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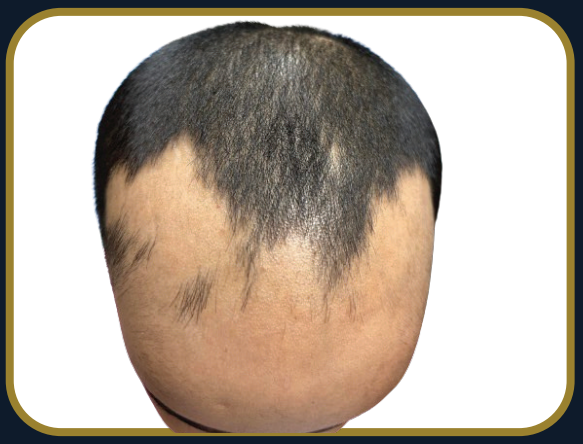

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Volume 04 Issue 01 January 2024

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Journal of Bangladesh Academy of Dermatology

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Editorial

Editorial: Alopecia areata: small areas conferring larger impacts

Alopecia areata (AA) is a common type of hair losing disorders affecting about 2% of world population with an estimated lifetime risk of alopecia areata 1.7–2.1%.[1-2] ”Alopecia” means hair loss and the word “areata” means patchy- because the disease cause patchy hair loss, it is called alopecia areata.[2] AA affects people irrespective of age and gender and approximately 20% of cases are children. [3] This is a disease of multifactorial background with genetics, autoimmunity, and environmental influences. This autoimmune mechanism mostly targets the anagen hair follicles leading to non-scaring alopecia. It also affects nails, and, sometimes the retinal pigment epithelium.[4] AA has a wide range of disease severity from single or few patches of hair loss to universal loss of hair from the whole of the body including the scalp called alopecia universalis (AU). A good proportion of cases experience spontaneous resolution though it is followed by an unpredictable relapse from unknown triggers.[5] AA significantly lowers patient's quality of life, social functioning, and psychological well-being imposing an extra financial burden for treatment costs.[6] In decision making for management of this complex disease a comprehensive understanding of the disease process, its psychosocial impact and available treatment options is crucial. Management modalities for AA are diverse ranging from non-pharmacological interventions (observation and waiting for spontaneous remission, using camouflage techniques, psychotherapy, microblading) to pharmacotherapy as the newer immuno-modulating Janus Kinase (JAK) inhibitors. Regarding pharmacotherapy for AA, most of the available therapeutic modalities lack satisfactory efficacy and safety records and still, there is no curative treatment. In many situations, long-term immunosuppressive therapy is required to prevent recurrence. Physicians have to play a predominant role in both educating patients and offering emotional support. More prospective studies are essential to evaluate the safety of newer agents JAK inhibitor therapy especially major cardiac events and malignant potentialities.

Prof. Dr. Muhammad Munir Rashid
Chairman, Dept. of Dermatology and venereology,
Bangabandhu Sheikh Mujib Medical University (BSMMU),
Dhaka-1000, Bangladesh.
Munir47@gmail.com

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Original Article:

Comparison Of Outcome Between Tofacitinib and Baricitinib in Alopecia Areata: A Retrospective Observational Study

AN Asma[1], Md Mahabubur Rahaman[2], Md. Mostaque Mahmud[3], Mohammad Asifuzzaman[4], Md. Shah Zaman[5], Humaira Afreen[6]

1. Dr. Anzirun Nahar Asma, Associate Professor and Head , Department of Dermatology, Popular Medical College, Dhaka.
2. Prof. Md Mahabubur Rahaman, Professor, Dept. Of Dermatology, City Medical College, Gazipur, Dhaka.
3. Md. Mostaque MahmudAssociate Professor, Dermatology & Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka.
4. Professor Mohammad Asifuzzaman, Professor & Head, Dermatology, Green Life Medical College Hospital.
5. Dr. Md. Shah Zaman, Dermatology & Venereology, Assistant Professor, Z.H. Shikder Women's Medical College.
6. Dr Humaira Afreen, Assistant Professor, Sir Salimullah Medical College Mitford Hospital.

Abstract

Introduction: Alopecia Areata is an immune-mediated, chronic inflammatory disorder that affects hair follicles, leading to nonscarring hair loss. Several treatment options are available, but none of them promise to cure. Recently, JAK inhibitors have been used as treatment options. Several studies provide data about the safety and efficacy of JAK inhibitors like Tofacitinib and Baricitinib. These drugs are also being used by dermatologists in Bangladesh. But to date, there is no published data about the comparison between Tofacitinib and Baricitinib in terms of safety and efficacy in our country. **Objective:** To compare the outcome of alopecia treatment with Tofacitinib and Baricitinib in terms of safety and efficacy. **Methodology:** In this retrospective observational study, 30 patients were included. Among them, 15 were administered Tofacitinib treatment, with 10 being female and 5 male. Where 15 patients received Baricitinib treatment, among which 8 were female and 7 male. **Results:** Both the Tofacitinib and Baricitinib groups exhibited positive responses, showing a mean improvement of 75.97% and 79.36% respectively. Despite a statistically significant difference, drawing conclusions is challenging due to the small sample size of this observational study.

