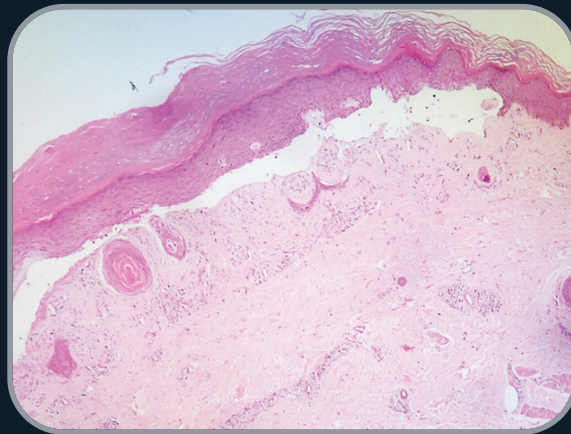


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Volume 02 Issue 01 January 2022



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Editorial

Artificial Intelligence in Dermatology: Prospects and Where Bangladesh Stands

The evolution of machines runs parallel to human eager, spirit and enterprise, and has evolved from simple tools to modern-day high-tech computers. Dependence and reliance on machines have penetrated almost every aspect of human life including medicine. One of the most discussed advancements of modern technologies in recent times is artificial intelligence (AI).

John McCarthy defined Artificial intelligence as “the science and engineering of making intelligent machines, especially intelligent computer programs”.¹ The term applies to a broad range of items in medicine such as robotics, medical diagnosis, medical statistics, and human biology.

Artificial intelligence has been applied in the field of medicine since as early as the 1950s when physicians made the first attempts to improve their diagnosis using computer-aided programs. AI is continuously evolving from conventional AI (100% humans) to machine learning (50% humans and 50% computers) to deep learning (10% humans and 90% computers).² One of the key components of AI is artificial neural network, which is a subset of machine learning, based on algorithms that are designed to recognize patterns that are inspired by the human neural network.

Artificial intelligence is used for medical tasks like diagnosis, prognosis, and therapy with the assistance of different imaging techniques. The difference between traditional statistical analysis and artificial intelligence is that the later utilizes data-mining and pattern recognition capabilities to analyze structured and unstructured data. AI techniques approved by the US Food and Drug Administration (FDA) for clinical use by September 2018 include products to identify signs of diabetic retinopathy in retinal images, recognize signs of stroke in CT scans, visualize blood flow in the heart, detect skin cancer from clinical images captured using a mobile app.²

In the last decade or so, AI is gradually finding its relevance in different fields of dermatology including skin cancer, eczema, and psoriasis. Automated detection of skin lesion using images has extended

beyond melanoma to encompass pigmentary skin lesions, non-melanocytic skin cancers, psoriasis, skin rash, and onychomycosis among other skin diseases.³ Researchers have been

exploring the usefulness of AI to improve or supplement current screening processes in melanoma and non-melanoma skin cancer.

Stanford University published a study on deep learning of skin tumors. They demonstrated classification of skin lesions using a single convolutional neural network. They trained a convolutional neural network using a dataset of 129,450 clinical images of 2,032 different diseases. They tested its performance against 21 board-certified dermatologists on biopsy-proven clinical images with two critical binary classification of cases: keratinocyte carcinomas versus benign seborrheic keratosis; and malignant melanomas versus benign nevi. It was found that the machine had a competence comparable to board-certified dermatologists in identifying and classifying skin cancer.⁴ Fujisawa et al. develop an efficient skin cancer classification system with a relatively small dataset (4867) of clinical images obtained from 1842 patients diagnosed with skin tumors. Overall classification accuracy was 76.5%.⁵ Han et al. tested the use of a deep learning algorithm to classify the clinical images of 12 skin diseases including melanoma with the average sensitivity and specificity for all the conditions was 85.1% and 81.3%.⁶ Brinker et al. also advocated for a melanoma classification benchmark, which they derived from their result for future comparisons. Their benchmark found that dermatologists had an overall sensitivity of 89.4% and specificity of 64.4% in detecting melanoma.⁷ Shrivasta et al., compared the ability of several applications at classifying the severity of psoriasis lesions. The systems described achieved average sensitivities between 93.81 and 99.76% and average specificities between 97 and 99.99%.⁸ Beyond psoriasis, applications have been described classifying acne, lichen planus, pityriasis lichenoides and dermatomyositis. Huang et al. developed a multi disease classifier that could analyze 34 attributes (e.g., erythema, scaling, definite borders, etc.) and differentiate several papulosquamous diseases such as psoriasis,

seborrheic dermatitis, lichen planus, pityriasis, and chronic dermatitis.⁹ Seite et al. developed A smartphone that grades and classifies types of acne lesions (e.g, comedonal, inflammatory, post inflammatory hyperpigmentation, etc).¹⁰

Although most of these experiments relied on images of skin, one application assessed muscle ultrasound images and differentiated between normal muscle, dermatomyositis, polymyositis, and inclusion body myositis with accuracies between 76.2 and 86.6%.¹¹ There are artificial neural networks for differentiating atopic dermatitis from unaffected skin using information derived directly from images.

Machine learning has been used in various aspects of patient identification, risk prediction, diagnosis, disease subtype classification, disease progression and outcome and monitoring and management of autoimmune disorders like systemic lupus erythematosus, systemic sclerosis, vitiligo, psoriatic arthritis, rheumatoid arthritis, and systemic vasculitis.

Different techniques have been applied in the field of AI. Confocal microscopy is a technique that uses lasers and fluorescence to create a three-dimensional image of a sample. Direct immunofluorescence (DIF) is a technique used in the laboratory to diagnose diseases of the skin, kidney, and other organ systems. It is also called the direct immune fluorescent test or primary immunofluorescence. Digital dermoscopy is able to identify a number of skin lesion using a pattern recognition method. Trichoscopy software Trichoscale AI is a revolution in the quantification of hair growth and pattern of hair loss.

Although AI is fast emerging in the field of dermatology, the term artificial intelligence is still novel in the context of Bangladesh. Dermatologists are still lagging behind in terms of using updated methods for diagnosing dermatological disease, e.g dermoscopy, trichoscopy and onychoscopy. DIF still has limited use, not available countrywide. A very lower percentage of dermatologists have their dermoscopy in place which is now widely being used in developed countries. Developing a dataset with pattern recognition images through neural network is the key step in combining AI with conventional methods. Such tool or software need to be developed for diagnostic accuracy. Correlation of clinical disease with biopsy proven skin lesion is the key to diagnosis, where there is limited option to cross check or compare with other similar lesions;

thus, increasing the probability of human error. Moreover, the competency of pathologists is crucial here which often poses a barrier in diagnosis. AI can offer a second opinion with better accuracy if it can be utilized properly. Not only development of tool is necessary, giving training to a vast majority of dermatologists is also essential to make it operational.

AI is fast emerging in the field of dermatology. The most progress thus far has taken place in the field of melanoma diagnosis, followed by ulcer and psoriasis assessment tools, then followed by numerous less frequently studied applications. It can revolutionize patient care, particularly in improving the sensitivity and accuracy of screening of skin lesions including malignancies. The success of such technology in dermatology will depend on the benefits it provides to the vast majority of the general population and also to the treating doctor. The application of computational methods is being used in dermatology for faster data processing to give better and more reliable diagnoses. Currently, most of the data are based on Western studies; hence, studies from this part of the world are essential. Particularly a country like Bangladesh where disease burden is high with variable presentation and limited scopes to achieve diagnostic accuracy.

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A comparative study of serum 25-hydroxy vitamin D level in patients with alopecia areata and healthy control

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Abstract

Background: Alopecia areata (AA) is a type of non-scarring patchy loss of hair in hair-bearing areas and is mostly of autoimmune origin. Vitamin D and its receptor are responsible for a normal hair cycle. Recent studies have shown that vitamin D deficiency is rather frequent among alopecia areata patients.

Objective: To assess serum 25-hydroxy vitamin D level in patients with alopecia areata and to correlate it with the severity of alopecia areata.

Methods: This case-control study included 30 clinically diagnosed cases of alopecia areata and 30 healthy individuals in the department of Dermatology & Venereology, BSMMU, Dhaka. This study was conducted from July 2018 to June 2020. Written informed consent was taken from each patient and interviewed by semi-structured questionnaire. Disease severity was measured by Severity of Alopecia Tool (SALT) score. Five milliliter of venous blood was collected from each patient and control; the sample was preserved and analyzed for 25(OH) D level by automated chemiluminescence immunoassay method in the Department of National Institute of Nuclear Medicine and Allied Sciences, BSMMU. Statistical analysis was carried out by using SPSS software version 23.0. For all statistical tests, a p-value of less than 0.05 was considered significant.

Result: The mean serum 25-hydroxy vitamin D levels of cases was 11.30 ± 4 ng/ml, in control group the mean was 19.62 ± 5.09 ng/ml, the difference was statistically significant ($P < 0.001$). A significant moderate negative correlation was found between SALT score and vitamin D level ($P < 0.024$; $r = -0.411$) but a non-significant weak negative correlation was found between the duration of the disease and vitamin D level ($P < 0.071$; $r = -0.342$).

Conclusion: The serum vitamin D level was low in patients of alopecia areata and normal healthy controls but it is lower in AA patients. There was a significant negative correlation between the levels of serum Vitamin D and the severity of alopecia areata.

Key Words: Alopecia areata, Vitamin D, BSMMU.

Introduction:

Alopecia areata (AA) is a common form of nonscarring alopecia characterized by hair loss with no clinical signs of inflammation and can affect the scalp and/or any hair-bearing area of the body.¹⁻²

It can occur at any age. The highest prevalence of alopecia areata is between 30-59 years of age.³ Family members are affected in 8.7-20% of cases.⁴ Scalp is the most common site (90%). AA is classified

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according to the extent and pattern of hair loss.⁵ It can be patchy AA, alopecia totalis in which entire scalp and alopecia universalis (AU) where total body hair is involved.⁶

The etiology of AA is not exactly known; however, genetic predisposition, autoimmunity, and environmental factors have been suggested to play a role.⁷ Autoimmune etiology has been proposed on the basis of its association with various autoimmune diseases, the presence of autoantibodies, the presence of inflammatory lymphocytes around and within the affected hair follicles and the ability to promote hair regrowth with the use of immunosuppressive agents.⁸ The connection between vitamin D deficiency and some autoimmune diseases, has been reported.⁹ Therefore, vitamin D deficiency may be a risk factor for the development of alopecia areata.¹⁰

AA is an autoimmune disease mediated by T-lymphocytes in which autoantigens play an important part in activating T-cells and is associated with other autoimmune diseases.¹¹⁻¹² IFN- γ , secreted by human CD4⁺ T cells expressed in alopecia areata lesional skin, is the main element of alopecia areata immunopathogenesis.¹³⁻¹⁴ The anagen hair follicle (HF) is normally an immune-privileged (IP) site. IFN- γ contributes to the collapse of the IP site through an increased follicular expression of MHC class I and II molecules.¹⁵ Vitamin D3 significantly inhibits the production of IFN- γ .¹⁶ In inactive SLE, higher levels of IFN- γ was found in lower levels of vitamin D deficient patients and IFN- γ was 150% higher in patients with vitamin D deficiency.¹⁷ So it is justified to assume that vitamin D might play a role in the collapse of IP of the anagen hair bulb.

Cytokines involved in the pathogenesis of AA, most notably interferon (IFN)- γ and interleukin (IL)-15, are dependent on the Janus kinase and signal transducers and activators of transcription (JAK-STAT) pathway.¹⁸ Vitamin D had an inhibitory effect on the JAK/STAT pathway.¹⁹

Nrf2 is the genes activated by vitamin D.²⁰ Nrf2 encodes the transcription factor, nuclear factor (erythroid-derived 2)-like 2 (Nrf2), is defined in the hair follicle and activation of Nrf2 can maintain hair growth during oxidative stress.²¹ 1,25(OH)₂D₃ prevents leptin-induced oxidative stress in human endothelial cells by activating the Nrf2 system. Active vitamin D3 deficiency causes higher oxidative stress through inhibiting transcription of Nrf2 and enhancing DNA damage.²² Currently, Vitamin D has

been shown as an antioxidant.²³

1,25-dihydroxy vitamin D inhibits the function of Th17 cells, which are potent inducers of autoimmune diseases and it enhances regulatory T cells, which play a key role in suppressing autoimmune responses.²⁴

In the light of this information about the role of vitamin D on autoimmunity and hair cycle, it can be hypothesized that vitamin D deficiency may have a role on alopecia areata. The aim of this study was to evaluate the vitamin D status in patients with alopecia areata and investigate its relationship with the severity of alopecia areata.

Methods:

This case-control study was conducted in the Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University and Department of National Institute of Nuclear Medicine and Allied Sciences, BSMMU, Shahbagh, Dhaka, from July 2018 to June 2020.

A total of 30 patients with alopecia areata were enrolled from the outpatient department (OPD) of dermatology and venereology (case) and the same number of age-sex matched healthy attendants of patients were included (control). Inclusion criteria were i. clinically diagnosed case of alopecia areata, ii. individual of either sex, iii. age >18years, iv. healthy adults who were age and sex matched with the cases and v. participants who were willing to give written consent to undergo the study. Exclusion criteria were: i. pregnancy, ii. lactation, iii. obesity (BMI >25), iv. smoking, v. alcoholism, vi. history of taking medication known to affect serum 25-hydroxy vitamin D level and vii. history of medical conditions known to affect serum 25-hydroxy vitamin D level.

Independent variables were age (year), sex (male/female), occupation, family history, sun exposure/day (minute), total number of alopecia areata patches, size of alopecia areata patches, location of alopecia areata patches, duration of alopecia areata, serum vitamin D level (ng/ml). Dependent variable was SALT score (%).

The study was approved by the institutional review board of BSMMU. All patients and control subjects gave their informed consent to take part in this study. Relevant history was taken regarding present illness, duration of the disease, onset, extension, family history. Every subject was subjected to full

history taking and physical examination for assessment of clinical type and/or pattern of hair loss according to the number of lesions: one patch, two patches, multiple patches, alopecia totalis (AT) or alopecia universalis, and extent/severity of hair loss according to SALT score. The scalp was divided into four areas, namely: (i) vertex: 40% (0.4) of scalp surface area; (ii) right profile of scalp: 18% (0.18) of scalp surface area; (iii) left profile of scalp: 18% (0.18) of scalp surface area; and (iv) posterior aspect of scalp: 24% (0.24) of scalp surface area. The percentage of hair loss in any of these areas was multiplied by the percentage of the surface area of the scalp in that area. SALT score was the sum of the percentage of hair loss in all the above-mentioned areas. Subgrouping of patients into SALT subclasses was done as follows: scalp (S): S0, no hair loss; S1, <25% hair loss; S2, 25–49% hair loss; S3, 50–74% hair loss; S4, 75–99% hair loss; and S5, 100% hair loss. Body (B) hair loss was assessed as: B0, no body hair loss; B1, some body hair loss; and B2, 100% body (Excluding scalp) hair loss.

Five milliliter of venous blood sample was collected from each subject. The serum concentration of 25-hydroxy vitamin D was measured by automated chemiluminescence immunoassay method introduced by siemens and adapted to an ADVIA centaur analyzer in the Department of National Institute of Nuclear Medicine and Allied Sciences, Bangabandhu Sheikh Mujib medical University. Particulars of the patients, SALT score and the serum level of vitamin D were recorded in a preformed data collection sheet.

Statistical analysis was carried out by using the Statistical Package for the Social Sciences (SPSS) software version 23.0 for windows (SPSS Inc, Chicago, Illinois, USA). Quantitative variables were expressed as mean $\pm$ standard deviation and categorical variables were expressed as percentages. Independent student t-test was used to compare serum vitamin D level in between patients with alopecia areata and healthy individuals. Chi-Square test was used for comparing other categorical variables. ANOVA test was done to see the difference among the groups of variable. Pearson's correlation coefficient test was used to see the relation between serum vitamin D levels and duration of the diseases in patients. A P-value was considered to be statistically non-significant if >0.05

and statistically significant if ≤ 0.05 .

Results:

Table I: Showed that 21(70.0%) patients in the case group and 19(63.3%) in the control group belonged to the age group 21-30 years, second common age group 31-40 years, in cases 20% and 36.7% control. The mean age was found 27.11 ± 5.0 years in the case group and 29.1 ± 4.7 in the control groups. There were no significant differences between the two groups regarding their mean age.

Table-1: Comparison of age between two groups (n=60)

Age (in years)	Group A (Case) (n=30) No. (%)	Group B (Healthy) (n=30) No. (%)	p-value
18-20	3(10.0%)	0(0.0%)	
21-30	21(70.0%)	19(63.3%)	
31-40	6(20.0%)	11(36.7%)	
Total	30(100.0%)	30(100.0%)	
Mean $\pm$ SD	27.1 $\pm$ 5.0	29.1 $\pm$ 4.7	0.111
Range (Years)	19-40	21-38	

Data were expressed as frequency and percentage and mean $\pm$ SD

Unpaired student t-test was performed to compare between two groups.

It was observed that 21(70.0%) alopecia areata (AA) patients were male and 9(30.0%) were female in the case group and in the control group 23(76.7%) patients were male and 7(23.3%) were female. Males were predominant in both groups. Statistical difference between the two groups was insignificant.

The majority of patients 19(63.3%) had a duration of disease below 1 year. Mean vitamin D gradually decreased with increased duration of disease, but statistically not significant ($p=0.067$). Maximum patients 13(43.33%) had multiple alopetic patches followed by one AA patches 8(26.66%), two patches in 6(20.0%) cases, 2(6.6%) alopecia totalis and 1(3.33%) ophiasis cases. Table II shows the number of alopetic patches that were presented in each patient

Table-II Distribution of the study AA patients by number of AA patches (n=30)

Number of AA patches	Frequency	Percentage (%)
One	8	26.66
Two	6	20
Multiple	13	43.33
Ophiasis	1	3.33
Alopecia totalis(AT)	2	6.66
Total	30	100

According to SALT scoring severity of AA, maximum 25 (83.3%) patients had severity S1 (<25%) followed by 6.7% patients had S2 (25-49%), 6.7% had S5 (100.0%) and 3.3% had S3 (50-74%) (table III)

Table III: Distribution of the cases according to SALT scoring (n=30)

Disease severity	Frequency	Percentage (%)
S1 (<25%)	25	83.3
S2 (25-49%)	2	6.7
S3 (50-74%)	1	3.3
S4 (75-99%)	0	0.0
S5 (100%)	2	6.7
Total	30	100

Serum mean vitamin D level in S1 (<25%) was 12.3 ± 4.23 ng/ml followed by 8.1 ± 0.49 ng/ml in S2(25-49%), 6.20 ng/ml in S3(50-74%) and 4.9 ± 0.50 ng/ml in S5 (100%). Mean Vitamin D was significantly different among the type of disease severity and gradually decreased according to disease severity ($p=0.043$). (table IV).

