰ Gastrointestinal and musculoskeletal adverse effects were found. A molecular study assessed the transcriptome in patients with PN after treatment with nemolizumab for 12 weeks & found downstream of inflammatory mediators.¹

Dupilumab: Dupilumab, a monoclonal antibody, is FDA approved treatment of chronic resistant PN.⁴¹ It inhibits both IL-4 & IL-13 by binding with IL-4 Ra that is shared by the IL-4 & IL-13 receptor complex.⁴² In a retrospective cohort study, patients with refractory PN were treated with Dupilumab and 63.2% of patients showed good improvement after 16 weeks of therapy.⁴³ Tanis R et al treated a refractory case of PN with initial 600 mg subcutaneously, followed by 300 mg at 2 weeks interval. After 8 weeks, reduction of lesions size & symptoms was observed.⁴³ Dupilumab is a well-tolerated drug with mild side effects.⁵ Current dose of dupilumab for PN is 600 mg subcutaneously as induction, followed by 300 mg at 2 weeks interval for maintenance.⁸

Emerging therapy: Cannabinoids are neuromodulators, have been studied for treatment of refractory pruritus, more studies are needed to determine its effects in PN treatment.^{1,8,44} Few studies found mycophenolate mofetil, an immune modulator, is beneficial for treatment of pruritus & PN.⁴⁵ Vixarelimab is a OSM beta receptor antagonist, found effective for treatment of PN.^{(5,46} Abrocitinib, a selective JAK1 inhibitor and Tofacitinib, selective JAK 1 and JAK 3 inhibitor, both showed efficacy in treatment of prurigo nodularis.^{5,47-48)}

Table I: Various antipruritic treatment modalities in patients with prurigo nodularis*

Therapy	Mechanism of action	Recommended dose	Side effects	Level of evidence (LOE)
Local corticosteroid Topical, IL injection	Anti-inflammatory	0.1% betamethasone valerate twice daily for 4 weeks. (18) 15-20 mg/ml IL Triamcinolone acetonide (TA) with 0.05-0.1 mL/lesions	Hypopigmentation, hyperpigmentation, telangiectasia	2b
Calcineurin inhibitors: Tacrolimus Pimecrolimus	Immunomodulation	0.1% tacrolimus twice daily 1% pimecrolimus twice daily for 8 weeks. (19)		2b
Calcipotriene	Immune mediated	Apply twice daily for 8 weeks (24)	Skin irritation	1b
Capsaicin	Substance P depletion	4-6 times daily for 2 weeks to 10 months (16)	Erythema, burning sensation, pruritus	2b
Ketamine, lidocaine, amitriptyline	neuronal	5-10% ketamine, 5% lidocaine and 5% amitriptyline 3 times daily (17)	Redness, burning, itching	4
Cryotherapy with IL		Cryotherapy followed by IL TA 10 mg/ml (21)	none	5
Phototherapy: UVB PUVA	Anti-inflammatory	UVB for 10 weeks (23) PUVA +/- UVB (22)	Transient erythema, burning, blisters	1b
Gabapentin	Neuromodulation	300mg/day, titrated up to 1200 mg/day. (25)	drowsiness	5
Pregabalin	Neuromodulation	75 mg/day for 3 months (26)	Dizziness, sedation	2b
Paroxetine	SSRI	10 mg/days for 3 days, then 20 mg/day, may increase up to 60 mg/day (28)	GI upset and CNS abnormalities	2b
Amitriptyline	TCA	60mg/day-3weeks, 30mg/day-2week, 10mg/day for 1 week (26)	Reduced concentration	2b
Aprepitant	NK1r antagonist	Aprepitant 80mg/day for 4 weeks (29)	Vertigo, nausea	2b
Serlopitant	NK1r antagonist	Serlopitant 5 mg/day for 8 weeks (31)	Fatigue, pharyngitis, diarrhea	1b
Methotrexate	Immunomodulator: Folic acid antagonist	7.5-20 mg/week (8)	Nausea, fatigue, elevated transaminase, myelosuppression	4
Cyclosporine	Immunomodulator: Calcineurin inhibitor	3-5 mg/kg (8)	Gingival hyperplasia, HTN, gastrointestinal upset	4
Azathioprine	Anti-inflammatory	50 mg twice daily (8)	Infection, myelosuppression, gastrointestinal upset, malignancy	5
Naltrexone	Mu-opioid receptor antagonist	50 mg/day (38)	Anorexia, fatigue constipation	4
Thalidomide	Neurotoxic effects	50/100 mg/day (39)	Teratogenicity, peripheral neuropathy	4
Nemolizumab	IL-31 inhibitor	0.5mg/kg every four weeks in subcutaneous route (8)	Gastrointestinal upset, musculoskeletal problem	1b