Introduction

Alopecia Areata (AA) is an immune-mediated disorder that causes non-scarring alopecia on the scalp and other body parts that bear hair.[1] Up to 2% of the population lifetime chance of being affected by Alopecia Areata worldwide.[2] This disease mostly affects the scalp hair. However, it can involve any hair-bearing area of the body and progress into complete scalp hair loss known as Alopecia Totalis, or body known as Alopecia Universalis. Disfigurement from the unpredictable course of Alopecia Areata reduces the quality of life significantly.[3,4] Several complex immune-mediated dysregulations are involved in the pathogenesis of AA. Disruption of immune privilege in the hair follicle is thought to be mediated by autoantigen directed towards the hair follicle, both melanocyte and keratinocyte-related autoantigens have been proposed to be involved. The immune attack has been attributed to the activation of Th1, Th2, and Th17 cytokines, with Th1 cytokines (IL-2, TNF, IL-12) and Th17 (IL17 and IL17E) also correlating with the disease activity.[5,6]

Corresponding author
Dr. Anzirun Nahar Asma, Associate Professor and Head , Department of Dermatology, Popular Medical College, Dhaka. Mail – anzirun@gmail.com

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In recent years, significant progress has been made in understanding the underlying mechanisms of Alopecia Areata (AA), leading to more targeted therapeutic approaches utilizing small molecules. Among the various treatment options, the Janus Kinase (JAK) Inhibitor, Baricitinib, which inhibits JAK1 and JAK2, was recently approved by the US FDA in June 2022 for severe AA in adult patients. Off-label use of other JAK inhibitors like Tofacitinib and Ruxolitinib has also been observed in treating AA. Additionally, there's ongoing development of more selective second-generation JAK inhibitors such as Lkeupadacitinib, Brepocitinib, Ritlecitinib, Abrocitinib, Jaktinib, Deucravacitinib, Ifidancitinib, and Delgocitinib. However, determining the most suitable JAK inhibitor in terms of both safety and efficacy remains uncertain. Dermatologists in Bangladesh have incorporated JAK inhibitors into their AA treatment protocols, yet limited published data exists, particularly in comparing the safety and effectiveness of Tofacitinib and Baricitinib.

Methodology:

This retrospective observational study involved the collection of data from various dermatologists who treated cases of Alopecia Areata with a severity of alopecia tool (SALT) scoring of 50 or higher using oral Tofacitinib or Baricitinib from January to December 2022. These dermatologists maintained comprehensive clinical and biochemical records and monitored the outcomes of the treatments. Improvement in SALT scoring after 6 months of treatment served as the measure of outcome, with specific percentage ranges indicating levels of improvement. The study included a total of 30 patients: 15 received oral Tofacitinib (10 female, 5 male) and 15 received oral Baricitinib (8 female, 7 male). Patients receiving additional treatments alongside oral JAK inhibitors, as well as those with SALT scores below 50 or incomplete data, were excluded. Data on demographics, treatment response, and adverse events were collected from electronic medical records with proper permission. Statistical analysis, conducted using SPSS version 25, involved comparing outcomes between the two treatment modalities, with a significance level set at $p < 0.05$.

Result

In this retrospective observational study, a total of 30 patients were included: 15 received oral Tofacitinib treatment (5mg to 10mg) for six months, with 10 females and 5 males; and 15 patients received oral Baricitinib (2mg to 4mg) for the same duration, with 8 females and 7 males (as depicted in Figure-1).

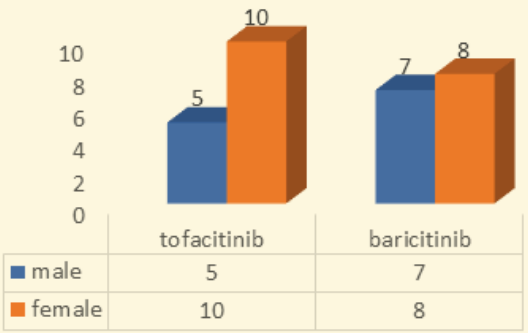

fig 1. Sex distribution of Tofacitinib and Baricitinib treated group

In both Tofacitinib and Baricitinib treated group female patient outnumber male.

The mean age of patients in the Tofacitinib group was 27.39 years (ranging from 13 to 48 years), and in the Baricitinib group, it was 22.73 years (ranging from 12 to 50 years) (Table 1).

Table-1:Distribution of age (in years) of included patients

	Tofacitinib	Baricitinib
Mean	27.93	22.73
Minimum	13	12
Maximum	48	50

In Tofacitinib treated group total number of patient 15 (n=15), in Baricitinib treated group total number of patient 15 (n=15)

In terms of alopecia types, 53% of the Tofacitinib-treated group had Alopecia Areata, 33% had Alopecia Totalis, and 13% had Alopecia Universalis, while in the Baricitinib-treated group, 67% had Alopecia Areata, 27% had Alopecia Totalis, and 7% had Alopecia Universalis (Figure 2).

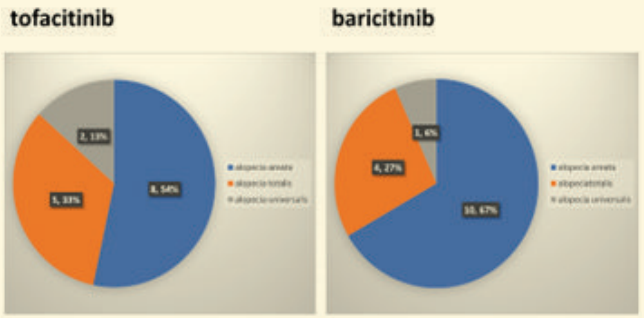

fig 2. Pattern of alopecia in both Tofacitinib and Baricitinib treated group

Total cases of Alopecia Areata outnumbers the cases of alopecia totalis and universalis in both Tofacitinib and Baricitinib treated cases.

The mean duration of disease was 20.27 months in the Tofacitinib group and 17.53 months in the Baricitinib group (Table 2),

Table -2: Duration of disease in months

Duration of disease in months	Tofacitinib	Baricitinib
Mean	20.27	17.53
Minimum	6	6
Maximum	60	54

with the maximum duration being 60 months for Tofacitinib and 54 months for Baricitinib. Most cases were not associated with other autoimmune diseases, although hypothyroidism was the most common among associated diseases, alongside Vitiligo, Atopic Dermatitis, and Psoriasis (Figure 3).

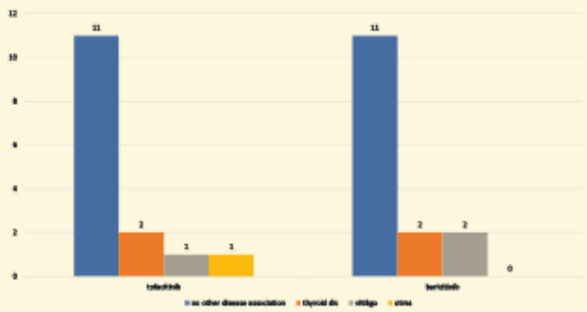

fig 3. Other disease association along with Alopecia Areata

Among the associated disease condition, thyroid diseases are most commonly found in both Tofacitinib and Baricitinib treated group.