Table IV: Serum vitamin D level in cases according to SALT scoring (n=30)

Disease severity	Serum vitamin D Mean $\pm$ SD ng/ml	p-value
S1 (<25%)	12.3 ± 4.23	.43 ^s
S2 (25-49%)	8.1 ± 0.49	
S3 (50-74%)	6.20	
S4 (75-99%)	-	
S5 (100%)	4.9 ± 0.50	
Total	11.30 ± 4.41	

Data were expressed as mean $\pm$ SD
p-value measured by ANOVA test, s= significant

Serum vitamin D level was 100% deficient in the case group and in the healthy control group 56.7% patients had vitamin D level deficient and 43.3% insufficient. The difference between the two groups was statistically significant (table V)

Table - V Distribution of the serum Vitamin D status between two groups

Serum Vitamin D (ng/ml)	Group A (Case) (n=30) No. (%)	Group B (Healthy) (n=30) No. (%)	P value
Deficient (<20 ng/ml)	30(100.0%)	17(56.7%)	<0.001
Insufficient (20-30 ng/ml)	0(0.0%)	13(43.3%)	
Total	30(100.0%)	30(100.0%)	

Figures in the parentheses indicate the corresponding percentage;
P value was obtained from Chi-squared Test (χ^2)

Pearson's correlation coefficient test was done to see the correlation of serum vitamin D level with the SALT score and duration of AA have shown in the table (VI). There is a significant moderate negative correlation with SALT score ($r = -0.411$, $p=0.024$) and an insignificant moderate weak negative correlation with duration of AA ($r = -0.342$, $p=0.071$).

Table -VI: Correlation of serum vitamin D (ng/ml) with SALT and duration of AA (n=30)

	Serum vitamin D level ng/ml		
	r value	p value	
SALT	-0.411	0.024	Significant
Duration of AA	-0.342	0.071	Not significant

Pearson's correlation coefficient test

Discussions:

The present study was designed to measure serum

vitamin D levels in patients with alopecia areata and to find out the relationship with severity of the disease. The mean age of the respondents in this study was 27.1 ± 5.0 years. Rehman F et al. reported the mean age of alopecia areata cases was 26 ± 12.89 years in their study.²⁵ In a study by Siddappa H et al. the mean age was 24.52 ± 10.06 years.²⁶ Daroach M et al. also found the mean age of alopecia areata patients 28.97 ± 9.96 years.²⁷ Gade VKV et al. reported the mean age of the cases as 32.73 ± 10.43 years.¹⁰ These findings are almost similar to the current study.

In this study male to female ratio was found 2.3:1. Rehman F et al. found the ratio as 2.06:1 in their study.²⁵ Siddappa H et al. in 2019 reported male to female ratio 2.57:1.²⁶ Abdel Fatth et al. also found male predominance in their study and the ratio was 3.5:1.²⁸ Daroach, M. observed male to female ratio as 1.8:1.²⁷ These findings are almost similar to this current study where male patients were predominant. On the other hand, there are several studies where female alopecia areata cases were predominant. Gade VKV et al. reported the male to female ratio as 1:2.21 in their study.¹⁰ Ghafoor R and Anwar MI also found female dominance and the ratio of male to female was 1:1.5.²⁹ Globally this ratio is considered as 1:1.³⁰

The present study found that maximum patients had multiple patches (43.33%). Ghafoor R and Anwar MI in their study found single patch 6(20%), multiple 15 (50%), ophiasis 3(10%), alopecia totalis (AT) 4(13.33) and alopecia universalis (AU) 2 (6.6%).²⁹ Erpolat S et al. conducted a case control study with 41 alopecia areata cases where he found 36.6% single patch and 63.4% multiple patches.³¹

This present study reported that the vitamin D level of alopecia areata patients was relatively much lower than the healthy group and was statistically significant (p value<0.001). A similar result was found in other studies. Bhat YJ et al in their study observed a significant lower level of serum vitamin D in comparison to the control (16.6 ± 5.9 ng/ml and 25.49 ± 1.02 ng/ml; $P < 0.001$).³² Siddappa H et al. found the mean serum vitamin D level significantly lower in cases as compared to the controls (18.90 ± 8.32 vs 28.21 ± 18.32 ng/mL; $P < 0.001$).²⁶ Mean serum Vit.D level in patients and controls was 7.65 ± 4.50 ng/ml and 15.8 ± 11.47 ng/ml, respectively with a statistically significant difference, $P = 0.001$ reported by Daroach M.²⁷ The current study found a high prevalence of vitamin D deficiency in both case and control groups. Daroach M reported 29 (96.7%)

patients and 22 (73.3%) controls were found to be Vit. D deficient in their study.²⁷ Siddappa H et al. found vitamin D deficiency among more cases than controls (64% vs 38%; $P < 0.001$).²⁶

Vitamin D deficiency among the normal population was variably detected in different studies. Mansour et al. demonstrated 90% prevalence of vitamin D deficiency in apparently healthy hospital staff and health care professionals.³³ Zargaret al. found that 82% of healthy subjects had vitamin D deficiency.³⁴ The present study measured the severity of alopecia areata of 30 patients by SALT scoring. The mean vitamin D level gradually decreased according to the severity of disease by SALT score and was statistically significant (p value-0.043). The study found a statistically significant negative correlation between serum vitamin D level and SALT scoring ($r = -0.411$, $p = 0.024$). Similarly, Siddappa H et al. found a statistically significant inverse correlation between SALT score and serum vitamin D levels ($r = -0.298$, $P < 0.05$).²⁶ A significant negative correlation between the severity of AA assessed by SALT score and Vitamin D levels ($P = 0.000$; $r = -0.474$) by Rehman F et al., Cerman AA et al., Attawa EM et al., Bhat YJ et al. and Daroach M et al. found a significant inverse correlation between SALT score and serum vitamin D levels.^{25,27,32,35-36}

The duration of disease ranged from 4 months to 10 years with a mean duration of 1.46 ± 1.81 years. The study observed a gradual declination of mean vitamin D with increasing duration but it was not statistically significant (p value-0.067). In this study, an insignificant negative correlation was found between serum vitamin D level and duration of the disease of alopecia areata patients ($P = 0.000$; $r = -0.474$). A similar result was found in the study of Bhat YJ et al. ($P = 0.05$; $r = -0.474$).³² On the other hand a negative significant correlation of serum vitamin D level and duration of the disease of alopecia areata was observed in the study of Daroach M et al. ($P = 0.03$; $r = -0.224$) and Gade VKV ($P = 0.01$; $r = -0.672$).^{27,10} So a further large studies incorporating cases of different duration are needed for a definitive conclusion.

Conclusions:

This study found that most of the cases of alopecia areata and more than half of the healthy controls were serum vitamin D deficient. The cases of alopecia were relatively more deficient than the healthy controls. There was a negative correlation between the vitamin D levels and the severity of AA.

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Conflict of interest:

No conflicts of interest

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Efficacy and safety of once-daily dapsone 7.5% gel monotherapy for mild to moderate acne vulgaris: A comparative study with adapalene 0.1% gel monotherapy

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Abstract

Background: Inflammation and infection are two important etio-pathological factors of acne. Dapsone has both anti-inflammatory and antibacterial functions in acne vulgaris. **Objective:** To see the efficacy and safety of once-daily dapsone 7.5% gel as monotherapy for mild to moderate acne vulgaris compared with adapalene 0.1% gel monotherapy. **Methods:** This was a randomized, open-label, comparative study, conducted over 47 patients with mild to moderate acne (lesion count 3-30). Patients were randomly enrolled into two treatment groups (A and B). Patients were instructed to apply a thin layer of dapsone 7.5% gel (group A, n=23) adapalene 0.1% gel (group B (n=24) on face. Inflammatory, non-inflammatory and total lesions were counted and adverse effects were assessed at weeks 0, 4, 8 and 12. **Results:** All forms of acne lesions were reduced from baseline to onwards in both groups. Percent reduction of total lesions and non-inflammatory acne lesions were statistically similar in both groups ($p>0.05$) but for inflammatory lesions, dapsone 7.5% gel is less effective than adapalene 0.1% gel ($p<0.05$). Adverse effects were also indifferent between the two groups ($p>0.05$). **Conclusions:** Dapsone 7.5 gel is effective and safe as monotherapy for acne vulgaris.

Keywords: Dapsone, Adapalene, Acne vulgaris.

Introduction:

Acne vulgaris is a common chronic inflammatory disease of the pilosebaceous gland that mostly affects teenagers irrespective of gender.¹ According to the Global Burden of Disease Study 2010 acne vulgaris is the eighth most common skin disease, with an estimated global prevalence (for all ages) of 9.38%.² Prevalence of acne ranges from 26.8% to 96% in different regions and age groups.³⁻⁴ Major pathogenic factors responsible for acne are i. raised sebum production related to androgen stimulation of sebaceous glands; ii. altered follicular keratinization (hyperkeratinization); iii. Increased follicular colonization of *Propionibacterium acnes* or other bacterial infection and iv. complex

inflammatory process along with both innate and acquired immunity.⁵ Another factor that causes increased chances of acne is oxidative stress induced by reactive oxygen species (ROS) of both endogenous and external origin. ROS has a significant contribution in the production of inflammatory mediators such as interleukin-8 (IL-8) and tumour necrosis factor- α (TNF- α) by monocytes/macrophages during the progression of acne. Also, excessive and repeated stimulation by invading organisms such as *P. acnes* and *S. epidermidis* causes overproduction of ROS.⁶ Though acne is not a life-threatening disease causing only a few minor features including itching, stinging,

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pain and rashes; it imposes a significant psychological burden due to scarring and pigmentation. It creates a negative impact on the relationship, friendships and job; reduces self-esteem; initiate shame, anger, concern, withdrawal and feeling stigmatized.⁷ Acne is associated with significant psychiatric comorbidities including anxiety, depression and suicidal ideation.⁸ Acne can be presented as seborrhea (increased oil-sebum secretion), comedones, papules, nodules, pustules and scars.⁹ In acne management topical agents are considered as the mainline therapy for mild to moderate disease. The most used topical drugs for acne include benzoyl peroxide, clindamycin, and retinoids (tretinoin, adapalene, isotretinoin, etretinate, retinaldehyde, tazarotene, α -retinoylglucuronideare). Though these have been proved effective in the treatment of acne of mild to moderate severity, they have limitations due to irritation, unfavourable tolerability and low patient adherence.¹⁰ Other topical agents include salicylic acid and azelaic acid, which have antibacterial, comedolytic, and anti-inflammatory properties. None of these treatment modalities can achieve the complete cure of the disease. They can control the disease with a variable rate of success.

The exact mechanism of action of dapsone in the treatment of acne is unknown. In addition to antimicrobial/antiprotozoal function, dapsone has anti-inflammatory activities similarly to non-steroidal anti-inflammatory drugs.¹¹ The efficacy of systemic dapsone in acne was described long ago in 1961 in a placebo control study where 9 patients out of 23 showed remarkable improvement of acne.¹² Systemic dapsone have some serious adverse effects including met-Hb formation, haemolysis and agranulocytosis.¹¹ Moreover its efficacy was proved less compared with isotretinoin in a later study.¹³ But dapsone still have a position to consider for some special situations including acne fulminans.¹⁴ Considering the serious adverse effects of systemic dapsone and its potential antibacterial and anti-inflammatory role, the use of a topical formulation was rationally attempted.

Methods:

Efficacy and safety of topical dapsone 7.5% gel in mild to moderate acne was assessed compared with topical adapalene 0.1% gel. This randomized, open-label, comparative study was conducted in Dhaka medical college hospital and Bangabandhu Sheikh Mujib Medical University (BSMMU) between

July 15, 2019 and 20, November 2021. From the outpatient department (OPD) of dermatology attended patients with acne vulgaris 25 individuals were randomly enrolled into each of two monotherapy groups (group-A, dapsone) and (group-B, adapalene). Two subjects from group A and one from group B were withheld themselves from the trial and were excluded. Efficacy and safety were assessed at weeks 0, 4, 8 and 12. Written and verbal consent to take medications as directed and come for the follow up was taken before enrolment to the study. Patients of both sex and age 12 years or older were included who had newly diagnosed (by a dermatologist) acne having ≥ 2 to ≤ 30 total lesions which could be inflammatory (papules and pustules) and/or non-inflammatory (open or closed comedones) over face with investigator's global assessment score (IGA) 2 or 3. Cases of nodulocystic acne, acne conglobation, acne fulminans, secondary acne (e.g., chloracne, drug-induced acne, or any other acne requiring systemic treatment) were not enrolled in the study.

Individual patients with severe acne vulgaris and who had a prior history of treatment with topical agents (15 days), oral antibiotics (one month), or oral isotretinoin (six months) were excluded from the study. Pregnant and lactating women, women who have menstrual irregularities, who are on hormonal contraception or individuals on any drugs having hormonal influence were also excluded.

Socio-demographic information and associated medical history were taken from all participants. Patients were instructed to apply a thin film of 7.5% dapsone gel (Group A) and 0.1% adapalene gel (Group-B) in the evening. No other medication was used during the treatment period.

The primary efficacy was assessed by the percentage of changes of non-inflammatory (open and closed comedones), inflammatory (papule and pustule) and total lesional counts and comparing between two groups. Only facial lesions were counted and photographs were taken from those who gave consent. Itching, burning, stinging and scaling were also observed for assessment of adverse effects at weeks 4, 8 and 12. Data were analyzed in SPSS. Unpaired t-test and Chi-square test were done to compare the demographic and clinical parameters of two groups. Mann-Whitney U test was done to test the changes in the lesional counts at each follow-up. Mann-Whitney U test was done to see the percent reduction of inflammatory, non-inflammatory and total count of acne in both groups. A p-value < 0.05

was considered significant.

Results:

Table I: Demographic and clinical parameters of patients with acne vulgaris.

Demographic/ clinical parameter	Dapsone 7.5% gel n=23	Adapalene 0.1% gel n=24	Total	p value
Age				
Mean $\pm$ SD	25.57 $\pm$ 9.52	22.33 $\pm$ 9.07	23.91 $\pm$ 9.34	0.240 ^a
Minimum, maximum	14-45	12-50	12-50	
Gender				
Male	7 (30.4%)	7 (29.2%)	14 (29.8)	0.942 ^b
Female	16 (69.6%)	17 (70.8%)	33 (70.2)	

^aUnpaired t test was done to measure the level of significance

^bChi-square test was done to measure the level of significance.

Overall mean age of patients with acne was 23.91 $\pm$ 9.34 years ranging from 12 to 50 years and their age distribution between two groups was statistically comparable ($p > 0.05$). Male to female ratio of the two groups has no significant difference ($p > 0.05$) Table I. Gender distribution of two groups was also statistically similar. Table II: Lesional count of two groups at week 0, 4, 8 and 12.

Table II: Median lesion count at week 0, 4, 8 and 12.

Lesional count (Median)	Dapsone 7.5% gel (Group A) n=23	Adapalene 0.1% gel (Group B) n=24	Total	p value ^a
Total				
Baseline	22	23	23	0.949
4 th weeks	20	20	20	0.369
8 th weeks	15	12	14	0.183
12 th weeks	10	8	9	0.098
Inflammatory				
Baseline	5	7	7	0.304
4 th weeks	6	6.5	6	0.814
8 th weeks	4	4	4	0.966
12 th weeks	2	2	2	0.290
Non-inflammatory				
Baseline	16	14	15	0.306
4 th weeks	15	12	12	0.198
8 th weeks	11	8	9	0.060
12 th weeks	7	5	7	0.129

^aMann-Whitney U test was done to measure the level of significance.

Median of lesional counts at baseline, 1st, 2nd and 3rd follow up of two groups had no significant difference. (Table II)

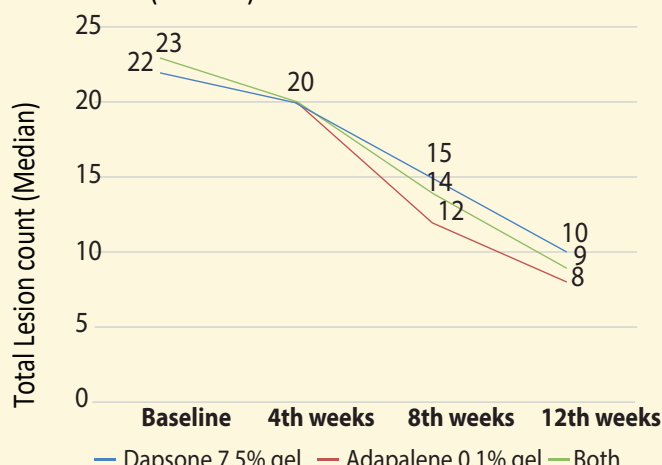


Figure I: Total lesion count of patients at week 0, 4, 8 and 12.

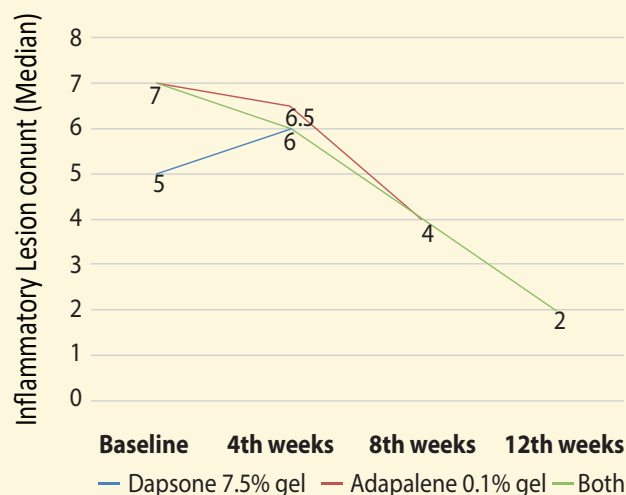


Figure II: Inflammatory lesion count (Median) of patients at week 0, 4, 8 and 12.

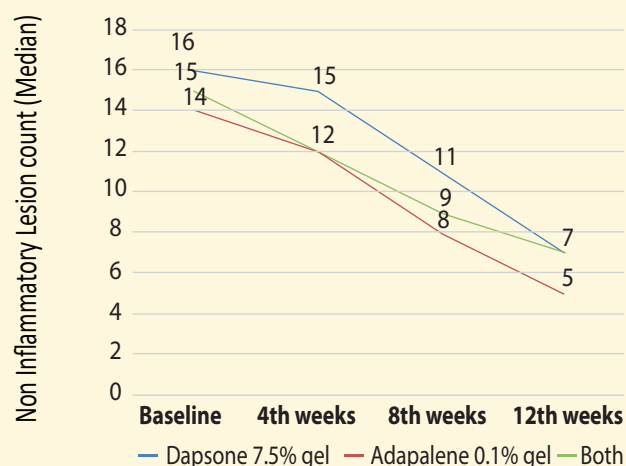


Figure III: Non-Inflammatory lesion count (Median) patients at week 0, 4, 8 and 12.