PUVA: psoralen plus ultraviolet A, UVB: ultraviolet B, *LOE (level of evidence) rating and criteria: 1a, systematic review of RCTs; 1b, individual RCT; 2a, systematic review of cohort studies; 2b, individual cohort study; 3a, systematic review of case-control studies; 3b, individual case-control study; 4, case series and poor-quality cohort

and case-control studies; 5, case reports or expert opinion. RCT, randomized controlled trial.

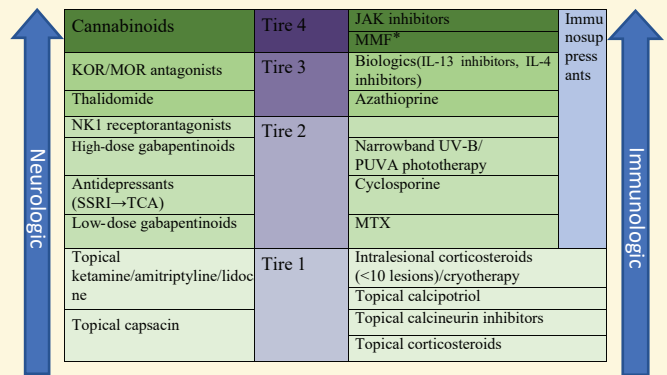


fig 1. PN treatment ladder. This ladder addresses both immunologic and neurologic mechanism (8). SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; UVB, ultraviolet B; PUVA, psoralen plus ultraviolet A; IL-31, Interleukin 31; JAK, Janus kinase; KOR, k-opioid receptor; MOR, μ-opioid receptor; NK1, neurokinin 1; *Investigational therapies

Conclusion

PN is a chronic distressing skin condition. Adequate treatment with neuro & immune modulators in a step-wise pattern, as well as proper skin care & behavioral therapy, helps to relieve pruritus. Further studies are needed to establish a proper treatment guideline.

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Case Series:

"Dermoscopic Perspective of Chik Sign: A Case Series of Post-Dengue Hyperpigmentation"

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Abstract

'Chik sign' is a pattern of facial hyperpigmentation often found in chikungunya and dengue fever. It is an underreported cutaneous manifestation. Here we have highlighted documents of ten patients who were NS1 positive and developed hyperpigmented facial lesions after recovering from dengue fever. This case series has emphasized on clinical presentation, dermoscopic findings and therapeutic outcomes of Chik sign. Dermoscopy revealed a pseudo-reticular pigment network, perifollicular pigment accentuation and brownish globules aiding differentiation from melasma and other pigmentary disorders. All patients responded favorably within 4 to 6 weeks following application of hydroquinone cream and strict sun protection. Awareness and early intervention can ensure favorable outcomes in these cases.

Keywords: Dengue fever, post-dengue hyperpigmentation, dermoscopy, post-inflammatory hyperpigmentation.