In the Tofacitinib group, 33.3% had previously been treated with systemic steroids, while 40% had been treated in the Baricitinib group. Additionally, intralesional steroids, MTX, and Cyclosporine were attempted before initiating JAK inhibitor treatment (Figure 4).

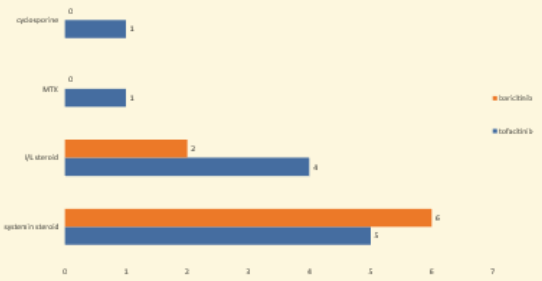

fig 4. Previous treatment modalities

In Tofacitinib group 33.3 % ware previously treated with systemic steroid and 40% in Baricitinib group. Il steroid , MTX and Cyclosporine also tried

Both the Tofacitinib and Baricitinib treatment groups demonstrated favorable responses, with an average improvement of 75.97% and 79.36% respectively (Table 3).

Table- 3: Treatment outcome (changes in SALT score from baseline):

Response	Tofacitinib (n-15)	Baricitinib (n-15)	P value
Mean ± SD	75.97 ± 19.13	79.36 ± 19.99	0.04
Low (0 -24%)			
Medium (25-49%)	1(6.7%)	0(0%)	
Good (50-74%)	4(26.7%)	8(53.3%)	
Excellent (75-99%)	8(53.3%)	2(13.3%)	
Complete (100%)	2(13.3%)	5(33.3%)	

Despite the statistically significant difference in outcomes between these two groups (p-value of 0.04), drawing definitive conclusions is challenging due to the small size of this observational study. However, it's noteworthy that fewer complications were observed in the Baricitinib-treated group compared to the Tofacitinib-treated group. Specifically, there was only one case of upper respiratory tract infection in the Baricitinib-treated group, whereas three cases were observed in the Tofacitinib-treated group.

Other complications noted included urinary tract infections, folliculitis, and headache in the Tofacitinib group, and abdominal pain and weight gain in the Baricitinib group (Figure-5).

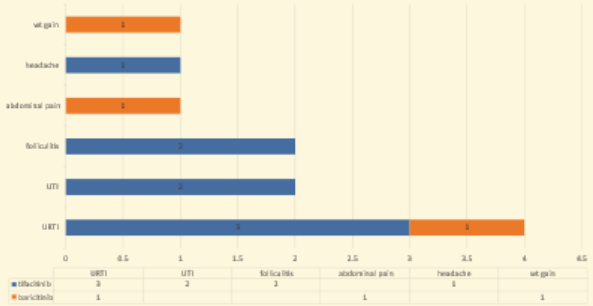

fig 5. Complications during treatment with Tofacitinib and Baricitinib

P value is < 0.05 that is statically significant. In both Tofacitinib and Baricitinib treated group upper respiratory tract infection commonly encountered complication.

No biochemical abnormalities were detected in any patient treated with either Tofacitinib or Baricitinib, except for a single case of lipid abnormality in the Tofacitinib-treated group. Children were also included in this observational study, with two in the Baricitinib-treated group and one in the Tofacitinib-treated group, aged between 12 and 15 years. No severe complications were observed, and the outcomes ranged from good to excellent in these children.

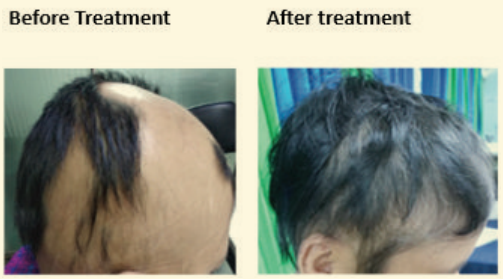

fig 6. Photograph showing before and after 6 months treatment with Baricitinib

fig 7. Photograph showing before and after 6 months treatment with Tofacitinib

Discussion

JAK inhibitors are immune modulating medications, which inhibits the activity of one or more of the Janus kinase family of enzymes (JAK1, JAK2, JAK3, TYK2), thereby interfering with the JAK-STAT signaling pathway in lymphocytes. There are several JAK inhibitors like Tofacitinib, Baricitinib, Ruxolitinib, that work on Alopecia proved by several published studies.[7,8,9]

The first case report on efficacy of Tofacitinib on a young male suffering from Alopecia Universalis and psoriasis was published by Craiglow and King in 2014 and was treated with oral Tofacitinib,15mg daily for 8 months and achieved complete regrowth of hair on all affected areas after completion of therapy.[10] Since then, a good number of research regarding the safety and efficacy of Tofacitinib in the treatment of Alopecia Areata, Alopecia Totalis and Universalis, in both adult and pediatric age group.[11,12]

Oral Baricitinib, selective JAK1/JAK2 inhibitor, found superior to placebo on hair growth after 36 weeks of treatment in adults with severe AA, in a phase 2 trial and recently in two phase 3 trials (BRAVE-AA1 and BRAVE-AA2).[13] On the basis of these trial results, Baricitinib approved by FDA for the treatment of adults with severe AA, On 13th June 2022.[14,15]

Liu et al. in their retrospective study of 90 AA, AU, or Alopecia Totalis (AT) patients on oral Tofacitinib 5-10 mg with or without prednisone and demonstrated >50% regrowth in 77% of patients. Of the 90 patients, 20% were complete responders (>90% reduction in SALT),[16] whereas 56.9% were intermediate to moderate responders (51%-90% reduction in SALT for intermediate responders and a 6%-50% reduction in SALT for moderate responders), and 23.1% were non-responders (≤5% reduction in SALT) . Jabbari et al 2018, in their recent open-label single-arm trial consisting of 12 patients (18–52 years) with moderate to severe AA or its variants, demonstrated that administering oral Tofacitinib ≥10mg daily for 6–12 months resulted in ≥90% regrowth.[13] In our study, with Tofacitinib 5mg to 10 mgfor 6 months in patient(total) , age ranges from 13 to 45 years, with severe Alopecia, Alopecia Totalis and Universalis we found medium response (based on is improvement of SALT scoring from baseline) that is 25 to 49% improvement in 6.7%, good response that is 50 to 74% improvement of SALT scoring seen in 26.7% cases , excellent response that is 75 to 99%

improvement of SALT scoring seen in 53.3% and complete response that 100 % improvement of SALT scoring seen in 13.3% cases.