Table III: Changes of the lesional count at week 12 (n=47)

Change of lesion count (median)*	7.5% Dapsone gel (Group-A) (n=23)	0.1% Adapalene gel (Group-B) (n=24)	P value
Total	-48.3	-59.5	0.011 ^a
Inflammatory	-52.3	-76.9	0.008 ^a
Non-inflammatory	-47.2	-52.6	0.102 ^a

^aMann-Whitney U test was done to measure the level of significance.

*Percent change

Percent changes of the lesional count of total and inflammatory acne from baseline to 12th week was significantly more in group B ($p < 0.05$). Percent changes of the lesional count of non-inflammatory acne from baseline to 12th week was comparable in both groups ($p > 0.05$) (table III).

Table IV: Adverse event of the drugs (n=47)

	7.5% Dapsone gel (Group-A) (n=23)	0.1% Adapalene gel (Group-B) (n=24)	P value
Itching	3 (13.0%)	4 (16.7%)	0.740 ^b
Burning	2 (8.7%)	1 (4.2%)	0.543 ^b
Redness	1 (4.4%)	2 (8.3%)	0.999 ^b
Scaling	1 (4.4%)	2 (8.3%)	0.494 ^b
No adverse effects	18 (78.3%)	17 (70.8%)	0.464 ^a

^aChi-square test was done to measure the level of significance.

^bFisher's Exact test was done to measure the level of significance.

*Multiple responses

Itching is the most common adverse effect in both groups of dapsone (13.0%) and adapalene (16.7%). Other adverse effects were burning, redness and scaling. No adverse effects were found in 78.3% of group A and 70.8% of group B ($p > 0.05$) (table IV).

Discussions:

Dapsone having both antibacterial and anti-inflammatory activities is rationally considered as a treatment option for acne vulgaris. Single daily topical use of 7.5% gel is approved by the United States Food and Drug Administration (FDA) for acne vulgaris in patients aged nine years and older.¹⁵ In 2005, topical dapsone 5% gel was approved by the FDA for twice-daily topical 10 treatment of acne vulgaris in

patients aged 12 years and older.¹⁶ To see the efficacy of 5% dapsone gel in acne vulgaris on the face Draelos et al. carried out 2 same type studies over 3010 patients. Dapsone gel was applied two times daily as a single agent for twelve weeks on 1506 person and vehicle gel containing in the same-looking tube was also applied on the same number of patients. All patients were assessed with the investigator's global acne assessment (IGA) and count of lesions (inflammatory, non-inflammatory and total) at weeks 0, 4, 8 and 12. Dapsone gel treated participants had a significant reduction of IGA and lesional number (percent change) at final follow up (week 12) ($P < 0.001$).¹⁷ Moore et al. in a study demonstrated that dapsone 7.5% gel was effective, safe, and well-tolerated for the treatment of acne in pediatric patients aged nine to 11 years.¹⁸ In the current study the efficacy once-daily application of dapsone 7.5% gel was tested in acne vulgaris patient of age ranging from 12 to 50 years.

In a randomized, double-blind, vehicle-controlled, Phase III clinical trials over a similar age group by Thiboutot et al. once-daily application of 7.5% dapsone gel was found effective.¹⁹ Here in the current study non-inflammatory, inflammatory and total number of acne lesions were significantly reduced from baseline to subsequent weeks. (table I, Fig I, II and III). In a study by Jawade SA et al. total lesions, inflammatory lesions and non-inflammatory lesions were reduced were by 57.8%, 63.1% and 52.4% respectively after 12 weeks of treatment.²⁰ In our study at 12 weeks all forms of acne lesions were significantly reduced from baseline (table III). The percent reduction of total, inflammatory and non-inflammatory acne lesion count in the dapsone at week 12 was 48.3%, 52.3% and 47.2%. Though we included mild to moderate with a total lesional count of less than thirty. In the study by Stein Gold et al. mean inflammatory lesions decreased by 55.5%, non-inflammatory lesions decreased by 44.4% and total lesions decreased by 48.7% with the dapsone 7.5% gel.²¹

All these studies are compared with vehicle only but in the current study efficacy and adverse effects of topical dapsone 7.5% gel was compared with 0.1% adapalene gel. Topical adapalene 11 gel has a good track record of safety and efficacy in the treatment of acne vulgaris both as monotherapy and in combination. We used only adapalene 0.1% gel for the treatment of inflammatory and non-inflammatory lesions of acne vulgaris in 24 patients on the face. Karan et al. in one study found

a significant reduction of inflammatory and non-inflammatory lesions from the baseline. After completing treatment of 12 weeks the total lesional count was reduced by 65.54%, non-inflammatory lesions were reduced by 56.60% and inflammatory acne was reduced by 69.98%.²² In a study by Rao et al. on the same type of acne severity (mild to moderate) found a significant decrease ($P < 0.05$) in the mean inflammatory and non-inflammatory lesion and total lesion counts from the 1st week onward. At 12 weeks, the total reduction was 66.7% for inflammatory lesions and 70.3% for open and around 50% for closed comedones. The decrease in total lesion count was 69% at 12 weeks.²³ In the current study patients treated with either dapsone gel or adapalene gel showed gradual reduction of total lesion count, inflammatory and non-inflammatory lesions from baseline toonward. The efficacy of both dapsone 7.5% gel and adapalene 0.1% gel was statistically significant after 12 weeks (table III). In the current study a 12 weeks treatment with adapalene 0.1% gel the reduction of the total lesional count, inflammatory acne and non-inflammatory acne were 59.5%, 76.9% 52.6%. In the group of patients treated with dapsone 7.5% gel, after the treatment of 12 weeks reduction of total lesional count (48.3%) is statistically indifferent ($p=0.011$) to the adapalene group (59.5%). Reduction of non-inflammatory acne in the dapsone group (47.2%) and adapalene group (52.6%) were also very close and statistically comparable ($p=0.102$). But percent reduction of inflammatory lesions was 52.2% with the treatment of dapsone which is significantly lower than 0.1% adapalene ($p=0.008$). Most of the patients in both dapsone (78.3%) and adapalene (70.8%) had no adverse effects. In both groups there were only some mild adverse effects among them itching was the most common followed by burning, redness and scaling. In a study by Thiboutot et al. dryness, 12 pruritus and pain were the reported adverse effects.¹⁹ None of our cases had to discontinue the treatment due to adverse effects. In previous studies by Draelos et al., Lucky et al. and Raimer et al. dapsone was found safe and well-tolerated.^{17,24-25} Here the tolerability profile of 7.5% dapsone gel was compared with adapalene 0.1% gel and there was no significant difference considering safety.

Conclusions:

Dapsone 7.5% gel is effective and safe in the

treatment of mild to moderate acne vulgaris. Its efficacy on acne vulgaris especially non-inflammatory lesions is similar to adapalene 0.1% gel, but on inflammatory acne, dapsone gel is less effective than adapalene.

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Maskne: A potential entity during the COVID-19 pandemic

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Abstract

Background: Maskne is a current issue among professionals as well as in the general public due to the regular wearing of face masks. **Objective:** To see the frequency of maskne among doctors serving at different hospitals during the COVID-19 pandemic. **Methods:** A cross-sectional survey was conducted among 61 doctors over 3 months by self-administered semi-structured survey questionnaire and also by google formed questionnaire. Means with standard deviations (SD) were used to describe continuous variables and for categorical variables frequency distribution was done. Categorical data were compared using the Chi-square. A p-value less than 0.05 was deemed to represent significance for all comparisons. **Results:** About 90.2 % of doctors under study developed facial dermatoses due to masks and 39.3% of them suffered from maskne. Female doctors (87.5%) were commonly affected, mostly those who had pre-existing acne, and these two factors were statistically significant (p-value< 0.05). **Limitations:** Studies related to maskne are limited. **Conclusions:** To facilitate maskne diagnosis and its prompt treatment, a dermatological guideline is needed.

Key Words: Maskne, Acne, Acne mechanica, COVID-19

Introduction:

The COVID-19 outbreak has affected personal habits and individual lifestyles globally.¹ The Center for Disease Control and Prevention and WHO has implored people to cover their mouth and nose with a mask as a preventive measure to mitigate the spread of the virus.² Everyone is wearing masks more often and longer than before, especially health workers who are working at a higher risk of transmission of infection. Thus, it leads to a local acne outbreak in the area of the face covered by a mask, which is popularly called “maskne” or “mask acne.” Maskne is a recognized subtype of acne mechanica. It is likely a disorder of follicular occlusion, directly

related to mechanical stress (pressure, occlusion, friction) and microbiomedysbiosis (heat, pH, moisture from biofluids). Both of these are afflicted by the increased duration of mask wear.³⁻⁴ Tropical climates and outdoor exposure (increased sweating) are risk factors for acne-susceptible populations (active young adults, seborrhea, and genetic predisposition).³⁻⁴

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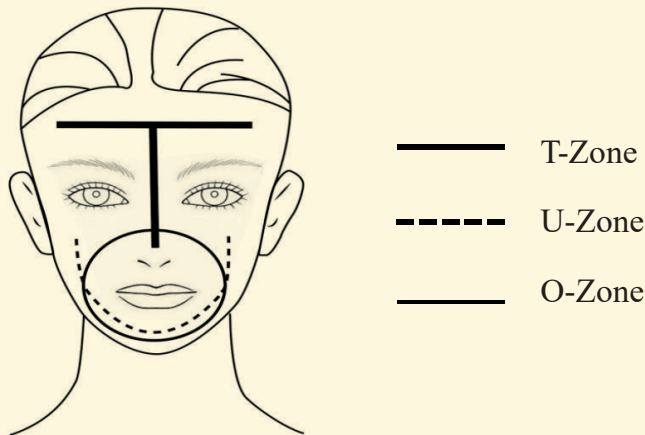


Fig 1: Distinct acne pattern seen in the T zone of physiologic acne, the U zone of adult acne and O zone of Maskne

^mMaskne should be diagnosed in case of (a) de novo acne occurred 6 weeks after regular mask wear or (b) worsen of pre-existence acne over the masked area, a distinct pattern, referred to as the O-zone in this report (Fig 1) (c) after exclusion of the main differential diagnoses including perioral dermatitis, seborrheic dermatitis, pityrosporum folliculitis, and acne rosacea.⁵

The lesions are mostly found in the area covered by the mask, and the severity varies from mild to severe in different literatures.⁶⁻⁸ Increased humidity and temperature in the covered area are the two possible factors of this particular localized outbreak. High temperature can affect the rate of sebum secretion and increased humidity progress the amount of squalene in the skin.⁹ Rising humidity and excess sweating also lead to swelling of the epidermal keratinocytes.¹⁰ All these alterations lead to acute obstruction and acne aggravation.⁹ Moreover, prolonged mask-wearing not only affects acne outbreak but also ascent the temptation of touching the face due to annoying acne or itch, which may increase the risk of COVID-19 transmission through the respiratory tract.¹¹

Several preventive measures can be implemented. Frequent break time of wearing a mask is highly recommended to shorten the duration and exposure of the mask. The surgical mask should be replaced after 4 hours and the N95 mask should be replaced after 3 days.⁷ Before wearing a mask, it is important to wash the face routinely with an appropriate cleanser; a strong alkaline soap is not recommended.¹² It is advisable to avoid any cosmetics or use light

cosmetics only. Finally, mild lesions can be treated with topical antibiotics or retinoids and moderate to severe conditions might be treated with systemic minocycline or isotretinoin.¹³

Methodology:

A cross-sectional survey was conducted to find out the mask-related skin conditions or maskne among the doctors working in different COVID and Non-COVID hospitals during COVID 19 pandemic in Bangladesh. Participation was voluntary and anonymous. Informed consent was taken from the participant before collecting the data. As it was a cross-sectional survey, there was no more than minimal harm to the study participants. No identity of the participants was disclosed and only group data was used in the study results.

Survey instrument:

The survey target population was all doctors of any discipline or training background or level who are either directly involved in the management of COVID-19 patients in a general ward or critical care setting or working in a non-COVID hospital during the COVID 19 pandemic. A self-administered semi-structured study-specific survey questionnaire was designed and also a Google form was created using the questionnaire. The questionnaire had 2 parts. In the first part, questions surrounding basic demographic and institutional work characteristics were elicited. No specific identifying data was requested. The second part comprised a series of questions regarding the use of PPE, along with skin conditions or maskne developed due to the use of PPE.

Survey administration:

The hard copy of the questionnaire was supplied to some doctors and they filled it up immediately and for the others, the Google form of the questionnaire was emailed and they filled it up and mailed it back. Questions were developed and the survey was pre-tested for ease of administration, flow, and content by some volunteers. Following iterative revisions, the final survey was developed. The questionnaire was prepared in English.

Data management and analysis:

Survey results were exported to and analyzed using the latest version of SPSS. Means with standard deviations (SD) were used to describe continuous variables and for categorical variables frequency

distribution was done. Categorical data were compared using the Chi-square. A p-value less than 0.05 was deemed to represent significance for all comparisons.

Results:

Figure 2 A-C: Sociodemographic characteristics of the study participants

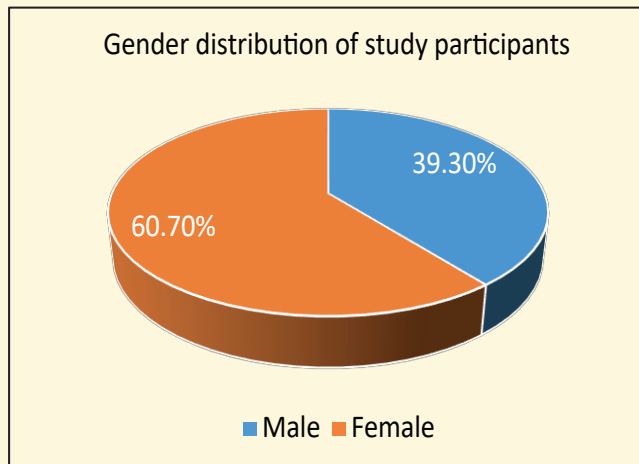


Figure 2A

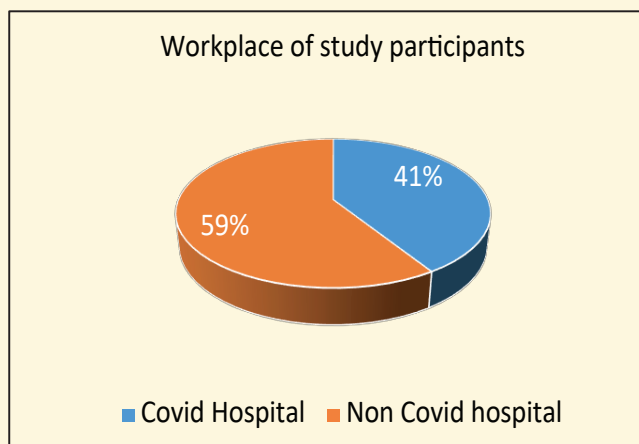


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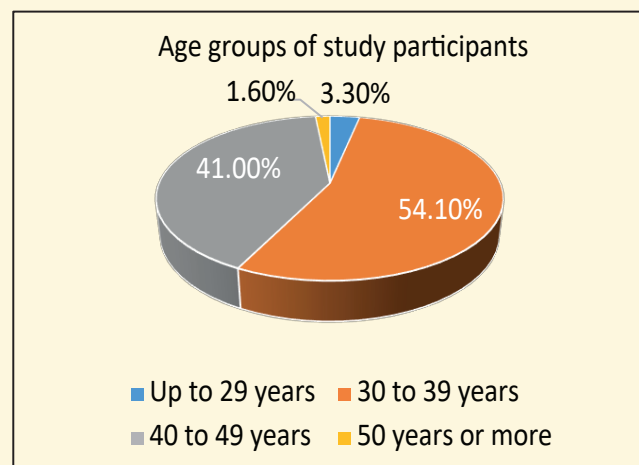
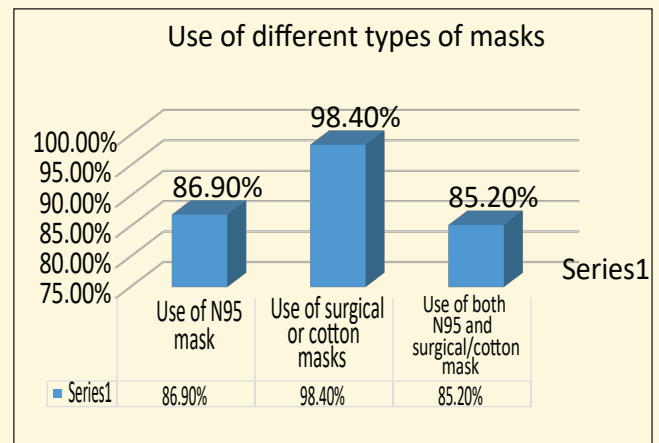


Figure 2C

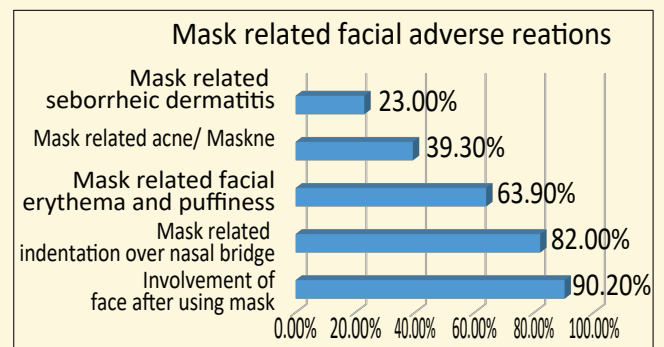
Among 61 doctors majority of the participants were female (60.7%) and most of them (54.1%) were between the age group of 30 to 39 years. The mean age of study participants was 38.22±4.49 years. 41% of doctors were from COVID hospitals, rest of the doctors were from different non-COVID hospitals and institutions. Most of the participants (72.1%) worked in a non-air conditioned environment.

Figure 3: Masks used by the participants



98.4% of doctors used surgical masks, 86.9% used N95 masks and among them, 85.2% used both types of masks. In most cases (47.5%) their average duration of mask-wearing was between 4 to 6 hours.

Figure 4: Mask related adverse skin reactions



Indentation over the nasal bridge, the most common (82%) mask-induced cutaneous effect found during this survey. Maskne was found among 39.3% of doctors.