Introduction

The "Chik sign," also known as "brownie nose sign" first described in a post-chikungunya fever patient. It is a distinct form of post-inflammatory hyperpigmentation (PIH) characterized by macular pigmentation. Recently, similar findings have been observed in many patients who recovered from dengue fever. Dengue fever is an arboviral disease and endemic in many tropical and subtropical regions. It has documented dermatological (cutaneous) manifestations like maculopapular rashes, petechies during the febrile phase. Post dengue hyperpigmentation, including the "Chik sign" is an underreported phenomenon.^{1,2} This pigmentation commonly involves the face, particularly the periorbital, perioral, nasal, malar and forehead regions, presenting as brown-black macules or patches.^{1,2,3} Dermoscopy serve as a vital diagnostic tool to identify distinguishing pattern in pigmentation, allowing differentiation from melasma, post-inflammatory hyperpigmentation and others melanosis.^{3,6}

This case series aims to document and analyze the clinical and dermoscopic findings of post dengue hyperpigmentation emphasizing the "Chik sign" and it's management outcomes.



fig 1. Chik sign in different patients of post dengue fever

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Case Presentation

Case 1

A 23-year-old lady presented with brown-black macular pigmentation on the periorbital, perioral and nasal areas 10 days after recovering from dengue fever. She denied itching, burning or prior pigmentary disorders.

Case 2

A 39-year-old woman with a 10 years history of melasma noticed few diffuse brown pigmentation over the ala of the nose, malar area, and forehead distinct from melasma, appeared two week after dengue fever. She experienced burning and erythema upon sun exposure.

Case 3

A 58-year-old man, presented with brownish macular hyperpigmentation on the tip & ala of his nose and cheeks seven days after subsiding of NS1 positive dengue fever. He has no other past illness.

Case 4

A 27-year-old man, reported brown hyperpigmented patches on cheeks and nose five to seven days after recovery from fever. He denied prior pigmentary disorders or chronic illness.

Case 5

A 38-year-old man, exhibited brown-black hyperpigmented patches around the perioral areas, nose, chin & cheeks one week post-dengue fever. The pigmentation increased after sun exposure. He denied prior pigmentary disorders.

Case 6

An 18-year-old man experienced mild itchy brownish hyperpigmented patches on the nose, cheeks, and chin 12 days after recovering from NS-1 positive dengue fever.

Case 7

A 22-year-old woman developed erythematous brown patches on her cheeks, nasal and perioral areas for few days after recovery from dengue fever. She denied any pigmentary disorders or systemic illness.

Case 8

A 30-year-old lady presented with mottled pigmentation on face 2 weeks after recovering from dengue fever. She had no other symptoms.

Case 9

A 28-year-old man developed brownish-black macules on the nasal bridge, tip of the nose, cheeks, and perioral area 8-10 days after recovering from dengue fever. He had no associated symptoms, history of melasma, or use of cosmetic products.

Case 10

A 24-years-old man presented with mild itchy brownish hyperpigmented patches over his nose, perinasal area, perioral area and chin for few days. This hyperpigmentation appears 1 week after his recovering

from dengue fever. He complained that pigmentation aggravated on sun exposure. He has no other pigmentary disorders.

Dermoscopic Finding

We did dermoscopy in all these cases and found similar findings:

1. Pseudo-reticular pigment networks.
 2. Patulous follicular opening.
 3. Perifollicular pigment accentuation.
 4. Brownish globules on a diffuse brown background.
- [Figure-2] These findings were consistent with post-inflammatory hyperpigmentation.^{4,6}

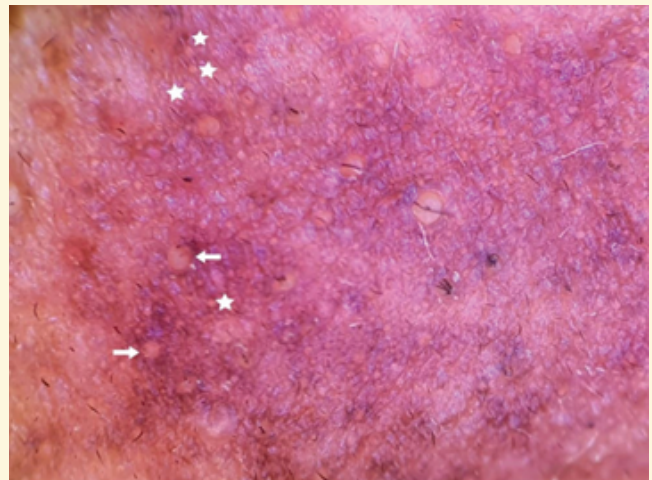


fig 2. **Dermoscopy finding:** Perifollicular pigment accentuation (arrows), patulous follicular opening with brownish background (stars), pseudo-reticular pigment networks