In two phase 3 trial BRAVE-AA1 (NCT03570749) and BRAVE-AA2 (NCT03899259) are parallel-group, randomized, double-blind, 36-week, placebo-controlled trials that included 654 and 546 patients, respectively.[15] At week 36, the percentage of patients achieving a SALT 20 score was 38.8%, 35.9% in the Baricitinib 4 mg group, 22.8%, 19.4% in the Baricitinib 2 mg group, and 6.2%, 3.3% in the PBO group, in BRAVE-AA1 and BRAVE-AA2, respectively15.In our study there was 15 patient, age ranges from 12 to 50 years with severe Alopecia Areata , Alopecia Totalis or Alopecia Universalis treated with 2mg to 4 mg Baricitinib for 6 months. We got good response that is 50 to 74% improvement of SALT scoring in 53.3% patient, excellent response that is 75 to 99% improvement of SALT scoring from baseline in 13.3% patient and complete response that is total regrowth of hair seen in 33.3% patient.

Upper respiratory tract infection was the most common complication found in both group but more commonly seen in Tofacitinib treated group (20%) compared to Baricitinib treated group (6.7%). Other complications in Tofacitinib treated group were UTI, folliculitis, and headache. In the Baricitinib group there were fewer complications found, except for upper respiratory tract infection we got only one case of abdominal pain and one case of weight gain. According to the statistical analysis, we found the p-value of 0.04 which is <.05 which means there is a significant difference between the outcome (percentage of improvement of SALT scoring) of treatment response between Tofacitinib and Baricitinib treated group. There are also fewer complications found in the Baricitinib group. So, we found both Tofacitinib and Baricitinib are effective in the treatment of AA. As our study was retrospective and only 15 patients were included in each group, we cannot conclude that Baricitinib is better than Tofacitinib in treating severe Alopecia Areata, Alopecia Totalis or Universalis based on this study.

Conclusion

According to various research and published findings, JAK inhibitors emerge as promising treatments for Alopecia Areata, offering potential alternatives to systemic steroids with their associated side effects.

Beyond Tofacitinib and Baricitinib, other JAK inhibitors like Ritlecitinib, Deuruxolitinib, and Brepocitinib have also shown promising outcomes in Alopecia Areata treatment. While both Baricitinib and Tofacitinib demonstrate effectiveness in treating Alopecia Areata with minimal side effects, further studies are warranted to ascertain which one provides superior efficacy and safety, along with considerations of cost-effectiveness and their suitability for pediatric populations.

Limitations of the study

Small sample size and no follow up about recurrence after discontinuation of drug.

Conflict of interest

There is no conflict of interest.

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Original Article:

Safety and efficacy of topical Crisaborole 2% ointment in the treatment of psoriasis on face, intertriginous and anogenital areas: A vehicle-controlled cross-over study

Mohammed Saiful Islam Bhuiyan[1], Abida Sultana[2], Noor Nabi Sayem[3], Anwarul Haque[4], Fatima Wahida[5], Mohammad Lutfur Rahman Rahat[6], Md. Shahidullah Sikder[7]

1. Professor, Dept. of Dermatology and Associate Professor, Dept. of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.
2. Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.
3. National Heart Foundation, Dhaka, Bangladesh.
4. Consultant, Dept. of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.
5. Consultant, Dept. of Dermatology and Venereology, Shaheed Suhrawardy Medical College (ShSMC), Dhaka, Bangladesh.
6. Consultant, Central skin and social health care, Agrabad, Chittagong, Bangladesh.
7. Professor, Dept. of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

Abstract

Background: Psoriasis in some sensitive areas like the face, anogenital and intertriginous areas significantly affects patients' quality of life, and psycho-social and sexual well-being. Due to the special structural and functional characteristics of these areas, all sorts of topical agents are not suitable for use on lesions in these areas. **Objective:** To study the safety and efficacy of crisaborole 2% ointment in treating psoriasis on the face, anogenital and intertriginous areas. **Methods:** It was a randomized vehicle-controlled cross-over study. Thirty-two patients with psoriatic lesions on the face, anogenital and intertriginous areas were enrolled purposively. Selected single lesion was treated with vehicle ointment twice daily for 4 weeks followed by 2 weeks washout period. Then each lesion was again treated with 2% crisaborole ointment twice daily for 4 weeks. Psoriasis disease severity will be measured by the Target Lesion Severity Scale (TLSS) at weeks 0, and 4 during both treatment periods. Changes in TLSS scores were compared between the two groups. **Result:** Topical 2% crisaborole is effective in the treatment of psoriatic plaques as the mean reduction of TLSS score of each treated lesion of the patients was significant after 4 weeks of application compared with baseline and it is significantly better ($p<0.001$) than vehicle ($p=0.257$. Few adverse effects were noted including burning, itching and redness. **Conclusion:** Topical 2% crisaborole ointment is a safe and effective non-steroidal option for treating psoriasis lesions on the face, anogenital and intertriginous areas though for complete lesional clearance a longer treatment period may be needed.
Key words: Crisaborole, PDE-4 inhibitor, anogenital psoriasis, intertriginous psoriasis, facial psoriasis

Introduction

Psoriasis is a common, chronic, recurrent inflammatory disease of the skin, characterized by circumscribed, erythematous, dry, scaly plaques of varying sizes.[1] The prevalence of psoriasis is highly variable from country to country and region to region ranging 0·1% in east Asia and 1·5% in western Europe.[2] The prevalence of psoriasis in Bangladesh is 0.7%.[3]