Table 1: Association of maskne with socio-demographic and other variables

Variables		Maskne		Pearson Chi-Square test
		Yes N(%)	No N(%)	P-value
Age group	Up to 39 years	17(70.8)	18(48.6)	0.087
	40 years and above	7(29.2)	19(51.4)	
Gender	Male	3(12.5)	21(51.4)	0.001
	Female	21(87.5)	16(43.2)	
Workplace	COVID	8(33.3)	17(45.9)	0.328
	Non-COVID	16(66.7)	20(54.1)	
Housing condition of the working place	Air-conditioned	4(16.7)	13(35.1)	0.116
	Air-conditioned	20(83.3)	24(64.9)	
The average duration of using a mask	A Less than 4 hours	2(8.3)	5(13.5)	0.663
	4 to 6 hours	13(54.2)	16(43.2)	
	More than 6 hours	9(37.5)	16(43.2)	
Users of N95 mask	Yes	23(95.8)	30(81.1)	0.095
	No	1(4.2)	7(18.9)	
Users of surgical mask	Yes	24(100)	36(97.3)	0.417
	No	0(0.0)	1(2.7)	
Users of both N95 and surgical mask	Yes	23(95.8)	29(78.4)	0.060
	No	1(4.2)	8(21.6)	
Pre-existing acne	Yes	9(37.5)	5(13.5)	0.030
	No	15(62.5)	32(86.5)	

*1P value of Pearson Chi-Square test

Female doctors (87.5%) commonly suffered from Maskne, especially those who had pre-existing acne, and these two factors were statistically significant (P-value< 0.05).

Discussions::

The epidemiology of skin diseases due to masks has been rarely documented in the past, with most publications being case reports in the health care settings during the severe acute respiratory syndrome (SARS) pandemic between 2002 and 2004.¹⁴ In this study, we observed that 90 % of doctors developed skin diseases due to masks and 39.3% of them suffered from maskne. A study discovered that 59.6% of individuals wearing masks regularly have experienced acne outbreak.¹⁵ This finding is supported by several literature resources highlighting this phenomenon.^{7,16-17}

Prolonged wearing of N95 and surgical masks can easily generate excessive sweating, moisture, and friction. Although N95 masks have an advantage over surgical masks in protecting against acute

respiratory infections, they are associated with more skin reactions than surgical masks, probably due to the higher air impermeability and more pronounced local pressure.¹⁸ But our survey didn't find any significant difference between the two in the case of maskne. Yu et al stated that allergic and irritant contact dermatitis is the most common mask-induced occupational dermatitis, followed by the acneiform eruption and contact urticaria.²⁰ In our study acneiform eruption was the 3rd common presentation of facial dermatoses following nasal indentation and facial erythema.

The present study showed that maskne was more prevalent in female doctors mostly those who had a history of pre-existing acne. In the case of pre-existing facial dermatoses, preventive equipment should not be used for long periods; non-comedogenic moisturizers should be applied before donning and after doffing masks and previous treatments should be continued under the guidance of dermatologists.¹⁹ Zuo et al suggested a higher prevalence of mask-related symptoms among female health workers might be related to a lower threshold for reporting adverse reactions.²⁰ Although it does not represent a life-threatening condition, maskne can have a significant impact on compliance and work performance in doctors. The quality of life and emotional well-being may be seriously impaired as a result of disfiguring facial lesions.

Conclusions:

Moreover, not only doctors fighting against COVID-19 are at increased risk, but other healthcare workers and the general population wearing different typed masks for prolonged periods are also prone to maskne. Appropriate guideline on mask-wearing and proper treatment under the supervision of dermatologists is obligate to lessen "The Maskne burden" in future.

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Dermatological Manifestations in Diabetes

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Abstract

Diabetes mellitus (DM) is a very common and debilitating chronic disease that affects almost all organs of the body including the skin. Between thirty and seventy percent of patients with DM, both type 1 and type 2, will present with a cutaneous complication of DM at some point during their lifetime. A wide array of dermatologic manifestations has been described in DM and these conditions vary in severity. But these skin changes can offer insight into patients' glycemic control status and may be the first sign of metabolic derangement in undiagnosed patients with DM in many instances. Early diagnosis and appropriate management of these conditions are important in maximizing the quality of life and in avoiding serious adverse effects in patients with DM.

Key words: Diabetes mellitus, Skin disease.

Introduction:

Chronic hyperglycemia in DM causes changes in several organ systems of the patients. Dermatologic manifestations of DM have various health implications ranging from those that are aesthetically concerning to those that may be life-threatening. Awareness of cutaneous manifestations of DM can provide insight into the present or prior metabolic status of patients. The recognition of such findings may aid in the diagnosis of DM or may be followed as a marker of glycemic control. The text that follows describes the relationship between DM and the skin, more specifically: (1) skin manifestations strongly DM, (3) dermatologic diseases associated with DM, (4) common skin infections in DM, and (5) cutaneous changes associated with DM medications.

Acanthosis nigricans (AN) is a classic dermatologic manifestation of DM that affects men and women of all ages. AN is more common in type 2 DM and is more prevalent in those with darker skin colour.¹⁻² AN is disproportionately represented in African Americans, Hispanics, Native Americans and Asians.³ AN is observed in a variety of endocrinopathies associated with resistance to insulin such as acromegaly, Cushing syndrome, obesity, polycystic ovarian syndrome, and thyroid dysfunction. Unrelated to insulin resistance, AN can also be associated with malignancies such as gastric adenocarcinomas and other carcinomas.⁴

Presentation

AN usually presents as multiple poorly demarcated plaques with grey to dark-brown hyperpigmentation and a thickened velvety to verrucous texture over months or years. In classical cases, AN has a symmetrical distribution and is located in intertriginous or flexural surfaces such as the back of

Skin Changes Strongly Associated with DM

Acanthosis nigricans:

Epidemiology

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the neck, axilla, elbows, palmer hands (tripe palms), inframammary folds, umbilicus, or groin and so on. The changes occur gradually, and the person is generally initially asymptomatic; however, extensive involvement may cause discomfort or fetor. Microscopic findings reveal hyperkeratosis and epidermal papillomatosis

with acanthosis. The skin changes are primarily a consequence of hyperkeratosis, not changes in melanin. In many cases, AN can present before to the clinical diagnosis of DM; the presence of AN should be promptly evaluated for DM and other signs of insulin resistance.



Figure 1: Acanthosis nigricans.

Pathogenesis:

The pathogenesis of AN is not determined yet. The most commonly accepted theory is that a hyperinsulinemic state activates insulin growth factor receptors (IGF), specifically IGF-1, on keratinocytes and fibroblasts, provoking cellular proliferation, resulting in the cutaneous manifestations in different parts of the body.⁵⁻⁶

Treatment:

AN is managed with lifestyle modifications such as dietary modifications, increased physical activity, and weight reduction. In patients with DM, pharmacologic adjuvants, such as metformin, that improve glycemic control and reduce insulin resistance are also beneficial.⁷ But, primary dermatologic therapies are usually ineffective especially in patients with generalized involvement. However, in those with thickened or macerated areas of skin, oral retinoids or topical keratolytics such as ammonium lactate, retinoic acid, or salicylic acid can be used to alleviate symptoms.⁸⁻¹⁰

Diabetic dermopathy:

Epidemiology

Diabetic dermopathy (DD) which is also known as pigmented pretibial patches or diabetic shin spots, is the most common dermatologic manifestation of DM, presenting in as many as one-half of those with DM.¹¹ Some consider the presence of DD to be pathognomonic for DM though some do not. DD has a strong predilection for men and those older than 50 years of age.¹² Although DD may antecede the onset of DM, it occurs more frequently as a late complication of DM and in those with microvascular disease. Nephropathy, neuropathy, retinopathy and other microvascular complications of DM are regularly present in patients with DD.¹³

Presentation:

DD presents initially with rounded, dull, papules of red colour that progressively evolve over one-to-two weeks into well-circumscribed, atrophic, brown macules with a fine scale. Normally after about 18 to 24 months, lesions dissipate and leave behind an area of concavity and hyperpigmentation. At any time, different lesions can present at different stages of evolution. The lesions are normally distributed over both the limbs and localized over bony prominences. Although other bony prominences such as the forearms, lateral malleoli or thighs may also be involved, the pretibial area is most commonly involved in DD. Aside from the aforementioned changes, patients are otherwise asymptomatic. DD is a clinical diagnosis that should not require a skin biopsy. DD is rather nonspecific histologically; it is characterized by lymphocytic infiltrates surrounding vasculature, engorged blood vessels in the papillary dermis, and dispersed hemosiderin deposits. Moreover, the histology varies based on the stage of the lesion. Immature lesions present with epidermal edema as opposed to epidermal atrophy which is representative of older lesions.¹⁴

Pathogenesis:

The origin of DD remains unclear, however, mild trauma to affected areas, hemosiderin and melanin deposition, microangiopathic changes, and destruction of subcutaneous nerves have all been suggested.¹⁵⁻¹⁸

Treatment:

Treatment is typically avoided given the asymptomatic and self-resolving nature of DD as well as the ineffectiveness of available treatments. However, DD often occurs in the context of

microvascular complications and neuropathies.¹² Hence, patients need to be examined and followed more rigorously for these complications. Although it is important to manage DM and its complications accordingly, there is no evidence that improved glycemic control alters the development of DD.

Diabetic Foot Syndrome:

Epidemiology

Diabetic Foot Syndrome (DFS) encompasses the neuropathic and vasculopathic complications that develop in the feet of patients with DM. Although potentially preventable, DFS is a significant cause of morbidity, mortality, hospitalization, and reduction in quality of life of patients with DM. The incidence and prevalence of DFS in patients with DM is 1% to 4% and 4% to 10%, respectively.¹⁹ DFS is slightly more prevalent in t1DM compared with T2DM.²⁰

Clinical features:

DFS usually presents with callosities and dry skin related to diabetic neuropathy. Subsequently, chronic ulcers and a variety of other malformations of the feet develop. About 20% (15% - 25% of patients with DM will develop ulcers.²¹ These ulcers may be neuropathic, ischemic or mixed. The most common type of ulcer is neuropathic ulcer, painless ulceration resulting from peripheral neuropathy. Ulcers associated with peripheral vascular ischemia are less common but often painful. Ulcers tend to occur in areas prone to trauma, classically presenting at the site of calluses or over bony prominences. It is common for ulcers to occur on the toes, forefoot, and ankles. Untreated ulcers usually heal within one year, however, fifty percent of patients with DM will have a recurrence of the ulcer within three years.²² The skin of affected patients, especially in those with type 2 DM, is more prone to fungal infection and the toe webs are a common port of entry for fungi which can then infect and complicate ulcers.²³ Secondary infection of ulcers is a serious complication that can result in gangrenous necrosis, osteomyelitis and may even require lower extremity amputation. Another complication, diabetic neuro-osteoarthropathy (charcot foot), is an irreversible, debilitating and deforming condition involving progressive destruction of weight-bearing bones and joints. Diabetic neuro-osteoarthropathy occurs most frequently in the feet and can result in collapse of the midfoot, referred to as "rocker-bottom foot." Moreover, a reduction of the intrinsic muscle

volume and thickening of the plantar aponeurosis can cause imbalance of the muscles that produces a clawing deformation of the toes. Furthermore, a complication of DM and neuropathy involving the feet is erythromelalgia. Erythromelalgia presents with redness, warmth, and a burning pain involving the lower extremities, most often the feet. Symptoms may worsen in patients with erythromelalgia with exercise or heat exposure and may improve with cooling.²⁴



Figure 2: Diabetic foot (Photograph : Dr. Mohammad Jamal Uddin and Dr. Khandaker Snigdha Malabika)

Pathogenesis:

A combination of inciting factors that coexist together: neuropathy, atherosclerosis, and impaired wound healing is involved in the pathogenesis of DFS.²⁵⁻²⁶ In the setting of long-standing hyperglycemia, there is an increase in advanced glycosylation end products, proinflammatory factors, and oxidative stress which results in the demyelination of nerves and subsequent neuropathy.²⁷⁻²⁸ The effect on sensory and motor nerves, can blunt the perception of adverse stimuli and produce an altered gait, increasing the likelihood of developing foot ulcers and malformations. Also, damage to autonomic nerve fibres causes a reduction in sweating which may leave skin in the lower extremity dehydrated and prone to fissures and secondary infection.²⁹ In addition to neuropathy, accelerated arterial atherosclerosis can lead to peripheral ischemia and ulceration.³⁰ Finally, hyperglycemia impairs macrophage functionality as well as increases and prolongs the inflammatory response, slowing the healing of ulcers.³¹

Management:

Treatment should involve an interdisciplinary team-based approach with a focus on the prevention and management of current ulcers. Prevention entails daily surveillance, appropriate foot hygiene, and proper footwear, walkers, or other devices to minimize and distribute pressure. An appropriate wound care program should be used to care for ongoing ulcers. Different classes of wound dressing should be considered based on the wound type. Hydrogels, hyperbaric oxygen therapy, topical growth factors, and biofabricated skin grafts are also available.¹⁹ The clinical presentation should indicate whether antibiotic therapy or wound debridement is necessary.¹⁹ In patients with chronic treatment-resistant ulcers, underlying ischemia should be considered; these patients may require surgical revascularization or bypass.

Diabetic thick skin:

Thickening of skin is frequently observed in patients with DM. Affected skin areas can appear thickened, waxy, or edematous. These patients are often asymptomatic but can have a reduction in sensation and pain. Although different parts of the body can be involved, the hands and feet are most frequently involved. Ultrasound evaluation of the skin can be diagnostic and exhibit thickened skin. Subclinical generalized skin thickening is the most common type of skin thickening. Diabetic thick skin may represent another manifestation of scleroderma-like skin change or limited joint mobility, which are each described in more detail below



Figure 3: Diabetic thick skin. (Photograph: Dr. Towhida Noor)

Scleroderma-Like Skin Changes (SLSC):

Epidemiology

SLSC are a distinct and easily overlooked group of findings that are commonly observed in patients with DM. Ten to 50% of patients with DM present with the associated skin findings.³² SLSC occurs more commonly in those with T1DM and those with longstanding disease.³³ There is no known variation in prevalence between males and females, or between racial groups.

Presentation

SLSC develop slowly and present with painless, indurated, occasionally waxy appearing, thickened skin. These changes occur symmetrically and bilaterally in acral areas. In patients with scleroderma-like skin changes the acral areas are involved, specifically the dorsum of the fingers (sclerodactyly), proximal interphalangeal, and metacarpophalangeal joints. Severe disease may extend centrally from the hands to the arms or back. A small number of patients with DM may develop more extensive disease, which presents earlier and with truncal involvement. The risk of developing nephropathy and retinopathy is increased in those with SLSC who also have T1DM.³³⁻³⁴ The aforementioned symptoms are also associated with diabetic hand syndrome which may present with limited joint mobility, palmar fibromatosis (Dupuytren's contracture), and stenosing tenosynovitis ("trigger finger").³⁵ The physical finding known as the "prayer sign" (inability to flatty press palmar surfaces on each hand together) may be present in patients with diabetic hand syndrome and scleroderma-like skin changes.³⁶ SLSC reveal thickening of the dermis on histology, minimal-to-absent mucin, and increased interlinking of collagen. Although on physical exam scleroderma may be difficult to distinguish from these skin changes, SLSC is not associated with atrophy of the dermis, Raynaud's syndrome, pain, or telangiectasias

Pathogenesis

Though not fully revealed, the pathogenesis is believed to involve the strengthening of collagen as a result of reactions associated with advanced glycosylation end products or a buildup of sugar alcohols in the upper dermis.³⁷⁻³⁸

Treatment

Scleroderma-like skin changes is a chronic condition that is also associated with joint and microvascular complication. Therapeutic options are extremely limited. One observational report has suggested that very tight blood sugar control may result in the narrowing of thickened skin.³⁹ In addition, aldose reductase inhibitors, which limit increases in sugar alcohols, may be efficacious.³⁸ In patients with restricted ranges of motions, physical therapy can help to maintain and improve joint mobility.

Limited Joint Mobility:

Limited Joint Mobility (LJM), also known as diabetic cheiroart flush press arthropathy, is a relatively common complication of long-standing DM. The majority of patients with LJM also present with scleroderma-like skin changes.^{38,40} The prevalence of LJM is 4% to 26% in patients without DM and 8% to 58% in patients with DM.⁴¹ LJM disorders present with progressive flexed contractures and restricted joint extension, most commonly involving the metacarpophalangeal and interphalangeal joints of the hand. The initial changes often begin in the joints of the fifth finger before then spreading to involve the other joints of the hand.³⁸ Patients may present with an inability to flushly press the palmar surfaces of each of their hands together ("prayer sign") or against the surface of a table when their forearms are perpendicular to the surface of the table ("tabletop sign").⁴² These changes occur as a result of periarticular enlargement of connective tissue. The pathogenesis likely involves hyperglycemia-induced formation of advanced glycation end-products, which accumulate to promote inflammation and the formation of stiffening cross-links between collagen.⁴³ LJM is strongly associated with microvascular and macrovascular changes and diagnosis of LJM should prompt a workup for the related sequel.⁴⁴ Patients with LJM may also be at increased risk for falls.⁴⁵ Currently there are no curative treatments for the condition. Symptomatic patients may benefit from non-steroidal anti-inflammatory drugs or targeted injection of corticosteroids.⁴³ LJM is best managed with improved glycemic control as well as, regular stretching to maintain and minimize further limitations in joint mobility.⁴⁶

Scleredema diabeticorum:

Epidemiology

Scleredema diabeticorum is a chronic and slowly progressive sclerotic skin disorder that is oftenseen in the context of DM. Whereas, 2.5% to 14% of all

patients with DM have scleredema, over 50% of those with scleredema present with concomitant DM.⁴⁷ Scleredema has a proclivity for those with a long history of DM. It remains unclear whether there is a predilection for scleredema in those with T1DMs compared to those with T2DM.⁴⁸ Women are affected more often than men.⁴⁹ Although all ages are affected, scleredema occurs more frequently in those over the age of twenty.⁴⁸⁻⁴⁹

Presentation

Scleredema presents with gradual worsening indurated and thickened skin changes occurring symmetrically and diffusely. The most commonly involved areas are the upper back, shoulders, and back of the neck. The face, chest, abdomen, buttocks, and thighs may also be involved; however, the distal extremities are classically spared. The affected areas are normally asymptomatic but there can be reduced sensation. Patients with severe longstanding disease may develop a reduced range of motion, most often affecting the trunk. In extreme cases, this can lead to restrictive respiratory problems. A full-thickness skin biopsy may be useful in supporting a clinical presentation. The histology of scleredema displays increased collagen and a thickened reticular dermis, with a surrounding mucinous infiltrate, without edema or sclerosis.