Discussion

The "Chik sign" or post-dengue hyperpigmentation is an underreported sequel of dengue fever. It represents a form of post-inflammatory hyperpigmentation (PIH) associated with viral infection, particularly Chikungunya and now dengue fever.^{3,4} The pigmentation results from melanocytic hyperactivity triggered by inflammatory cytokines, vascular damage and subsequent melanogenesis. UV exposures may exacerbate the condition.⁵

Dermoscopy, a noninvasive valuable tool helps to differentiate post-dengue hyperpigmentation, commonly referred to as "Chik Sign", from other pigmentary disorders such as melasma, lichen planus pigmentosus (LPP), and sebomelanosis. Post-dengue hyperpigmentation is characterized by a pseudo-reticular pigment network, patulous follicular openings, perifollicular pigment accentuation, and brownish globules on a diffuse brown background.⁶ These features are distinct from melasma, which typically shows a homogeneous light brown to gray-brown background with an accentuated pigment network but lacks perifollicular

accentuation and patulous follicular openings.³ In lichen planus pigmentosus, the dermoscopic findings include gray-blue dots or globules, a coarse pigment network, and perifollicular hypopigmentation, which differ significantly from the diffuse and uniform pigment distribution of post-dengue hyperpigmentation.⁷ Seborrheic keratosis, on the other hand, presents with diffuse brownish pigmentation often accompanied by yellowish scales or greasy texture, with sparing of hair follicles, which is not observed in post-dengue cases.⁸ These dermoscopic differences highlight the unique features of "Chik Sign" in post-dengue hyperpigmentation, underscoring its distinction from other pigmentary conditions, thereby aiding in accurate diagnosis and management.

Treatment & Outcome

All patients were treated with hydroquinone cream (a tyrosinase inhibitor) and advised strict sun protection. Results were satisfactory with significant improvement of pigmentation after 4-6 weeks of treatment.[Figure-3].



fig 3. Showing post treatment improvement of Chik sign

Conclusion

The "Chik sign" traditionally associated with chikungunya, is an emerging cutaneous sequel of post-dengue fever. Dermoscopy aids, its differentiation from other pigmentary disorders, enabling effective management with topical hydroquinone and photoprotection. Early intervention is crucial to prevent chronic pigmentation.

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Case Report:

Angiolymphoid hyperplasia with eosinophilia

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Abstract

Angiolymphoid hyperplasia with eosinophilia (ALHE) is a rare benign reactive inflammatory lesion causing blood vessel proliferation and a dense eosinophilic inflammatory infiltrate presents as subcutaneous nodules in middle-aged women's head and neck region. It commonly presents reddish pruritic nodules and papules of the ear and the periauricular region, which is difficult to eradicate. Orbit, colon, peripheral arteries, lacrimal gland, parotid gland, and throat are the extracutaneous sites.

Keywords: Angiolymphoid hyperplasia with eosinophilia, (ALHE)

Introduction

Angiolymphoid hyperplasia with eosinophilia (ALHE) is a rare vascular disorder described in 1969 by Wells and Whimster.¹ This idiopathic condition presents in adults as isolated or grouped papules, plaques, or nodules in the skin of the head and neck. Lesions in the skin of the periauricular region, forehead or scalp are the most presented sites. Hands, shoulders, breasts, penis, oral mucosa and the scrotum are the rarely involved site. Extracutaneous sites have also been noted to include the orbit, peripheral arteries, the colon, the mandible, the lacrimal gland, the parotid gland and the throat.²⁻⁴ It by preference involves females between 20 and 40 years old, being of benign character. Vascular malformation or local trauma are considered as the potential etiological factors. ALHE usually manifests as a cluster of lesions on the skin of the head and neck with classic red-brown nodules. Similar cutaneous lesions may also appear on the trunk, extremities, and genitalia.²⁻⁴ Though the lesions are benign, they may be hemorrhagic (25%) in addition to causing itching (37%) or pain (20%). Peripheral eosinophilia has been found in up to 20% of cases.⁵⁻⁶ As the name implies, the diagnosis is made histologically by the presence of vascular proliferation (angio-hyperplasia), lymphoid follicles (lymphoid hyperplasia) and a prominent eosinophilic infiltrate (eosinophilia).⁷