Sixty-three percent of adults with psoriasis develop psoriatic lesions in the genital and intertriginous area at least once during their lifetime.[4] Though the high prevalence of genital psoriasis, about 50% of patients with genital lesions do not share their problem with a physician.[5] It has a significant negative impact on the

Corresponding author
Mohammed Saiful Islam Bhuiyan, Associate Professor, Dept. of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbagh, Dhaka-1000, Bangladesh. Email: drsaifulib@bsmmu.edu.bd
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quality of life and sexual health of patients, especially women who suffer from high levels of sexual distress.[6] Face is involved in 20-50% of cases of psoriasis; it is the most important area of cosmetic concern and social activity and is also considered as a marker of severe psoriasis.[7-8] Inverse or intertriginous or skin-fold psoriasis, is a rare form of psoriasis that affects 3-36% of patients.[9] It typically involves flexural areas – the groin, axillae, umbilicus, intergluteal cleft and external genitalia.[9] Psoriasis in genital and intertriginous areas is remarkably neglected due to a lack of communication and awareness resulting in diagnosis, under-treatment and subsequent risk of inappropriate self-treatment. Treatment of these sensitive areas of the body is challenging and several factors including high percutaneous absorption of topical steroids and alcohol in skin folds and greater potential for local adverse events such as atrophy, striae, and telangiectasia should be taken into account.[10]

Crisaborole ointment is a nonsteroidal phosphodiesterase-4 inhibitor. By inhibiting phosphodiesterase 4 it increases levels of 3′5′-cyclic adenosine monophosphate in inflammatory cells, leading to activation of nuclear factor κB and nuclear factor of activated T-cell signaling pathways and subsequent suppression of inflammatory cytokine release.[11]

It is a safe non-steroidal anti-inflammatory agent for even infants. Initially, topical crisaborole 2% was approved by the FDA for children over two years of age for mild to moderate atopic dermatitis in 2016 and after 4 years the approval was extended further for using children of three months and above.[12]

Apremilast, an oral PDE4 inhibitor has already been approved and is effective for psoriasis though adverse effects restrict its routine use. Roflumilast, a topical PDE4 inhibitor has also recently been approved for psoriasis and shows promise in clinical trials.[13] So it is reasonable to conduct a study to see the safety and efficacy of topical Crisaborole in psoriasis. Initially Lee et al., in 2019 reported two cases of psoriasis treated successfully treated with crisaborole.[14]

Topical crisaborole ointment was found safe and effective in the treatment of facial, anogenital and intertriginous psoriasis in a study by Hashim et al. conducted on 21 patients.[15]

In the current study, we studied the efficacy and safety of this non-steroidal topical agent to treat single plaque psoriasis of the face, anogenital and facial regions.

Method

It was a vehicle-controlled cross-over study carried out in the dept. of dermatology and venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from June 2021 to July 2023 after the approval by IRB (No.BSMMU/2021/3529 Date:06-04-2021). Thirty-two patients of psoriasis having localized and limited plaque on the face, anogenital or intertriginous areas (axillae, groin, gluteal cleft, undersurface of breasts) of ≥6 months' duration. Patients who were on current or past (less than 2 weeks) treatment with any systemic and other topical antipsoriatic medications or phototherapy (PUVA within the last 4 weeks) or Laser therapy were excluded. Patients having plans for lesional sun exposure were also spared from the study. Cases of guttate, erythrodermic, exfoliative or pustular psoriasis were not enrolled. Informed-written consent from patients or their legal guardians were taken.

Table I: Distribution of the demographic variables (n=32)

Variables	Mean (SD), Median (Min-Max)
Age (year)	21.7 (15.3), 19.0 (1-56)
Gender	f (%)
Male	20 (62.5)
Female	12 (37.5%)

f: Frequency

The selected single lesion was treated with vehicle ointment twice daily for 4 weeks followed by 2 weeks washout period and then each lesion was again treated with 2% crisaborole ointment twice daily for 4 weeks. Psoriasis disease severity was measured by the Target Lesion Severity Scale (TLSS) at weeks 0, and 4 during both treatment periods. TLSS was calculated by measuring the redness, thickness, and scaliness of target plaques. Each parameter was graded on a 0 to 4 scale (0 = clear, 1 = slight, 2 = mild, 3 = moderate, 4 = severe), and the sum of the individual scores provides the overall score. The sum score ranges from 0 to 12 points. Changes in TLSS scores were compared between the two groups. Wilcoxon Signed Ranks Test was done to measure the levels of significance of changes of severity with two treatment modalities (Table III).

Table II: Distribution of the site of involvement (n=32)

Site of involvement	f (%)
Anogenital	20 (62.5)
Face	10 (31.3)
Intertrginous	2 (6.3)

f: Frequency

Table III: TLSS score after vehicle and Crisaborole at 0 week and 4 weeks (n=32)

	0 week	4 weeks	p value#
TLSS score treatment with vehicle			0.257
Mean ± SD	8.1 ± 2.2	7.9 ± 2.2	
Min-Max	4-12	4-12	
Median	8.0	8.0	
Q1-Q3	7.0-9.8	6.0-9.8	
TLSS score after treatment with Crisaborole			<0.001
Mean ± SD	8.1 ± 2.3	4.7 ± 1.6	
Min-Max	4-12	2-8	
Median	8.5	5	
Q1-Q3	6.3-10.0	3.3-5.8	

#Wilcoxon Signed Ranks Test was done to measure the level of significance. Q1:First quarter, Q3: Third quarter

Table IV: Distribution of the adverse event (n=32)

Adverse event	f (%)
Burning	4(12.5)
Itching	2 (6.3)
Redness	2 (6.3)
None	24 (75.0)

f: Frequency

Result

In this vehicle-controlled cross-over study, 32 patients of psoriasis with a mean age of 21.7(±15.3) were recruited among which 62.5% were male and 37.5% female. Lesions were located at anogenital areas in 20 (62.5%) cases, face 10 (31.3%) and intertriginous area 2 (6.3%) (Table II). The mean Target Lesion Severity Scale score of the patients at baseline was 8.1 ± 2.2. After treatment of each selected lesion with the vehicle for 4 weeks, the mean TLSS score was 7.9 ± 2.2 ranging from 4 to 12 (p=0.257). After 2 weeks washout period lesions were treated with 2% crisaborole ointment, at baseline the mean TLSS was8.2 ± 2.3ranging from 4 to 12 after treatment for 4 weeks mean TLSS was 4.7 ± 1.6 ranging from 2 to 8 (<0.001). Regarding adverse effects 75% had no adverse effects, burning, itching and redness were reported in 12.5%, 6.3% and 6.3% cases respectively.