Figure 4: Scleredema diabeticorum (Photograph : Dr. Marshad Hossain)

Pathogenesis

Although many theories focus on abnormalities in collagen, there is no consensus regarding the pathogenesis of scleredema. The pathogenesis of scleredema may involve an interplay between non-enzymatic glycosylation of collagen, increased

fibroblast production of collagen, or decreases in collagen breakdown.⁵⁰⁻⁵¹

Treatment

Scleredema diabeticorum is generally unresolving and slowly progressive over years. Optimum glycemic control may be an important means of prevention, but evidence shown no clinical improvements in those already affected by scleredemadiabeticorum. A variety of therapeutic options have been proposed with variable efficacy. Some of these therapies include immunosuppressants, corticosteroids, intravenous immunoglobulin and electron-beam therapy.⁵² Phototherapy with UVA1 or PUVA may be effective in those that are severely affected.⁵² Independent of other treatments, physical therapy is an important therapeutic modality for patients with scleredema and reduced mobility.⁵³

Necrobiosis Lipoidica:

Epidemiology

Necrobiosislipoidica (NL) is a rare chronic granulomatous dermatologic disease that is seen most frequently in patients with DM as well as in others. Although nearly 25% of patients presenting with NL also have DM, less than 1% of patients with DM develop NL.⁵⁴ NL expresses a strong predilection for women compared to men, but the reason is unclear still.⁵⁵ NL generally occurs in type 1 DM during the third decade of life, whereas, in type 2 DM it commonly presents in the fourth or fifth decades of life.⁵⁴ Frequently NL presents years after a diagnosis of DM; however, about 20% (14% to 24%) of cases of NL may occur before or at the time of diagnosis.⁵⁶

Presentation

NL usually begins as a single or group of firm well-demarcated rounded erythematous papules. The papules then expand and aggregate into plaques characterized by circumferential red-brown borders and a firm yellow-brown waxy atrophic centre containing telangiectasias. NL usually occurs symmetrically and exhibits Koebnerization. The lesions are almost always found on the pretibial areas of the lower extremities. The forearm scalp, distal upper extremities, face, or abdomen may be affected occasionally, and the heel of the foot or glans penis even more infrequently. About 15% of lesions will resolve within twelve years if left untreated. Despite the pronounced appearance of the lesions, NL is

often remaining unnoticed over years. However, there may be pruritus and hypoesthesia of affected areas, and pain may be present in the areas of ulceration. Ulceration occurs in about 31% of lesions and has been associated with secondary infections and squamous cell carcinoma. The histopathology of NL primarily involves the dermis and is marked by palisading granulomatous inflammation, necrobiotic collagen, a mixed inflammatory infiltrate, blood vessel wall thickening, and reduced mucin.

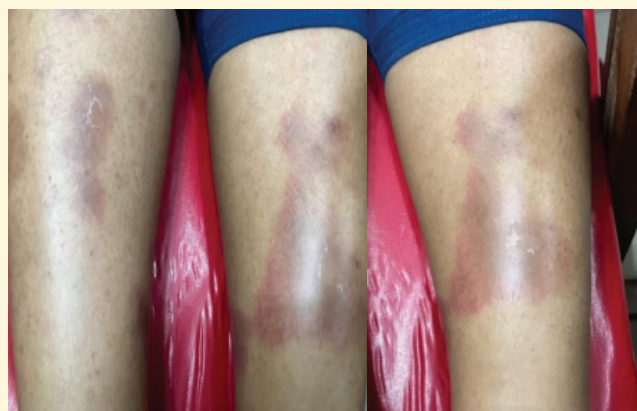


Figure 5: Necrobiosis lipoidica

Pathogenesis

The pathogenesis of NL is not well understood yet. The relationship between DM and NL has led some to theorize that DM-related microangiopathy is related to the development of NL.⁵⁴ Other theories focus on irregularities in collagen, autoimmune disease, neutrophil chemotaxis, or blood vessels.⁵⁷

Treatment

NL is a chronic, disfiguring condition that can be debilitating for patients and difficult for clinicians to manage. Differing degrees of success have been reported with a variety of treatments; however, the majority of such reports are limited by inconsistent treatment responses in patients and a lack of large controlled studies. Corticosteroids are often used in the management of NL and may be administered topically, intralesionally, or orally. Corticosteroids can be used to manage active lesion, but is best not used in atrophic areas. Success has also been reported with calcineurin inhibitors (e.g. cyclosporine), anti-tumor necrosis factor inhibitors (e.g. infliximab), pentoxifylline, antimalarials (e.g. hydroxychloroquine), PUVA, granulocyte colony stimulating factor, dipyridamole and low-dose aspirin.⁵⁴ Appropriate wound care is important for ulcerated lesions; this often includes topical

antibiotics, protecting areas vulnerable to injury, emollients and compression bandaging. Surgical excision of ulcers typically has poor results. Some ulcerated lesions may improve with split-skin grafting. Although still recommended, improved control of DM has not been found to lead to an improvement in skin lesions.

Bullosis diabeticorum:

Epidemiology

Bullosis diabeticorum (BD) is an uncommon eruptive blistering disorder that presents in patients with DM. Although BD can occasionally present in early-DM.⁵⁸ It often occurs in long-standing DM along with other complications such as neuropathy, nephropathy, and retinopathy. In the United States, the prevalence of BD is around 0.5% amongst patients with DM and is believed to be higher in those with type 1 DM.¹³ BD is significantly more common in male patients than in female patients.⁵⁹ The average age of onset is between 50 and 70 years of age.⁵⁹

Presentation

BD presents at sites of previously healthy-appearing skin with the abrupt onset of one or more non-erythematous, firm, sterile bullae. Shortly after forming, bullae increase in size and become more flaccid, ranging in size from about 0.5 cm to 5 cm. Bullae frequently present bilaterally involving the acral areas of the lower extremities. However, involvement of the upper extremities and even more rarely the trunk can be seen. The bullae and the adjacent areas are nontender. BD often presents acutely, classically overnight, with no history of trauma to the affected area. Generally, the bullae heal within two to six weeks, but then commonly reoccur. Histological findings are often non-specific but are useful in distinguishing BD from other bullous diseases. Histology, typically shows an intraepidermal or subepidermal blister, spongiosis, no acantholysis, minimal inflammatory infiltrate, and normal immunofluorescence.



Figure 6: Bullosis Diabeticorum (Photograph : Dr. Mohammed Jamal Uddin)

Pathogenesis

There is an incomplete understanding of the underlying pathogenesis of BD and no consensus regarding a leading theory. Various mechanisms have been proposed, some of which focus on autoimmune processes, exposure to ultraviolet light, variations in blood glucose, neuropathy, or changes in microvasculature.⁶⁰

Treatment

BD resolve without treatment and are therefore managed by avoiding secondary infection and the corresponding sequelae (e.g. necrosis, osteomyelitis). This involves protection of the affected skin, leaving blisters intact (except for large blisters, which may be aspirated to prevent rupture), and monitoring for infection. Topical antibiotics are not necessary unless specifically indicated, such as with secondary infection or positive culture.

Nonspecific signs and Symptoms of Skin:

Ichthyosiform changes of the shins

Ichthyosiform changes of the shins presents with large bilateral areas of dryness and scaling (sometimes described as “fish scale” skin). Although cutaneous changes may occur on the hands or feet, the anterior shin is most classically involved. These cutaneous changes are related to rapid skin aging and adhesion defects in the stratum corneum.⁶¹ The prevalence of ichthyosiform changes of the shins in

those with type 1 DM has been reported to be between 22% to 48%.^{62, 33} These changes present relatively early in the disease course of DM. There is no known difference in prevalence between males and females.³³ The development of ichthyosiform changes of the shins is related to the production of advanced glycosylation end products and microangiopathic changes. Treatment is limited but topical emollients or keratolytic agents may be beneficial.⁶¹

Xerosis

Xerosis is one of the most common skin presentations in patients with DM and has been reported to be present in as many as 40% of patients with DM.⁶³ Xerosis refers to abnormally dry skin. Affected skin may present with scaling, cracks or a rough texture. These skin changes are most frequently located on the feet of patients with DM. In patients with DM, xerosis occurs often in the context of microvascular complications.⁴⁰ To avoid complications such as fissures and secondary infections, xerosis can be managed with emollients like ammonium lactate.⁶⁴

Acquired perforating dermatosis:

Epidemiology

Perforating dermatoses refers to a broad group of chronic skin disorders characterized by a loss of dermal connective tissue. A subset of perforating dermatoses, known as acquired perforating dermatoses (APD), encompasses those perforating dermatoses that are associated with systemic diseases. Although APD may be seen with any systemic diseases, it is classically observed in patients with chronic renal failure or long-standing DM.⁶⁵ APD occurs most often in adulthood in patients between the ages of 30 and 90 years of age.⁶⁵⁻⁶⁶ The prevalence of APD is unknown. It is estimated that of those diagnosed with APD about 15% also have DM.⁶⁷ In a review, 4.5% to 10% of patients with chronic renal failure presented with concurrent APD.⁶⁸⁻⁶⁹

Presentation

APD presents as groups of hyperkeratotic umbilicated nodules and papules with centralized keratin plugs. The lesions undergo koebnerization and hence the extensor surfaces of the arms and more commonly the legs are often involved; eruptions also occur frequently on the trunk. However, lesions can develop anywhere on the

body. Lesions are extremely pruritic and are aggravated by excoriation. Eruptions may improve after a few months but an area of hyperpigmentation typically remains. Histologically, perforating dermatoses are characterized by a lymphocytic infiltrate, an absence or degeneration of dermal connective tissue components (e.g. collagen, elastic fibres), and transepidermal extrusion of keratotic material.



Figure 7-a & 7-b: Acquired perforating dermatoses (Photograph : a. Dr. Tauhidur Rahman; b. Dr. Afrina Jahan)

Pathogenesis

The underlying pathogenesis is disputed and not fully understood. It has been suggested that repetitive superficial trauma from chronic scratching may induce epidermal or dermal derangements.⁷⁰ The glycosylation of microvasculature or dermal components has been suggested as well. Other hypotheses have implicated additional metabolic disturbance or the accumulation of unknown immunogenic substances that are not eliminated by dialysis.⁶⁵

Treatment

APD can be challenging to treat and many of the interventions have variable efficacy. Minimizing scratching and other traumas to involved areas can allow lesions to resolve over months. This is best achieved with symptomatic relief of pruritus. Individual lesions can be managed with topical agents such as keratolytics (e.g. 5% to 7% salicylic acid), retinoids (e.g. 0.01% to 0.1% tretinoin), or high-potency steroids.⁷¹ Refractory lesions may respond to intralesional steroid injections or cryotherapy.⁷¹ A common initial approach is a topical steroid in combination with emollients and an oral antihistamine. Generalized symptoms may improve with systemic therapy with oral retinoids, psoralen

plus UVA light (PUVA), allopurinol (100 mg daily for 2 to 4 months), or oral antibiotics (doxycycline or clindamycin).⁷² Nevertheless, effective management of the underlying systemic disease is fundamental to the treatment of APD. In those with DM, APD is unlikely to improve without improved blood sugar control. Moreover, dialysis does not reduce symptoms; however, renal transplantation can result in the improvement and resolution of cutaneous lesions.

Eruptive xanthomas:

Epidemiology

Eruptive xanthomas (EX) is a clinical presentation of hypertriglyceridemia, generally associated with serum triglycerides above 2,000 mg/dL.⁷³ However, in patients with DM, lower levels of triglycerides may be associated with EX. The prevalence of EX is around one percent in type 1 DM and two percent in type 2 DM.⁷⁴⁻⁷⁵ Serum lipid abnormalities are present in about seventy-five percent of patients with DM.⁷⁶



Figure 8: Eruptive Xanthomas

Presentation

EX has been reported as the first presenting sign of DM, granting it can present at any time in the disease course. EX presents as eruptions of clusters of glossy pink-to-yellow papules, ranging in diameter from 1 mm to 4 mm, overlying an erythematous area. The lesions can be found on extensor surfaces of the extremities, the buttocks, and in areas susceptible to koebnerization. EX is usually asymptomatic but may be pruritic or tender. The histology reveals a mixed inflammatory infiltrate of the dermis which includes triglyceride containing macrophages, also referred to as foam cells.

Pathogenesis

Lipoprotein lipase, a key enzyme in the metabolism of triglyceride rich-lipoproteins, is stimulated by insulin. In an insulin-deficient state, such as poorly controlled DM, there is decreased lipoprotein lipase activity resulting in the accumulation of chylomicrons and other triglyceride-rich lipoproteins.⁷⁷ Increased levels of these substances are scavenged by macrophages.⁷⁸ These lipid-laden macrophages then collect in the dermis of the skin where they can lead to eruptive xanthomas.

Treatment

EX can resolve with improved glycemic control and a reduction in serum triglyceride levels.⁷⁹ This may be achieved with fibrates or omega-3-fatty acids in addition to an appropriate insulin regimen.⁸⁰

Acrochordons

Acrochordons (also known as soft benign fibromas, fibroepithelial polyps, or skin tags) are benign, soft, pedunculated growths that vary in size and can occur singularly or in groups. The neck, axilla, and periorbital area are most frequently involved, although other intertriginous areas can also be affected. Skin tags are common in the general population but are more prevalent in those with increased weight or age, and in women. It has been reported that as many as three out of four patients presenting with acrochordons also have DM.⁸¹ Patients with acanthosis nigricans may have acrochordons overlying the affected areas of skin. Although disputed, some studies have suggested that the number of skin tags on an individual may correspond with an individual's risk of DM or insulin resistance.⁸² Excision or cryotherapy is not medically indicated but may be considered in those with symptomatic or cosmetically displeasing lesions.

DM-Associated pruritus

DM can be associated with pruritus, more often localized than generalized. Affected areas can include the scalp, ankles, feet, trunk, or genitalia.⁸³⁻⁸⁴ Pruritus is more likely in patients with DM who have dry skin or diabetic neuropathy. Involvement of the genitalia or intertriginous areas may occur in the setting of infection (e.g. candidiasis). Treatments include topical capsaicin, topical ketamine-amitriptyline-lidocaine, oral anticonvulsants (e.g. gabapentin or pregabalin), and, in the case of candida infection, antifungals.

Huntley's papules (Finger pebbles)

Huntley's papules, also known as finger pebbles, are a benign cutaneous finding affecting the hands. Patients present with clusters of non-erythematous, asymptomatic, small papules on the dorsal surface of the hand, specifically affecting the metacarpophalangeal joints and periungual areas. The clusters of small papules can develop into coalescent plaques. Other associated cutaneous findings include hypopigmentation and induration of the skin. Huntley's papules are strongly associated with type 2 DM and may be an early sign of diabetic thick skin.⁸⁵⁻⁸⁶ Topical therapies are usually ineffective; however, patients suffering from excessive dryness of the skin may benefit from 12% ammonium lactate cream.⁸⁷

Keratosis pilaris

Keratosis pilaris is a very common benign keratotic disorder. Patients with keratosis pilaris classically present with areas of keratotic perifollicular papules with surrounding erythema or hyperpigmentation. The posterior surfaces of the upper arms are often affected but the involvement of the thighs, face and buttocks can also be seen. Compared to the general population, keratosis pilaris occurs more frequently and with more extensive involvement of the skin in those with DM.^{33, 62} Keratosis pilaris can be treated with various topical therapies, including salicylic acid, moisturizers, and emollients.

Pigmented purpuric dermatoses

Pigmented purpuric dermatoses (also known as pigmented purpura) is associated with DM, more often in the elderly, and frequently coexists with diabetic dermopathy.⁸⁸⁻⁸⁹ Pigmented purpura presents with non-blanching copper-colored patches involving the pretibial areas of the legs or the dorsum of the feet. The lesions are usually asymptomatic but may be pruritic. Pigmented purpuric dermatoses occur more often in late-stage DM in patients with nephropathy and retinopathy as a result of microangiopathic damage to capillaries and sequential erythrocyte deposition.⁹⁰

Palmar erythema

Palmar erythema is a benign finding that presents with symmetric redness and warmth involving the palms. The erythema is asymptomatic and often most heavily affects the hypothenar and thenar eminences of the palms. The microvascular

complications of DM are thought to be involved in the pathogenesis of palmar erythema.⁹¹ Although DM associated palmar erythema is distinct from physiologic mottled skin, it is similar to other types of palmar erythema such as those related to pregnancy and rheumatoid arthritis.

Periungual telangiectasias

As many as one in every two patients with DM are affected by periungual telangiectasias.⁹² Periungual telangiectasias presents asymptotically with erythema and telangiectasias surrounding the proximal nail folds.⁷¹ Such findings may occur in association with "ragged" cuticles and fingertip tenderness. The cutaneous findings are due to venous capillary dilatation that occurs secondary to diabetic microangiopathy. Capillary abnormalities, such as venous capillary tortuosity, may differ and can represent an early manifestation of DM-related microangiopathy.⁹³

Rubeosis faciei

Rubeosis faciei is a benign finding present in about 7% of patients with DM; however, in hospitalized patients, the prevalence may exceed 50%.⁹⁴ Rubeosis faciei presents with chronic erythema of the face or neck. Telangiectasias may also be visible. The flushed appearance is often more prominent in those with lighter colored skin. The flushed appearance is thought to occur secondary to small vessel dilation and microangiopathic changes. Complications of DM, such as retinopathy, neuropathy, and nephropathy are also associated with rubeosis faciei.⁹⁰ Facial erythema may improve with better glycemic control and reduction of caffeine or alcohol intake.

Yellow skin and nails

It is common for patients with DM, particularly elderly patients with T2DM, to present with asymptomatic yellow discolourations of their skin or fingernails. These benign changes commonly involve the palms, soles, face, or the distal nail of the first toe. The accumulation of various substances (e.g. carotene, glycosylated proteins) in patients with DM may be responsible for the changes in complexion; however, the pathogenesis remains controversial.⁹⁵

Dermatological Diseases Associated with DM:

Generalized granuloma annulare

Epidemiology

Although various forms of granuloma annulare exist,

only generalized granuloma annulare (GGA) is thought to be associated with DM. It is estimated that between ten and fifteen percent of cases of GGA occur in patients with DM.⁹⁶ Meanwhile, less than one percent of patients with DM present with GGA. GGA occurs around the average age of 50 years. It occurs more frequently in women than in men, and in those with T2DM.⁹⁷

Presentation

GGA initially presents with groups of skin-coloured or reddish, firm papules which slowly grow and centrally involute to then form hypo- or hyper-pigmented annular rings with elevated circumferential borders. The lesions can range in size from 0.5 cm to 5.0 cm. The trunk and extremities are classically involved in a bilateral distribution. GGA is normally asymptomatic but can present with pruritus. The histology shows dermal granulomatous inflammation surrounding foci of necrotic collagen and mucin. Necrobiosis lipoidica can present similarly to GGA; GGA is distinguished from necrobiosis lipoidica by its red color, the absence of an atrophic epidermis, and on histopathology: the presence of mucin and lack of plasma cells.