Case Report

A 22-year-old patient presents an unremarkable medical history. Initially, she consulted another institute with multiple pruritic right ear auricle skin lesions for one and a half years. The lesions started as reddish papules that gradually enlarged to form nodules with the development of new papules. There was mild bleeding after itching. She noticed ulcerations and discrete bleeding after scratching caused by pruritus. On examination, discrete, well-defined, erythematous papules and nodules of different sizes were found over the right auricular and post-auricular region and the nodules were firm and tender. She didn't suffer local trauma or any constitutional symptoms (Pic. 1 & 2). Her physical examination proved insignificant, without any lymphadenopathies or salivary gland enlargements. Dermoscopy revealed Yellow to orange areas on the lesions intersected by fine horizontal telangiectasia. Consequently, a laboratory workup and an excisional biopsy of one dermatologic lesion were conducted. The Biopsy exhibited Mild acanthosis in the epidermis, dense perivascular infiltration of lymphocytes and eosinophils with thick-walled blood vessels in the dermis. The patient underwent electrofulguration for the skin lesions, which resulted in complete resolution with no recurrence. This successful outcome demonstrates the potential effectiveness of this treatment method for ALHE. Follow-up: Six-month monthly follow-ups were done,

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followed by six-month follow-ups every six months for any possible progression, the appearance of new lesions, and potential therapeutic changes. No new lesion was seen up to 1 year.

Discussion

ALHE is a benign, slowly growing tumour with a still unclear etiopathogenesis. It can be self-limited and characterised by intense vascular proliferation.⁷ More clarity exists in the literature regarding ALHE and Kimura's disease. Both present nodules, preferably on the head and cervical region but in ALHE, they tend to be much more erythematous than in Kimura's disease, where the lesions are normochromic. They also have similar histopathological features, such as involvement of the dermis and subcutaneous infiltrate comprising lymphocytes and eosinophils, proliferation of endothelial cells and the absence of adnexal structure involvement.^{3,7} Asian males are more prone to Kimura's disease, which has a triad of painless subcutaneous masses, usually unilateral, in the head and neck region. There is peripheral eosinophilia and a significant increase in immunoglobulin E levels in the tissues. Salivary gland enlargement may also occur. Histopathologically Kimura's disease differs from ALHE for being mainly a disorder of the lymphoid follicles, without irregular blood vessels and with non-protruding endothelial cells in the vascular lumen but always presenting an increased number of eosinophils that may extend to the muscular fascia.⁸

Surgical excision is indicated where relapse is common. Other reported treatments include cryotherapy, local radiotherapy, topical or intralesional corticosteroids, imiquimod, acitretin and laser therapy (dye laser, CO2 laser). While these treatments may be effective, they also risk potential complications or side effects, which should be considered when choosing a therapeutic approach.

Follow-up: Six-month monthly follow-ups were done, followed by six-month follow-ups every six months for any possible progression, the appearance of new lesions, and potential therapeutic changes.

Conclusion

Angiolymphoid hyperplasia with eosinophilia presents a therapeutic dilemma due to the wide variety of proposed treatments, but there is a lack of comprehensive data on most of them. Although the disease is not deadly by itself, it usually presents with disfiguring lesions that can severely affect the patient's quality of life. This underscores the urgent need for further research and concerted efforts to find an effective cure and a unified therapeutic approach.



fig 1. Discrete, well-defined, erythematous papules and nodules on right auricle (a) and post auricular region (b) before treatment



fig 2. post-treatment follow up after one year

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Conflict of interest: None

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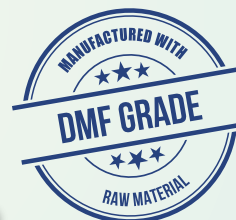
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