Discussion

Psoriasis in some special areas significantly impacts patient's quality of life and there is lack of agreement among practitioners regarding the management of psoriasis these atypical areas which are more resistant to treatment or too sensitive to be treated with strong topical drugs, resulting in more frequent use of systemic drugs.[16] Genital and intertriginous areas are affected in more than sixty percent patients with psoriasis and these areas are involved at least once during their lifetime.[17]

In the current series of patients, the mean age was 21.7(±15.3) ranging from 1 year to 56 years. Psoriasis in genital areas can affect patients of any age from newborns to the elderly, with a bit of predilection for younger males with comparatively more severity.[17] Though genital psoriasis is more common in males, the disease severity is higher in females.[5] Psoriatic plaques involving sensitive private areas of the body significantly reduce their quality of life compared with psoriasis in other areas regarding itching, sexual activities, sexual health, sexual stress, refusal from partners, embarrassment, shame, and psychological depression.[5] In the current study most (63.2%) of participating patients were male, which may be due to females reasonably feel ashamed and neglect to seek treatment for these private part lesions.

In the current study majority of the lesions were located on genital areas. Face is involved in 20% of cases of psoriasis and it is the most important area of cosmetic concern and social activity.

Some studies have even found that facial psoriasis could be considered a marker of severe psoriasis. In the current study, 31% of lesions were located on the face. [18]

Management of psoriasis in these sensitive areas with topical agents deserves a special consideration of the unique anatomical and physiological character of the areas including less thickness of skin, higher

percutaneous absorption and greater potential for local adverse events such as atrophy, striae and telangiectasia. These issues are particularly more problem for infants, who have a high surface area-to-body mass ratio, predisposing them to systemic side effects. However low-to-mid-potency topical corticosteroids are recommended as the first-line treatment for genital psoriasis. The first-line recommended other topical treatments are calcineurin inhibitors and vitamin D analogs. The efficacy and tolerability of topical calcineurin inhibitors tacrolimus are proven in several studies.[19] Calcipotriol and calcitriol, are other non-steroidal treatment modality suitable for prolonged use for genital and inverse psoriasis though less effective compared with topical corticosteroids or TCI.[20] Though the efficacy of these agents is proved however the use of these agents have special safety concern for potential risk for developing malignancy in future.[21] As a novel topical nonsteroidal agent Crisaborole, a phosphodiesterase-4 inhibitor have been reported as effective and tolerable agent for anogenital, intertriginous and facial psoriasis in two available articles.[14-15]

In the current study lesions treated with a vehicle have not achieved significant change of severity (TLSS) after 4 weeks of application. After the application of 2% crisaborole ointment on each lesion the mean TLSS score was reduced significantly from the baseline after 4 weeks of treatment, none achieved complete clearance whereas in the lone previous study by Hashim et al. complete clearance was noted in 70% of patients after treatment of 8 weeks.[15] So for achieving a complete clearance the duration of treatment may be longer. Lesional improvement (TLSS change) was significantly better than a vehicle. Mild adverse cutaneous reactions to topical crisaborole including lesional contact urticaria, irritation, pain, burning, and/or stinging have been experienced among patients treated for atopic dermatitis.[22] In the current study no adverse effects were noted in most of the cases, with lesional burning in 12.5% and equal two persons reported lesional itching and redness. The same kind of mildcutaneous adverse effects were also experienced in using topical tacrolimus for psoriatic lesions on the groin.[19] Topical crisaborole 2% ointment can be considered a tolerable and effective topical treatment option for limited lesions of psoriasis in the face, anogenital and intertriginous areas.

Conclusion

For treating psoriasis in sensitive areas of the body including the face, anogenital and intertriginous areas topical 2% crisaborole ointment is a safe and effective non-steroidal option but for complete clearance of the lesion a longer treatment period may be needed.

Limitations

The sample size was small and treatment period should be longer.

Conflict of interest

None.

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Original Article:

Delusional Parasitosis: A seven-year retrospective analysis of 25 cases in tertiary level hospital

Farzana Rabin[1], Mahmudur Rahman[2], Shaila Ahmed[3], Md. Aminur Rashid[4], Sonia Nasreen Ahmed[5], Towhida Noor[6]

1. Head & Associate Professor, Dept. of Psychiatry, Holy Family Red Crescent Medical College, Dhaka, Bangladesh.
2. Head & Associate Professor, Dept. of Dermatology and Venereology, Holy Family Red Crescent Medical College, Dhaka, Bangladesh.
3. Associate Professor, Dept. of Dermatology and Venereology, Holy Family Red Crescent Medical College, Dhaka, Bangladesh.
4. Assistant Professor, Dept. of Dermatology and Venereology, Holy Family Red Crescent Medical College, Dhaka, Bangladesh.
5. Associate Professor, Dept. of Medicine, Holy Family Red Crescent Medical College, Dhaka, Bangladesh.
6. Consultant, Matador Skin Center, Dhaka. Bangladesh.