Pathogenesis

The pathogenesis of GGA is incompletely understood. It is believed to involve an unknown stimulus that leads to the activation of lymphocytes through a delayed-type hypersensitivity reaction, ultimately initiating a pro-inflammatory cascade and granuloma formation.⁹⁸

Treatment

GGA has a prolonged often unresolving disease course and multiple treatments have been suggested to better manage GGA. However, much of the support stems from small studies and case reports. Antimalarials, retinoids, corticosteroids, dapsone, cyclosporine, PUVA, and calcineurin inhibitors have been suggested as therapies.⁹⁸

Psoriasis

Psoriasis is a chronic immune-mediated inflammatory disorder that may present with a variety of symptoms, including erythematous, indurated, and scaly areas of the skin. Psoriasis is associated with a variety of risk factors, such as hypertension and metabolic syndrome, that increase the likelihood of cardiovascular disease. The development of DM, an additional

cardiovascular risk factor, has been strongly associated with psoriasis.⁹⁹ In particular, younger patients and those with severe psoriasis may be more likely to develop DM in the future.⁹⁹

Lichen planus

Lichen planus is a mucocutaneous inflammatory disorder characterized by firm, erythematous, polygonal, pruritic, papules. These papules classically involve the wrists or ankles, although the trunk, back and thighs can also be affected. Many studies have cited an association between lichen planus and abnormalities in glucose tolerance testing. Approximately one in four patients with lichen planus have DM.¹⁰⁰ Although the association is contested, it has been reported that patients with DM may also be more likely to develop oral lichen planus.¹⁰¹

Vitiligo

Vitiligo is an acquired autoimmune disorder involving melanocyte destruction. Patients with vitiligo present with scattered well-demarcated areas of depigmentation that can occur anywhere on the body, but frequently involves the acral surfaces and the face. Whereas about 1% of the general population is affected by vitiligo, vitiligo is much more prevalent in those with DM. Vitiligo occurs more frequently in women and is also more common in type 1 than in T2DM.^{96,98} Coinciding vitiligo and T2DM may be associated with endocrine autoimmune abnormalities of the gastric parietal cells, adrenal, or thyroid.¹⁰²

Hidradenitis suppurativa

Hidradenitis Suppurativa (HS) is a chronic inflammatory condition characterized by nodules and abscesses located in intertriginous areas such as the axilla or groin. These lesions are often painful and malodorous. HS is frequently complicated by sinus formation and the development of disfiguring scars. HS occurs more often in women than men and usually presents in patients beginning in their twenties.¹⁰³ Compared to the general population, DM is three times more common in patients with HS.¹⁰⁴ Patients with HS be screened for DM. There is no standardized approach to the treatment of HS, although some benefits have been reported with the use of antibiotics, retinoids, antiandrogens, or immunomodulators such as tumor necrosis factor (TNF) inhibitors.¹⁰⁵

Glucagonoma

Glucagonoma is a rare neuroendocrine tumor that most frequently affects patients in their sixth decade of life.¹⁰⁶ Patients with glucagonoma may present with a variety of non-specific symptoms. However, necrolytic migratory erythema (NME) is classically associated with glucagonoma and presents in 70% to 83% of patients.¹⁰⁶⁻¹⁰⁷ NME is characterized by erythematous erosive crusted or vesicular eruptions of papules or plaques with irregular borders. The lesions may become bullous or blistered and may be painful or pruritic. The abdomen, groin, genitals, or buttocks are frequently involved, although cheilitis or glossitis may also be present. Biopsy at the edge of the lesion may demonstrate epidermal pallor, necrolytic edema and perivascular inflammatory infiltrate.¹⁰⁸ Patients with glucagonoma may also present with DM. In patients with glucagonoma, DM frequently presents before NME.¹⁰⁷ Approximately 20% to 40% of patients will present with DM before the diagnosis of glucagonoma.^{107,109} Of those patients diagnosed with glucagonoma but not DM, 76% to 94% will eventually develop DM.¹¹⁰

Skin Infections

The prevalence of cutaneous infections in patients with DM is about 1 in every 5 patients.¹¹¹ Compared with the general population, patients with DM are more susceptible to infections and more prone to repeated infections. A variety of factors are believed to be involved in the vulnerability to infection in patients with uncontrolled DM, some of these factors include: angiopathy, neuropathy, hindrance of the anti-oxidant system, abnormalities in leukocyte adherence, chemotaxis, and phagocytosis, as well as, a glucose-rich environment facilitates the growth of pathogens



Figure 9: Cellulitis and erysipelas.

Bacterial

Erysipelas and cellulitis are cutaneous infections that occur frequently in patients with DM. Erysipelas presents with pain and well-demarcated superficial erythema. Cellulitis is a deeper cutaneous infection that presents with pain and poorly-demarcated erythema. Folliculitis is common among patients with DM and is characterized by inflamed, perifollicular, papules and pustules. Treatment for the aforementioned conditions depends on the severity of the infection. Uncomplicated cellulitis and erysipelas are typically treated empirically with oral antibiotics, whereas uncomplicated folliculitis may be managed with topical antibiotics. Colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) is not uncommon among patients with DM.¹¹² However, it is debated as to whether or not colonized patients are predisposed to increased complications; such as bullous erysipelas, carbuncles, or perifollicular abscesses.¹¹³ Regardless, it is important that appropriate precautions are taken in these patients and that antibiotics are selected that account for antimicrobial resistance.

Infection of the foot is the most common type of soft tissue infection in patients with DM. If not managed properly, diabetic foot infections can become severe, possibly leading to sepsis, amputation, or even death. Although less severe, the areas between the toes and the toenails are also frequently infected in patients with DM. Infections can stem from monomicrobial or polymicrobial etiologies. Staphylococcal infections are very common and complications with infection by *Pseudomonas aeruginosa* are also frequent.¹¹⁴⁻¹¹⁵ Pseudomonal infection of the toenail may present with a green discolouration, which may become more pronounced with the use of a Wood's light. Treatment frequently requires coordination of care from multiple medical providers. Topical or oral antibiotics and surgical debridement may be indicated depending on the severity of the infection.

Necrotizing fasciitis is an acute life-threatening infection of the skin and the underlying tissue. Those with poorly controlled DM are at an increased risk for necrotizing fasciitis. Necrotizing fasciitis presents early with erythema, induration, and tenderness which may then progress within days to hemorrhagic bullous. Patients will classically present with severe pain out of proportion to their presentation on physical exam. Palpation of the affected area often illicit crepitus. Involvement can occur on any part of the body but normally occurs in a single area, most commonly affecting the lower extremities. Fournier's gangrene refers to necrotizing fasciitis of the perineum or genitals, often involving the scrotum and spreading rapidly to adjacent tissues. The infection in patients with DM is most often polymicrobial. Complications of it include thrombosis, gangrenous necrosis, sepsis, and organ failure. Necrotizing fasciitis has a mortality rate of around twenty percent.¹¹⁶ In addition, those patients with DM and necrotizing fasciitis are more likely to require amputation during their treatment.¹¹⁷ Treatment warrants promptness and includes extensive surgical debridement and broad-spectrum antibiotics. Erythrasma is a chronic cutaneous infection, usually asymptomatic, most often attributed to *Corynebacterium minutissimum*. DM, as well as obesity and older age are associated with erythrasma. Erythrasma presents with non-pruritic non-tender clearly demarcated red-brown finely scaled patches or plaques. These lesions are commonly located in the axilla or groin (in intertriginous areas). Due to similarity of appearance

and location, erythrasma is commonly mistaken for dermatophytosis or Candidal infection; in such cases, the presence of coral-red fluorescence under a Wood's light can confirm the diagnosis of erythrasma. Treatment options include topical erythromycin or clindamycin, Whitfield's ointment, and sodium fusidate ointment. More generalized erythrasma may respond better to oral erythromycin.

Malignant otitis externa is a rare but serious infection of the external auditory canal that occurs most often in those with a suppressed immune system, DM, or of older age. Malignant otitis externa develops as a complication of otitis externa and is associated with infection by *Pseudomonas aeruginosa*. Patients with malignant otitis externa present with severe otalgia and purulent otorrhea. The infection can spread to nearby structures and cause complications such as chondritis, osteomyelitis, meningitis, or cerebritis. If untreated, malignant otitis externa has a mortality rate of about 50%; however, with an aggressive treatment, the mortality rate can be reduced to 10% to 20%.¹¹⁸ Treatment involves long-term systemic antibiotics with appropriate pseudomonal coverage, hyperbaric oxygen, and possibly surgical debridement.

Fungal Candidiasis is a frequent presentation in patients with DM. Moreover, asymptomatic patients presenting with recurrent candidiasis should be evaluated for DM. Elevated salivary glucose concentrations and elevated skin surface pH in the intertriginous regions of patients with DM may promote an environment in which candida can thrive.¹¹⁹⁻¹²⁰ Candida infection can involve the mucosa (e.g. thrush, vulvovaginitis), intertriginous areas (e.g. intertrigo, Erosio interdigitalis blastomycetica, balanitis), or nails (e.g. paronychia). Mucosal involvement presents with pruritus, erythema, and white plaques which can be removed when scraped. Intertriginous Candida infections may be pruritic or painful and present with red macerated, fissured plaques with satellite vesiculopustules. Involvement of the nails may present with periungual inflammation or superficial white spots. Onychomycosis may be due to dermatophytes (discussed below) or Candidal infection. Onychomycosis, characterized by subungual hyperkeratosis and onycholysis, is present in nearly one in two patients with T2DM. Candidiasis is treated with topical or oral antifungal agents. Patients also benefit from improved glycemic control and by keeping the affected areas

dry.

Although it remains controversial, dermatophyte infections appear to be more prevalent among patients with DM.¹²¹⁻¹²³ Various regions of the body may be affected but tinea pedis (foot) is the most common dermatophyte infection affecting patients; it presents with pruritus or pain and erythematous keratotic or bullous lesions. Relatively benign dermatophyte infections like tinea pedis can lead to serious sequelae, such as secondary bacterial infection, fungemia, or sepsis, in patients with DM if not treated hastily. Patients with diabetic neuropathy may be especially vulnerable.¹²⁴ Treatment may include topical or systemic antifungal medications depending on the severity.

Mucormycosis is a serious infection that is associated with T1DM, particularly common in those who develop diabetic ketoacidosis. A variety of factors including hyperglycemia and a lower pH, create an environment in which *Rhizopus oryzae*, a common pathogen responsible for mucormycosis, can prosper. Mucormycosis may present in different ways. Rhino-orbital-cerebral mucormycosis is the most common presentation; it develops quickly and presents with acute sinusitis, headache, facial edema, and tissue necrosis. The infection may worsen to cause extensive necrosis and thrombosis of nearby structures such as the eye. Mucormycosis should be treated urgently with surgical debridement and intravenous amphotericin B.

Lastly, abnormal toe web findings (e.g. maceration, scale, or erythema) may be an early marker of irregularities in glucose metabolism and of undiagnosed DM.¹²⁵ Additionally, such findings may be a sign of epidermal barrier disruption, a precursor of infection.¹²⁵

Cutaneous changes associated with DM

Insulin

Subcutaneous injection of insulin is associated with many localized changes. The most common local adverse effect is lipohypertrophy, which affects less than thirty percent of patients with DM that use insulin.¹²⁶⁻¹²⁷ Lipohypertrophy is characterized by localized adipocyte hypertrophy and presents with soft dermal nodules at injection sites. Continued injection of insulin at sites of lipohypertrophy can result in delayed systemic insulin absorption and capricious glycemic control. With the avoidance of subcutaneous insulin at affected sites, lipohypertrophy normally improves over a few months. Furthermore, lipoatrophy is an uncommon

cutaneous finding which occurred more frequently before the introduction of modern purified forms of insulin. Lipoatrophy presents at insulin injection sites over a period of months with round concave areas of adipose tissue atrophy. Allergic reactions to the injection of insulin may be immediate (within one hour) or delayed (within one day) and can present with localized or systemic symptoms. These reactions may be due to a type one hypersensitivity reaction to insulin or certain additives. However, allergic reactions to subcutaneous insulin are rare, with systemic allergic reactions occurring in only 0.01% of patients.¹²⁶ Other cutaneous changes at areas of injection include the development of pruritus, induration, erythema, nodular amyloidosis, or calcification.

Oral Medications

Oral hypoglycemic agents may cause many cutaneous adverse effects such as erythema multiforme or urticaria. DPP-IV inhibitors, such as vildagliptin, can be associated with inflamed blistering skin lesions, including bullous pemphigoid and Stevens-Johnson syndrome, as well as, angioedema.^{128, 129} Allergic skin and photosensitivity reactions may occur with sulfonylureas.¹³⁰ The sulfonylureas, chlorpropamide and tolbutamide, are associated with the development of a maculopapular rash during the initial two months of treatment; the rash quickly improves with stoppage of the medication.¹³¹⁻¹³² In certain patients with genetic predispositions,³² chlorpropamide may also cause acute facial flushing following alcohol consumption.¹³³ Canagliflozin, as SGLT-2 inhibitor, has been associated with an increased risk of genital fungal infections.¹³⁴

Conclusions:

DM is associated with a wide array of dermatologic disorders. Many of the sources describing dermatologic changes associated with DM are antiquated; larger research studies utilizing modern analytic tools are needed to better understand the underlying pathophysiology and treatment efficacy. Although each condition may respond to a variety of specific treatments, many will improve with improved glycemic control. Hence, patient education and lifestyle changes are key in improving the health and quality of life of patients with DM.

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Case Report

Lepromatous Hansen's Disease Simulating Still's Disease: A Parodying Case Report with Diagnostic Conundrum

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Abstract

Leprosy, caused by *Mycobacterium leprae*, is an ancient chronic granulomatous infectious disease which is known to affect human beings and continues to be an important prevalent disease in several developing nations. Since leprosy mimics connective tissue disease, several case reports have mentioned that it mimics common rheumatologic diseases like rheumatoid arthritis (RA), seronegative spondyloarthritis (SpA) and systemic lupus erythematosus (SLE). After extensive literature search we failed to find case report of leprosy with type two reaction simulating still's disease. Hence we hereby report a case of an 18 year old male with lepromatous Hansen's disease with type 2 reaction misdiagnosed and mismanaged as Still's disease.

Keywords: Lepromatous Hansen's Disease, Still's Disease, Erythematous Nodules

Introduction:

Leprosy is an ancient chronic granulomatous infectious disease which is known to affect human beings and continues to be an important prevalent disease in several developing nations.¹ *Mycobacterium leprae* is the causative organism for leprosy. It is globally distributed; however, it is especially prevalent in developing countries in Asia, Africa, and Central/South America, while it is quite rare in developed countries.² Since leprosy mimics connective tissue disease, several case reports have mentioned that it mimics common rheumatologic diseases like rheumatoid arthritis (RA), seronegative spondyloarthritis (SpA) and systemic lupus erythematosus (SLE).³⁻⁴ It is also known to present

with clinical and laboratorial findings that mimic autoimmune connective tissue diseases and vasculitis.⁵ One to five percent of leprosy patients are reported to develop arthritis of small joints of hands and feet akin to that seen in rheumatoid arthritis.¹ We hereby report a case in which leprosy presented with features similar and thus initially diagnosed and treated as still's disease. In areas endemic for leprosy it is imperative to keep in mind the myriad presentations of leprosy including its musculoskeletal manifestations, as consequences of misdiagnosis, mistreatment can be catastrophic, especially in the era of increasing use of biologic disease modifying agents.⁶

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Case Report :

An 18 year old male presented with multiple red colored nodules to plaques with erosions on few lesions of both upper and lower limb of size 1x2 cm to 2x3 cm on and off since 6 years and Joint pain on and off since 6 years. On detailed history patient had multiple joint pain involving large and small joints with high grade fever with multiple red colored raised lesions over bilateral upper limb and lower limb (Figure1). Patient was on treatment from rheumatologist diagnosing him to have Still's disease and accordingly he was treated with high dose corticosteroids during the period of exacerbation, which would give symptomatic relieve followed by reappearance of symptoms when patients is off steroids. Due to long term steroid use patient developed cushingoid facies and hypertension. He was also given disease modifying agents like methotrexate and mycophenolate mofetil. Disease severely affected the quality of life and not able to do his daily activities due to pain. On Examination submental, bilateral inguinal and right axillary lymph nodes were enlarged and with bilateral edematous hands. Patient also had hepatosplenomegaly. On cutaneous examination erythematous nodules to plaques with few erosions was present over bilateral upper limb and bilateral lower limb. Multiple hyperpigmented macules were also present over bilateral upper limb and lower limb. Nerve examination revealed bilateral ulnar, superficial radiocutaneous and common peroneal nerve thickening with neuritis. Hence differential diagnoses were Hansen's disease with Type 2 lepra reaction and Still's disease. Routine investigations revealed anaemia, leucocytosis and raised liver enzymes. C reactive protein was positive. Slit skin smear for AFB was Positive. Diagnosis of Hansen's disease with type 2 reaction was further confirmed on histopathology and Fite-Faraco staining. Microscopically, H&E stained section of skin biopsy showed presence of unremarkable epidermis. Dermis shows presence of clusters of macrophages. These macrophages showed abundant pink to pale cytoplasm which corresponds to numerous intracellular organisms. There is also presence of diffuse lymphocytic infiltrate (Figure 2). Fite-Faraco stained sections showed presence of large aggregates of red coloured leprosy bacilli within the macrophages (Figure 3). Multibacillary antileprosy treatment, corticosteroids and thalidomide for type 2 reaction was started. Patient showed excellent response to treatment.

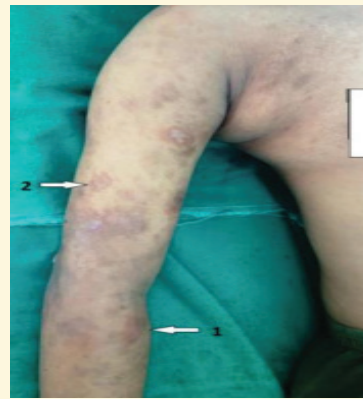


Figure 1: Multiple erythematous nodules (arrow no. 1) with multiple post inflammatory hyperpigmented patches seen (arrow no. 2)

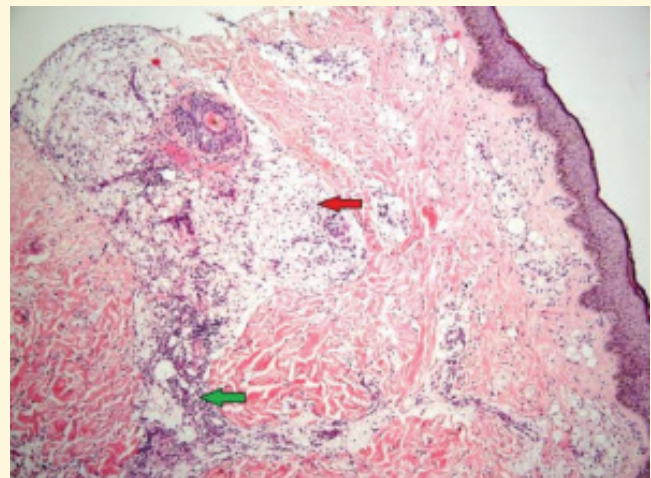


Figure 2: Large clusters of macrophages (red coloured arrow) within the dermis along with lymphocytic infiltrate (green coloured arrow) (H&E, x400).

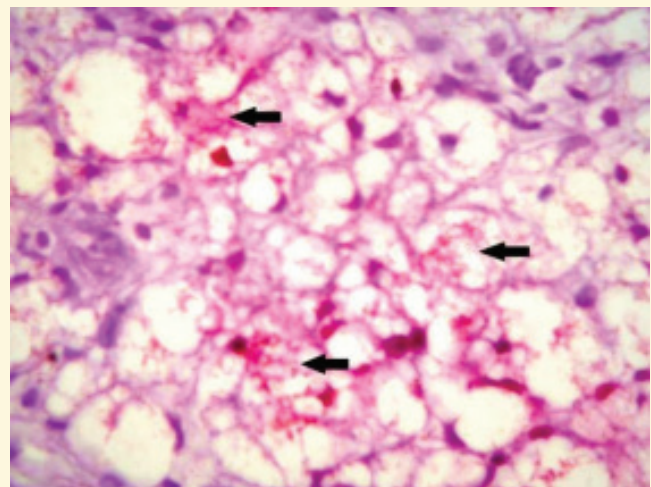


Figure 3: Large aggregates of red coloured leprosy bacilli (black coloured arrows) within the macrophages (Fite-faraco, x1000).

Discussions:

Leprosy displays a wide spectrum of clinical and histological manifestation, reflecting the broad range of cellular immune response to *Mycobacterium leprae*. The disease spectrum ranges from a form with a strong immune response and fewer organisms as in case of tuberculoid or paucibacillary to a form with a weaker immune response and higher organisms as in case of lepromatous or multibacillary.⁶ Articular involvement in leprosy is the third most frequent manifestation, after dermatological and neurological involvement.² Stills disease present with the skin lesions which are evanescent, salmon colored, macular or maculopapular cutaneous eruption, usually non pruritic in nature, occurs along with fever and disappears during a febrile period. The rash predominantly involves trunk, extremities but can also involve palms, soles and occasionally the face. Leprosy patients have various forms of skin lesions such as macules, papules, nodules, plaques, diffuse infiltration, and ulcers. Patients of leprosy have a number of auto antibodies which add to the confusion. These include ASO, RF, ANA, ANCA and even antiphospholipid antibodies, ds-DNA, and anti-CCP and C reactive protein.³ Our patient had multiple erythematous nodules to plaques with fever, lymphadenopathy, anaemia, leucocytosis and positive C reactive protein which is common for both the diseases. In our case, histopathological and Fite Faraco staining helped us to confirm the diagnosis of Hansen's disease. Multibacillary leprosy may be initially misdiagnosed as Still's disease due to sharing of similar clinical manifestations. Hansen's disease is a great mimic and needs an astute clinical sense with a high index of clinical suspicion to capture it early enough for an effective and complete cure.¹ Moreover, this case report is aimed to create awareness for possibility of leprosy patient visiting rheumatology out-patient from endemic areas and getting misdiagnosed. We conclude that an unexplained high grade fever accompanied by skin rash from endemic areas should be actively ruled out clinically and if necessary with investigations for excluding mycobacterium infection before diagnosing, a rare, diagnosis of exclusion autoimmune disorder like Still's disease to save patients from needless anti-rheumatic treatment

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Case Report

Flegel's disease (FD) or hyperkeratosis lenticularis perstans (HLP): A case report

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Abstract

Flegel's disease (FD), is a rare dermatosis and benign cornification disorder. Four cases of Flegel's disease were reported for the first time in Bangladesh. Cases presented with symmetrically distributed erythematous or brownish hyperkeratotic papules and plaques on leg, upper arm and upper back. All cases had familial association. Clinical diagnosis of FD was confirmed by histopathological examination. Histopathological findings showed compact hyperkeratosis, orthokeratosis, thinning of stratum mulpighii and band like lymphocytic infiltration in the dermis. This rare dermatosis requires clinical and histopathological correlation to diagnose at an early stage and to avoid under-reporting.

Key words: Flegel disease, Hyperkeratosis lenticularis perstans.

Introduction:

Hyperkeratosis lenticularis perstans (HLP) or Flegel's disease (FD), is a rare dermatosis and benign cornification disorder first described in 1958 by Flegel.¹ FD is characterized by asymptomatic small erythematous or brownish hyperkeratotic papules from 1 to 5 mm in size that is generally distributed symmetrically on the limbs, particularly the dorsal feet and lower part of the legs.¹⁻² FD is more commonly reported to occur in women and is inherited as an autosomal dominant condition, although sporadic cases were also reported.³ FD is considered a rare disorder; no data exist on the prevalence of the disease. To our knowledge, no documented case was reported in Bangladesh before. However, four cases of this rare disease were reported for the first time in Bangladesh.

Case reports:

Case 1

A 36-year-old woman presented to the Dermatology

outdoor of BSMMU with multiple erythematous mildly pruritic hyperkeratotic papules and plaques on both legs with hyperpigmented border for 16 years. Skin lesions have progressed at a very slow rate. Initially, lesions were yellowish, discrete, hyperkeratotic papules involving the middle of the leg. In course of time it became larger, fused as plaques and extended almost the whole anterior aspect of leg. Papules and plaques were bilaterally symmetrically distributed. She has no history of excessive sun exposure, trauma, atopic or systemic diseases. She was previously treated with several medications, including topical corticosteroid and emollients, but there was no satisfactory response. On different occasions clinically she was diagnosed as a case of hypertrophic lichen planus, prurigo nodularis and lichen amyloidosis. She gave no history of consanguinity of marriage. She has two daughters and one son. Only one of her daughters had developed the same type of skin disease. On

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examination, there were numerous red-brown hyperkeratotic papules 1-5mm in size with discrete irregular margins on extensor aspects of both legs, on removing the keratotic scales from a lesion, a non-exudative erythematous base was revealed (i.e., "cornflake sign") with multiple bleeding points. There was no koebnerization, Wickham's striae or follicular involvement. Mucous membranes, nails and hair follicles were intact. The clinical appearance of the skin eruption was typical of Flegel's disease.



Figure 1 case 1: Multiple hyperkeratotic papules & plaque

Case 2

A 20-year-old woman, daughter of case one presented with multiple moderately pruritic, hyperkeratotic, hyperpigmented, bilaterally symmetrical discrete papules on both legs for 6 years. Routine laboratory examinations reveal no abnormality. She is otherwise in good health.



Figure 2 case 2: Multiple hyperkeratotic papules & plaque

Case 3:

A 13-year-old female presented with mildly pruritic erythematous hyperkeratotic papule in the anterior leg, dorsum of feet, upper arm and upper back for 3 years. The patient was in good health. Laboratory examinations were normal. One of her sisters is affected with a similar skin lesion.



Figure 3 Case 3

Figure 4 Case 3

Case 4:

A 10-year-old female (Sister of case 3) presented with moderately pruritic erythematous hyperkeratotic papule in the anterior leg, dorsum of feet, upper arm and upper back for 4 years. On examination, erythematous base revealed on removing the keratotic lesion. Koebner phenomenon was positive. Routine laboratory tests were all normal.



Figure 5 Case 4

Figure 6 Case 4

Table: Case list

Patient no.	Age of onset	Duration (years)	Site	Symptoms
Case-1 (mother)	20	16	Anterior leg, dorsum of feet	Mild pruritus
Case-2 (daughter)	14	6	Anterior leg, dorsum of feet	Moderate pruritus
Case-3 (sister)	13	3	Anterior leg, dorsum of feet, upper arm, upper back	Mild pruritus
Case-4 (sister)	10	4	Anterior leg, dorsum of feet, upper arm, upper back	Moderate pruritus (Koebner phenomenon positive)

Basic investigations of all four cases including complete blood count, blood sugar, ESR, thyroid, renal and liver function tests were all normal. White structure-less areas on the surface were the dermoscopic findings in all patients. Histopathological examination of lesional skin biopsy showed compact hyperkeratosis, orthokeratosis, thinning of stratum mulpighii and granular layer, atrophy of epidermis, band like lymphocytic infiltration in the dermis and dilated dermal vessels. Histological features are compatible with the clinical diagnosis of Flegel's disease (2,3,4).

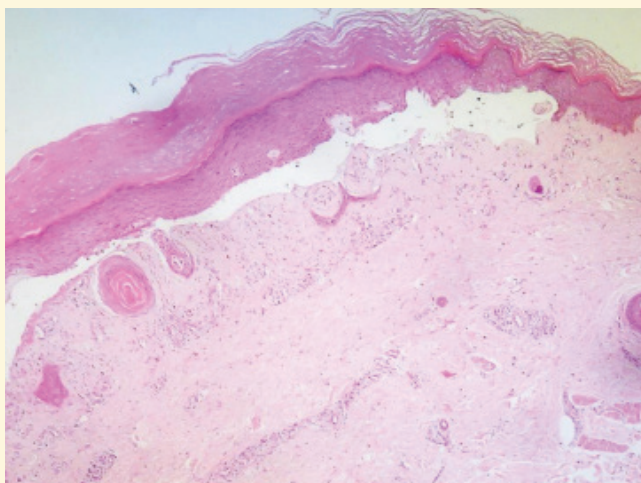


Figure 7: Histopathology of FD in (4x magnification) showing compact hyperkeratosis, orthokeratosis, thinning of stratum mulpighii and band like lymphocytic infiltration in the dermis

Discussions:

Flegel disease is presented as a chronic eruption of numerous symmetric hyperkeratotic papules, located primarily on the dorsal feet and lower legs. Rarely it can present in the trunk, buttock, upper extremities, neck (found in our case), palm & sole (3,4). FD typically manifests in the fourth to the fifth decade of life, however has been reported in individuals as early as 13 years of age.⁴ In our context, all four cases have early presentation in their second decade, as early as 10 years of age. Interestingly all cases have a familial association which supports the autosomal dominant inheritance pattern of FD.⁵ Although most cases reported worldwide were sporadic. Pathogenesis of FD is still not well established, most discussed findings are the qualitative and quantitative alterations in membrane coating granules (MCGs); also known as (lamellar granules, odland bodies) in the epidermis. Lamellar granules are thought to have a role in the formation of epidermal permeability and their absence/reduction results in reduced desquamation of stratum corneum and in retention hyperkeratosis.⁶⁻⁷ No culprit gene or specific triggering factors have been identified to date. FD has been reported to be associated with adult-onset diabetes mellitus, hyperthyroidism and hyperaldosteronism.⁷ Though in our cases, no systemic disease association was evident. The clinical features of FD are not distinctive. Clinically it resembles hypertrophic lichen planus, prurigo nodularis, keratotic diseases like Kyrle's disease, stucco keratosis, disseminated superficialis actinic porokeratosis etc.⁷⁻⁸ Therefore, histopathological confirmation is mandatory to exclude other keratotic diseases.⁹ Treatment of FD is challenging and there is no standard therapy exist.¹⁰ Cases have been reported with variable results using topical corticosteroids, topical 5-FU, topical and systemic retinoids, vitamin D3 synthetics, PUVA and ablative treatment including (local excision, curettage, cryotherapy, CO2 laser, electrocoagulation).^{7,9,11-12} We have suggested following treatment protocol, cryotherapy for mother-daughter case, topical retinoid-calcipotriol combination and systemic retinoid for two sisters. The outcome of treatment is yet to be determined.

From our experience, FD is an under-reported disease mostly because of its asymptomatic clinical manifestation and clinical resemblance to other diseases, which takes a longer time to diagnose until

skin biopsy is done. Therefore, we assume that the actual prevalence of disease would be much higher. Also, as it is mostly an aesthetic concern, female patients are more prone to seek medical advice and get their skin biopsy done compared to male patients. So, there could be a bias in reporting male female-ratio. The rarity of the disease and the chance of under-reporting prompted us to present this case report.

Conclusions:

FD is a rare disease. But with the combination of proper clinical findings and histopathology, we can diagnose the disease during the early phase of manifestation, which can provide us with better treatment outcomes and patient satisfaction.

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Case Report

Autosomal recessive Cutis laxa with an inguinal hernia: a rare inherited disorder of connective tissue

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Abstract

Cutis laxa (CL) is a rare connective tissue disorder characterized by loose, sagging, and redundant skin. Both inherited and acquired forms are known. A 16-month-old boy, presented with loose, redundant skin chiefly below the chin, trunk, extremities since birth with scrotal swelling and difficulty in micturition. The patient had a characteristic senile bloodhound appearance. Histopathological examination showed markedly reduced elastic fibres in the dermis. There is no definitive treatment available at present. Differential diagnosis includes Ehlers–Danlos syndrome, congenital disorders of glycosylation syndrome, and pseudoxanthoma elasticum. That case is an important subject to report for its rarity and complex systemic involvement.

Key words: Cutis Laxa, Elastolysis, Autosomal recessive cutis laxa.

Introduction:

Cutis laxa (CL) is a rare disorder of elastic tissue. Only over 200 cases reported worldwide so far.¹ It is characterized by elastolysis or loss of elasticity of the skin. Patients usually presented with a characteristic old appearance with loose, sagging skin over the face, extremities and trunk. Both inherited and acquired forms are found. Inherited forms of CL may be autosomal dominant, autosomal recessive (AR), and X-linked.² Normally the disease can be diagnosed clinically with minimal laboratory support. There is no treatment for cutis laxa. Some supportive, symptomatic and or cosmetic treatment options can improve the quality of life of patients.

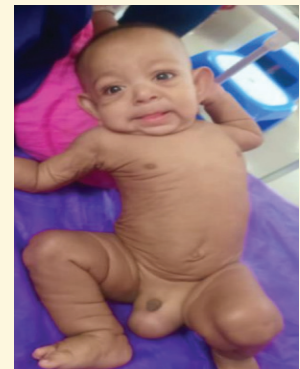
Case report:

A 16-month-old boy the third and only living child of a consanguineous parent presented with loose and inelastic skin over the face, trunk and extremities noticed since the 4th month of life. The boy looked

like an old man. His IQ and developmental milestones are up to the mark. The patient's mother had complaint of his difficulty in micturition and gradual swelling of the scrotum. He had no other systemic complaint



(A)



(B)

Figure 1: a) A case of cutis laxa b) Scrotal swelling

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His eldest sister was a case of cutis laxa and died with pulmonary emphysema and corpulmonale when she was at the age of 16 months. His elder brother died at his first month of life due to pneumonia. He was not diagnosed as a case of cutis laxa. His imaging and the echocardiographic report were normal but ultrasonographic study confirms bilateral inguinal hernia. There was a loss of elastic tissue in the dermis with Verhoeff-Van-Gieson stain in the histopathological report. Ptosis, low set, prominent ears, large forehead, long philtrum, and hanging cheeks were present over the face, giving the child an aged appearance. He was at first diagnosed as a case of progeria might be for his characteristic facies.

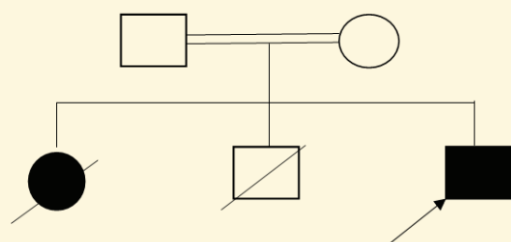


Figure 2: Pedigree chart of patient

The child was born out of a first-degree consanguineous marriage. His mother stated that her antenatal period and labour were uneventful. Finally, the patient was diagnosed as a case of autosomal recessive cutis laxa type 1 (ARCL-1). He was sent for consult with a pediatric surgeon for his hernia.

Discussions:

Generalized CL is also known as generalized elastolysis.³ The calculated prevalence is 1/1,000,000.⁴ ADCL is a milder form and usually appears in childhood or early adulthood. It presents with characteristic facial features with loose skin and systemic involvement such as gastrointestinal diverticula, herniae, uterine prolapse, and aortic dilatations.^{2,4} Autosomal recessive cutis laxa (ARCL) is the most severe form of CL. ARCL-1 presents at birth with cutaneous manifestations affecting the whole body. Systemic manifestations include pulmonary emphysema, gastrointestinal and bladder diverticula, arterial aneurysms, pulmonary artery stenosis, hernia, etc., and are severe and life-threatening.⁵ Child's developmental milestones and intelligence quotient are normal. FBLN5 and FBLN4/EFEMP2 genes are affected.⁴ In ARCL-2, there

is intrauterine growth restriction, skeletal involvement, and developmental delay. Loss of function mutations is present in ATP6V0A2, resulting in abnormal glycosylation.^{2,4,6} ARCL-3 (de Barsy syndrome) presents with severe mental retardation, athetoid movements, and corneal opacities.⁷ In X-linked form (occipital horn syndrome), bladder diverticula, inguinal hernias, slight skin laxity and hyperextensibility, joint laxity, coarse hair, and skeletal abnormalities are associated. Mutation in copper transporter gene ATP7A is seen, resulting in low-serum copper, and ceruloplasmin levels.^{2,4} Differential diagnosis includes Ehler's–Danlos syndrome in which there are hyperextensible joints with hypermobility, but not lax skin. There is quick recoil of skin on stretching.^{2,4,8} Pseudoxanthoma elasticum is characterized by fragmented and calcified elastic fibres. The face is spared, and the skin is yellow.^{2,4} The exact pathogenesis of CL is not known, but the various hypothesis has been proposed such as immune-mediated mechanism, altered copper metabolism, and excess elastase.^{2,4} In our case, the child had similar complaints in siblings, which is suggestive of AR inheritance. In our case, there was a severe wide range of systemic involvement (pulmonary hypertension, emphysema, bronchopneumonia, chronic cystitis and bladder diverticula) which are life-threatening.⁹ Hence, continuous monitoring and active management for the associated complications were needed. Diagnosis of ARCL-1 was done based on clinical features, extracutaneous findings, and histopathological findings with the exclusion of differential diagnosis. There is no effective treatment available for ARCL-1.^{10,11} Symptomatic management for the associated complications remains the mainstay of treatment. Genetic counselling of the affected family is essential.¹² Due to financial constraints the genetic studies could not be performed in our case. It might be the first reported case of cutis laxa in Bangladesh. Conclusion: We report this case of ARCL-1 with complex systemic involvement for its rarity.