Abstract

Background: Delusional parasitosis (DP) is a delusional state with a fixed false belief of having an infestation of insects, mites, lice, worms or other organisms. It is a rare psycho-cutaneous disease entity mostly misdiagnosed initially by non-psychiatrist medical practitioners making early diagnosis and management challenging. **Objective:** To analyse socio-demographic and clinical profiles of delusional parasitosis. **Methods:** This retrospective study was carried out in the dept. of psychiatry, holy family red crescent medical college, Dhaka, Bangladesh over 7 years (January 2017- December 2022). From 12940 registered cases of different psychiatric illnesses diagnosed by psychiatrists according to DSM-5, 25 cases of DP were diagnosed sorted out and enrolled for analysis. Data of sociodemographic profile and clinical information especially psychiatric history and diagnosis and other comorbidities especially dermatological complains and manifestations were reviewed by psychiatrist and dermatologist. **Result:** The frequency of DP among psychiatric illnesses is 0.2%. The mean age of the patients of DP was 54.56±6.02 years ranging from 45 to 69, female to male ratio was 1:2.6. The Majority (76%) of the DP patients were of secondary type with comorbid medical and psychiatric illness including major psychiatric disorders such as schizophrenia, substance use disorder (cannabis, amphetamine and alcohol), obsessive-compulsive disorder, major depressive disorder and trichotillomania. The mean duration of delusional symptoms was 9.88 ±2.64 months. Among 25 patients of DP, 17 were initially treated by non-psychiatrists (mostly dermatologists). **Conclusion:** For early diagnosis and management of delusional parasitosis exclusion of suspected dermatological conditions and timely referral to a psychiatrist is crucial to minimize the burden of psychiatric manifestation and reduce the cutaneous discomfort and disfigurement.

Key words: Delusional parasitosis, Delusional infestation, Dermatological delusion, Ekbom syndrome

Introduction

About one-third of patients seen in dermatological patients present with psychiatric complaints and delusional parasitosis (DP) is one of the complex psycho-cutaneous issues[1]. DP, a rare but unique psychotic disorder presenting with the unwavering fixed false belief of an individual having an infestation of living organisms on the skin without any medical evidence supporting this belief1.1 Skin-related delusional diseases with unspecific status and/or status without dermatological findings, among others 'dermatological delusion', are categorized as 'delusional disorders'[2]. As the patient typically denied the existence of such a delusional

Corresponding author
Dr. Farzana Rabin, Head and Associate Professor, Dept. of Psychiatry, Holy Family Red Crescent Medical College, Dhaka, Bangladesh. Email: shormi26@gmail.com
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condition, it can be reasonably considered that DP is underreported. The incidence of DP was estimated as 1.9 cases per 100,000 person-years in a population-based survey[3]. This is typically a disease of middle-aged socially isolated women (the average age is 57 ± 14 years)[4]. Though the exact neurobiological or pathological mechanisms of DP are not fully clear, Huber et al. proposed that the dysregulated functioning of striatal dopamine transporter (DAT), which is responsible for increased extracellular dopamine level, could potentially be an important etiological factor for both (primary and secondary) forms of delusional parasitosis[5]. DP is a monosymptomatic hypochondriacal psychosis also termed as delusional infestation, or Ekbom syndrome. According to DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition code 297.1 F22) required diagnostic criteria: i. suffering with delusion for >1 month which does not fit with the required criteria for schizophrenia; ii. the patient is functioning in general outside of the delusion of parasitosis; iii. mood episodes have been brief relative to the duration of the delusional period(s), and where the disturbance is not attributable to medical conditions, substances, or another disorder[6]. DP can be classified as i. primary, ii. secondary (functional), and iii. organic forms. In primary DP, the subject presents with the delusion of being infested with parasites but no background psychiatric or organic disorders are identified. In secondary (functional) DP background psychiatric disorders are associated whereas in organic variants of DP associated organic disease is present.[7-8] An individual with DP fails to be satisfied with the delusional character of their misapprehension by disagreement or lack of proof and seems to be mentally healthy when addressing issues other than their own "infestation." Some of the patients of DP are afraid of contaminating other people, especially members of their family, and perform various preventive actions. Numerous disinfectants, creams, soaps, and chemicals are used excessively to get rid of the "parasite" or to alleviate symptoms.[9] Patients of DP frequently presented with itching, skin rashes, burning, stinging, or formication for six months or longer and had no physical findings present. On physical examination of skin excoriations or scars can be noticed due to the patient's past attempts to undertook to remove "organisms" using various objects or their fingernails. They can also present with irritant dermatitis as they will sometimes turn to alternative treatments and home products in an attempt to remove the "organism."[10]

Diagnosis of DP is a particular challenge classically for months or years. Presenting features of DP are very real and distressing to the patient, making patients engaged to seek help from multiple specialists including family practitioners, dermatologists, and parasitologists, which leads to financial losses due to absence from work, cleaning costs, and visits to medical specialists. Though DP usually does not impair the patient's capacity to normal functioning, rather serves as a barrier and persistent complaint. However, in some instances, it can lower their quality of life significantly.[10] For establishing a diagnosis of DP the dermatological conditions causing a sensation of crawling of the parasite, itching, stinging and excoriations including scabies, dermatitis herpetiformis, and prurigo simples should be ruled out.[11] The presence of physical features including puncture, sting, bites or specific rashes would lead to consider parasitic infestation. Other diseases that should be considered and excluded include Alzheimer's dementia, HIV/AIDS, recreational use/abuse of drugs (e.g., cocaine, stimulants, narcotics) and adverse effects of therapeutic drugs such as antiparkinsonian agents, stimulants, antidepressants, antihypertensives, antiepileptic.[11] In the present study, the demographic and clinical data of 25 patients with delusional parasitosis are analysed.