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Case Report

Undifferentiated pleomorphic sarcoma (UPS) or Malignant fibrous histiocytoma (MFH)

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Abstract

Malignant fibrous histiocytoma (MFH), currently classified as undifferentiated pleomorphic sarcoma, is the most frequent soft tissue sarcoma in adulthood, but it is not as common as a primary skin tumour. We report a case of 50-year-old male cultivator with no significant previous medical history who presented with a solitary painless ulcerated tumour on the right knee. Histopathological findings of ulcer showed pleomorphic cells in the dermis, areas of necrosis and mitotic figures and histopathology of lymph nodes showed tumour metastasis. Probably we are reporting this type of case for the first time in Bangladesh.

Key words: Undifferentiated pleomorphic sarcoma; Malignant fibrous histiocytoma

Introduction:

Undifferentiated pleomorphic sarcoma (UPS), previously known as malignant fibrous histiocytoma (MFH), was first described in 1960 by O'Brien and Stout and histological features of UPS were first described by Kempson and Kyriakos¹. UPS usually occurs in older adults, men account for two-thirds of cases and the Caucasian population is more commonly affected. It can occur anywhere in the body, typically involves the extremities (70-75%) with lower extremities accounting for 59% of cases and less commonly the retroperitoneal spaces, abdominal cavity or other sites such as visceral organs². Soft tissue sarcomas generally manifest as deep lesions, but they may affect the skin and subcutaneous tissue³. The most common clinical presentation is large solitary painless soft-tissue mass in the lower extremities, typically 5-10 cm in diameter. The majority of tumours are

intramuscular. At gross pathologic examination, the lesion is multi-lobulated with necrosis, degeneration or extensive haemorrhage can be present. Well defined border of the tumour may appear. Microscopically, a malignant cell with variably pleomorphic nuclei are characteristic.⁴ UPS is often diagnosed in advanced stages, with a tendency to local recurrence and systemic metastasis. Since tumour thickness and size are identified as major prognostic factors, early recognition becomes crucial to improve prognosis. The mainstays of treatment for UPS are complete surgical excision most often supplemented with adjuvant radiation therapy.

Case Report:

A 50-year-old male cultivator presented with a solitary painless ulcerated tumour on the right knee for 2 years. The ulcer was small to larger within the last

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few months, size about 5 cm x 6 cm. The patient's medical history was unremarkable. On examination, the patient was a healthy individual with normal vital signs. The ulcer was localized, deep, firm, non-tender; base was edematous, weepy; the floor was covered by inflammatory exudates, serosanguinous fluid and necrotic tissue; edge was raised, circular, well demarcated but irregular (Figure-1). The colour and temperature of the surrounding skin and rest of the leg were normal. No cyanosis and gangrene was present



Figure 1: Clinical image of lesion shows solitary ulcerated plaque, size about 5 cm x 6 cm

The lymph node was palpable on the right inguinal region, 3 to 4 in number, isolated but grouped, 1.5 cm x 1.5 cm in size approximately, firm, non-tender, not fixed with the overlying skin and underlying structure. The differential diagnosis included an atypical fibroxanthoma and a pleomorphic dermal sarcoma, leiomyosarcoma, myxofibrosarcoma. Basic investigations including complete blood count with ESR, blood sugar, chest x-ray (P/A view), ultra-sonogram of the whole abdomen, thyroid, renal and liver function tests were all normal. Histopathological examination of the ulcer revealed the dermis and subcutis present a tumour made of spindle-shaped cells. The tumour cells show moderate pleomorphism. Areas of necrosis and mitotic figures are seen. The surgical margin is involved by the tumour (Figure-2, 3)

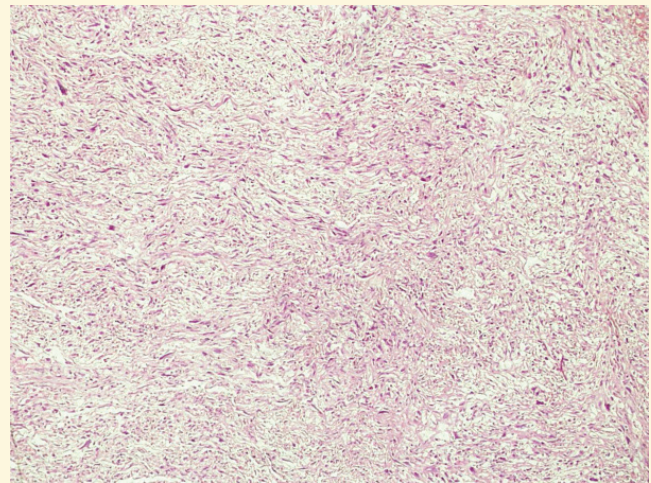


Figure 2: Neoplastic proliferation of spindle-shaped cells (H and E)

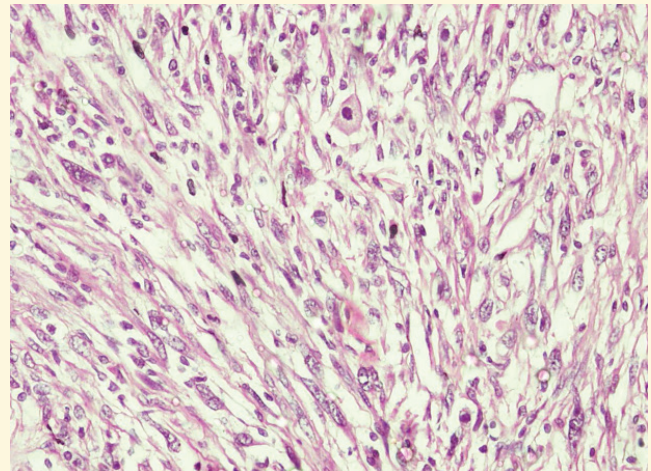


Figure 3: Mitotic figures in malignant cells (H and E)

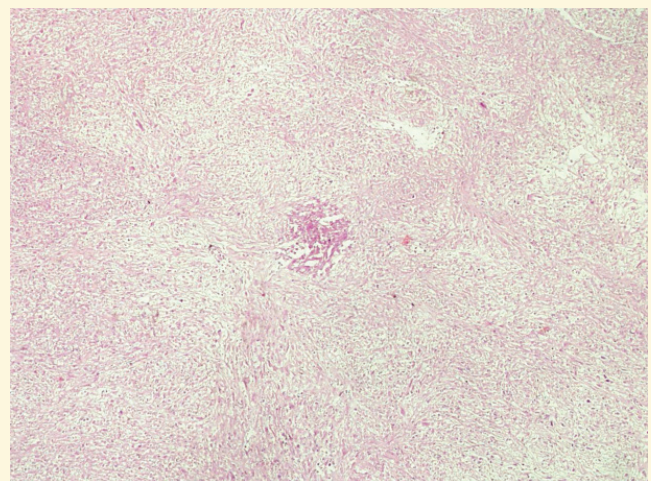


Figure 4: Metastatic tumour in lymph node (H and E)

Histopathology of lymph nodes showed tumour metastasis (Figure-4)

The diagnosis of undifferentiated pleomorphic sarcoma (UPS) was done based on clinical history, lesion morphology and pathologic findings.

Discussions:

The term “Malignant Fibrous Histiocytoma (MFH)” has been changed by the WHO to Undifferentiated Pleomorphic Sarcoma (UPS) not otherwise specified.⁵ According to the histology MFH is classified into five types—storiform/pleomorphic, giant cell, inflammatory, myxoid (myxofibrosarcoma) and angiomatoid.² In such cases, an alternate name of undifferentiated high-grade pleomorphic sarcoma is being advocated by the WHO in its 2002 classification of soft tissue tumours. The diagnosis of storiform-pleomorphic MFH is one of exclusion when no line of differentiation is identified. Pleomorphic is the most commonly seen histological variant of tumour and our case also belonged to this subtype.⁵ However, undifferentiated pleomorphic sarcoma (UPS) is a rare entity, which is a member of spindle cell neoplasms arising from the skin or soft tissue and can show variable clinical courses, despite being histopathologically similar.⁶ Dermal UPS is called by different names in the literature, such as atypical fibroxanthoma (AFX), superficial malignant fibrous histiocytoma (MFH), superficial UPS or pleomorphic dermal sarcoma (PDS).⁷⁻⁹ However, undifferentiated pleomorphic sarcoma not only encompasses skin neoplasms but also a heterogeneous group of soft tissue malignant neoplasms of the internal organ, retroperitoneal, and osteoid origins.¹⁰⁻¹¹ The mutation of telomerase reverse transcriptase (TERT) is present in 76% of the skin UPS cases and appears to be associated with UV damage.⁷ Thus, the increased incidence in the sun-exposed or UV-damaged skin areas such as head and neck can be explained by TERT mutation.¹³ On the other hand, the presence of a rapidly growing aggressive lesion on the non-UV-exposed skin areas, particularly in elderly patients, it is recommended to rule out other possible malignancies before diagnose UPS due to its rarity.¹³ USP may also arise at sites of chronic ulceration.⁴ USP usually affects the proximal limbs, although it has been described in the cephalic location. It usually presents as a slow-growing tumorous lesion, though no clinical characteristic allows differentiation from other sarcomas. Tumour size and depth have been identified as the main prognostic factors. Therefore, establishing an accurate and early diagnosis is crucial in improving

the tumour prognosis.¹ In the present report, the case was a painless deep seated ulcerated plaque on the right knee with a slow-growing tumorous lesion with no significant previous medical history. The diagnosis of USP is clinically difficult to identify, especially in cases where the tumour is deep and is usually diagnosed after the removal¹⁰. The definitive diagnosis of UPS relies on histological studies and showed malignant cells with nuclei pleomorphism and atypical mitotic figures. There is no characteristic immunohistochemical profile. Immunohistochemical analysis is used to help exclude other tumours that may have a pleomorphic appearance.⁴ In our case report, the diagnosis of UPS was confirmed by a combination of clinical history, clinical examination and histologically.

UPS treatment options vary based on factors such as: (i) whether the UPS is localized or metastatic, (ii) location of the tumour, (iii) patient's age and general health. In general, treatment options for UPS may involve surgery and chemotherapy. Treatment of localized UPS may include chemotherapy followed by surgery to remove the tumour and surrounding tissue. Prognosis of Undifferentiated pleomorphic Sarcoma (UPS) is influenced by the depth of tumour infiltration into the surrounding tissue, the mass of the tumour and anatomic location of the tumours.

Conclusions:

UPS is a rare entity with relatively difficult to diagnose. So, the final diagnosis should be made based on the correlation of the clinical history, lesion morphology, and pathologic findings.

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Case Report

'Coral reef' pigmentation in lip Discoid lupus erythematosus

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Abstract

Discoid lupus erythematosus (DLE) is a chronic inflammatory disorder. Histopathology was the method of choice for diagnosis previously. Though histopathology still remains the main mode of diagnosis, with the advent of dermoscopy, it has replaced biopsy in many cases. With new findings coming in, the diagnosis of dermatological diseases, the activity of disease and assessment of treatment response have become much easier. We describe a 32 years old female presented with lip DLE which was clinically and histopathologically confirmed. The dermoscopic findings from the lip were brown-red pigment spots, white structureless areas, scales palisade pigmentation and 'coral reef' pigmentation. In dermoscopy, it is an array of findings that point to a diagnosis rather than a single finding and hence this pattern of pigmentation simulating 'coral reef' can be added to the spectrum of dermoscopic findings noted in lip DLE and thereby can aid in diagnosis.

Key words: Case report, Dermoscopy, DLE, Pigmentation, Coral reef, Mucoscopy

Introduction:

Dermoscopy is a tool that is highly being utilized in the diagnosis of discoid lupus erythematosus (DLE), the commonly noted findings being a loss of follicular ostia, follicular keratotic plugs, branching vessels, honeycomb pigmented networks, dyschromia and variable scaling. It has also been used to determine the activity of the disease. Dermoscopy of mucosal DLE differs from cutaneous DLE in lacking follicular plugs, perifollicular halo, and a reduced number of follicular ostia.¹

Case description:

We present a 32-year female with multiple lesions on the lower face with a single large lesion on lower lip and scalp for two years. The lesions were slowly increasing in size without any symptoms. On examination, there were well-defined papules and

plaques with the centre showing erythema with scaling and periphery showing a hyperpigmented border with no crater (Figure 1). The rest of the mucocutaneous examination revealed a lesion on the scalp also.

A biopsy from the scalp lesion was taken which showed epidermis with hyperkeratosis, loss of rete ridges, hydropic degeneration of basal cells, dyskeratosis, follicular plugging with dermis showing lymphoplasmacytic infiltrate along dermo-epidermal junction, around hair follicles and pilosebaceous units with pigment incontinence, extravasation of RBCs and vasodilatation and increase in collagen layers. Dermoscopy was done using a DERMLITE DL3N dermatoscope in both polarised and non-polarised mode at 10X magnification. There were brown-red pigment

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spots, palisade pigmentation, white structureless areas, scales and peripheral red-brown pigmentation arranged in branching pattern with mottling pigmentation simulating 'coral reef' just along the inner aspect of 'palisade pigmentation' along the periphery (Figure 2A and 2B). Based on clinical, dermoscopic, and histological features, a diagnosis of DLE was made.



Figure 1: Multiple well-defined scaly plaques with central erythema and peripheral hyper-pigmented border

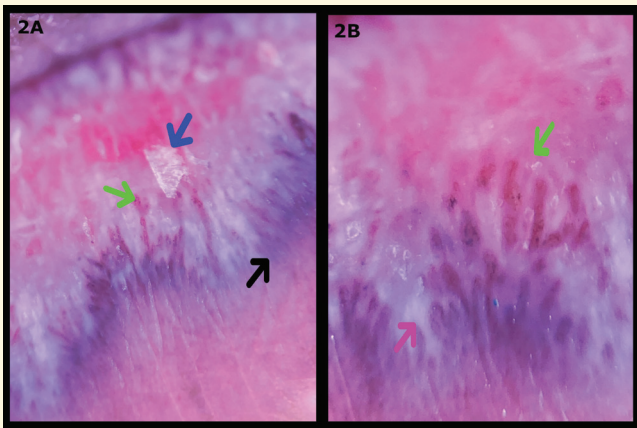


Figure 2: A. Dermoscopy under polarized mode using Dermlite DL3N X10 magnification and showing palisading pigmentation (black arrow) along the periphery, inside of which there is red-brown branching pigmentation with mottling resembling coral reef (green arrow) and scales (blue arrow). B. Dermoscopy under polarized mode using Dermlite DL3N X10.



Figure 3: Coral reef.

Discussions:

Discoid lupus erythematosus of the lip can mimic actinic lichen planus, squamous cell carcinoma and porokeratosis. It is mostly a combination of dermoscopic findings that help in the diagnosis rather than a single finding. Dermoscopy of lip DLE has been reported to show brown pigment spots, telangiectasia, storiform/hairpin vessels, white structure-less areas, ulceration, erosion, bleeding spots and scales.² Hyperpigmentation was observed on dermoscopy in 43.6% cases of DLE, 49.1% of the corresponding biopsies showing pigmentary incontinence.³ Varying patterns of pigmentation have been described in dermoscopy of DLE like honeycomb pigment pattern, blue grey dots and globules, blue-white veil and speckled brown pigmentation.⁴ 'Palisade pigmentation' has been described along the periphery in late stage.⁵ Our patient demonstrated pigmentation simulating 'coral reef' just along the inner aspect of palisade pigmentation (Figure 3). Unlike palisade pigmentation, this pattern showed branching in acute angles.

Conclusions:

Dermoscopy can be a method of diagnosis in DLE when a biopsy is deferred by the patient and when the site of biopsy is a high-risk site or difficult-to-access

site. This pattern of pigmentation simulating 'coral reef' can be added to the spectrum of dermoscopic findings noted in lip DLE.

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Presentation at a meeting:

None

Conflict of interest:

There are no conflicts of interest

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1. An optimal clinical picture contributes to visual information that will be useful to other physicians.

2. The purpose of this section is to provide high quality images to illustrate an important dermatological disorder, which should be interesting and educational. Good images relevant to daily practice are welcome.

3. Most formats are acceptable, including JPEG (preferable), TIFF, BMP, GIF, Adobe Photoshop, Adobe Illustrator. The most important factor is that the images are clear (at least 1-4 MB in size) and of not less than 300 dpi.

4. A brief description regarding the patient history and the condition, management must be provided. (around 500 words) A

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- o At least two clinical images should be submitted, pre and post treatment, clearly indicating the change after treatment. Images must be in jpeg or jpg format, minimum 300 dpi.

- o The mechanism of action of the reported modality should be mentioned or logical explanation should be given.

- o The utility of newer technique in comparison to conventional treatment modality should either be evident by clinical response or should be explained in manuscript.

- Letters to the editor: Letters to the Editor (Correspondence) may be in response to issues arising from recently published articles, or short, free-standing pieces expressing an opinion. These should be formatted in one continuous section, normally be no more than 750 words in length, may have up to 5 references and a maximum of three photographs. No abstract is required.

- History: An article (up to 2500 words in length) on the history of pigmentary disorder, also a biographic account of a historic or noteworthy figure in dermatology. No abstract is required.

- Perspective: An article of 500-1000 words length with 0- 5 references on matters of interest to readers may be submitted. The author may express his or her opinion without complete documentation. No abstract is required.

- Focus: Short reviews (up to 1500 words) on instruments, equipment, drugs or procedures of dermatological disorders may be submitted after consulting the editor on the selection of subject. No abstract is required.

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- Spot the diagnosis: A classic clinical case with short history, examination, one to three good photographs and investigation findings (up to 150 words). It should be followed by the answer in the form of the diagnosis and a short review of the condition. Manuscripts submitted for this section could be authored by not more than four authors and could include up to 500 words excluding references. It could have up to 5 references.

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- Title of the article
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Abstract:

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- Preferably within about 200 words
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Text:

Text should be arranged into following sections: Introduction, Materials and Methods, Results, Discussion, Acknowledgement and References

Introduction:

- Statement of the problem with a short discussion of its importance and significance
- Review of the literature related to the problem

with pertinent reference

- Objectives/hypothesis/benefits expected stated in 1-2 paragraphs

Materials and Methods:

- Study type, place and time
- Description of study variables
- Description of study subjects and grouping
- Selection criteria
- Approval of the study involving human subjects by ethical review committee and description of the ethical aspects in such study
- Description of procedure, methods, apparatus, drugs or chemicals as applicable
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