Method

This retrospective study was conducted in the Department of Psychiatry, holy family red crescent medical college, Dhaka, Bangladesh. In the mentioned department suspected patients of psychiatric illness are attended by a consultant psychiatrist and data of all diagnosed patients are recorded and preserved carefully. The psychiatric diagnoses are done according to the structured clinical interview, Mini International Neuropsychiatric Interview, Psychiatric history and examinations were carried out by a psychiatrist. The Mini-Mental Status Examination (MMSE) is also applied to all patients. Data from 12,940 patients with psychiatric illness (who attended the psychiatry OPD and were referred from other departments, especially dermatology) from January 2017 to December 2022 were analysed. From all patients of psychiatric illness persons having delusional parasitosis were primarily identified from the registrar. The cases of delusional parasitosis who were diagnosed by a specialist psychiatrist according

to DSM-5 were finally enrolled. Data of sociodemographic profiles including age, gender, occupation, residence, socioeconomic condition and marital status were collected. Along with the final psychiatric diagnosis, comorbid medical conditions including dermatological, neurological, endocrine and other associated medical conditions were taken as a multidisciplinary approach and recorded. Patients' present or past diagnoses that were specially done by dermatologists and the prescribed medications were also noted. The data on available laboratory tests were also summarized which was used to exclude potential secondary delusional parasitosis. Informed consent was taken from each patient. Privacy of all information and data was strictly ensured at every level.

Result

A total of 25 patients were identified from 12,940 registered individuals of psychiatric illness with a prevalence of 0.2%. Among the DP patients, 6 were male and 19 were females with a male-female ratio of 1:2.6. The mean age of the patients of DP was 54.56±6.02 years, with a range of 45 to 69 years (Table I).

Table I: Summary of patients' demographic and clinical characteristics (n=25)

Demographic and clinical characteristic of patients of delusional parasitosis

Age: Mean±SD, range (years)	54.56±6.02, 45-69	Associated psychiatric disease	
Gender (M:F)	1:2.6	Schizophrenia	3
Duration of delusional symptoms Mean±SD, range (months)	9.88±2.641 (2-24)	SUD (multiple response)	Alcohol 3, Amphetamine 1, Cannabis 2
Types of DP		OCD	2
Primary	6	MDD	3
Secondary	19	Trichotillomania	1
Comorbid-medical disease (multiple response)		Source of referral	
-Dementia	5	Dermatologist	7
-DM	7	Medicine specialist	4
-HTN	5	Neurologist	3
-COPD/Br. Asthma	3	Endocrinologist	1
-Parkinson's Disease	4	Self	9
-Hypothyroidism	4	Self	
-Stroke	1		

Their occupation was service holder 20%, business 16%, housewife 40%, and others (1 cultivator and 2 teachers). Two patients are unemployed and 1 patient left his job due to disease. The majority (84%) were married, 8% unmarried and 8% divorced. Sixty-four percent hailed from urban areas, 24% from semi-urban and 12% from rural areas. Sixty percent of patients belonged to a middle-class family. 16% from upper class and 24% from lower class families. Regarding comorbidities diabetes mellitus (28%), dementia (20%), hypertension (20%), hypothyroidism (20%), Parkinson's disease (16%), COPD/ Bronchial Asthma (12%) and 4% had a history of stroke. Regarding comorbid psychiatric illness, 16% of respondents had Substance-related disorders (alcohol, cannabis and amphetamine), 12% had Schizophrenia, 12% had major depressive disorder and 8% had obsessive-compulsive disorder (OCD). One patient had Trichotillomania. 76% had secondary DP due to comorbid medical and psychiatric illness, and 24% had primary DP. The duration of their delusional symptoms was from 2 months to 2 years. 28% of patients were referred by dermatologists, 16% by medicine specialists, 12% by neurologists and 4% by endocrinologists. 36% of patients directly attended Psychiatry OPD.

Discussion

DP is not a common psychiatric disorder so detailed epidemiological study regarding its frequency is not widely available which is mostly encountered in dermatological practice. In a study by Winokur in 1977 PD has a prevalence of 0.1 to 0.4% among delusional disorder in psychiatric inpatients and in a Japanese study the prevalence is 1.2% among psychiatric patients attended in OPD. In the current study prevalence of PD is 0.2 among all registered patients with psychiatric illness12-13. Among the elderly (older than 50 years) patients with DP of females are predominantly affected with a male-to-female ratio is 1:314. In the present study male: female ratio is 1:2.6 which is compatible with other studies. Regarding the age of onset of the disease, DP is reported to show a double peak with higher numbers of patients present between the ages of 20-30 and 50-69.15 In the current study the mean age of the study was 54.56±6.02 years ranging from 45 to 69 years.

The majority of patients of DP seek health care from non-psychiatric medical professionals including dermatologists, neurologists, general practitioners, dentists and internists who do have not enough expertise to diagnose and manage these complicated psychiatric issues. Szepietowski et al., described that 84.7% of dermatologists had given consultation to at least one patient with delusional parasitosis during their professional career.[16] A detailed dermatological consultation including physical examination, laboratory and microbiological tests as well as

mineral oil skin scraping is crucial to establish the diagnosis by excluding dermatological causes especially real parasitic infestation.[17,10] In the present study, 17 out of 25 patients were initially treated by a non-psychiatrist (mostly dermatologist). In most of the instances, DP presents as an insidious onset after suffering for more than six months.[18] In the current study, the mean duration of delusional symptoms was about 10 months.

DP can be classified as primary or secondary. When delusion occurs on its own like a mono-delusional disorder it can be graded as the primary type satisfying criteria of the International Classification of Diseases, 10th revision (ICD-10), for persistent delusional disorder and criteria of the Diagnostic and Statistical Manual of Mental Disorders, (DSM-5, Fifth edition) for delusional disorder, somatic type.[19] In the current series of DP cases, 24% were comprised of a primary psychotic disorder referred to as a primary delusional disorder type according to the present classification system.[20-21] In 76% of DP cases of our study had underlying major psychiatric disorders such as Schizophrenia, substance use disorder (cannabis, amphetamine and alcohol), obsessive-compulsive disorder, major depressive disorder and trichotillomania that exhibited typical symptoms of DP, which can be termed as secondary DP. This group also included DP secondary to a physical illness like diabetes, hypertension, hypothyroidism, COPD etc or a neurological disease like dementia, Parkinson's disease and stroke. In many studies, several organic conditions have been causally related to DP, including substance abuse, and infectious and endocrine disorders.[22-23] Although DP is known to occur in a wide variety of these physical illnesses, previous studies also found a primary psychotic disorder as the main cause of DP4,[14,24]. In our study, thyroid disease, diabetes, Parkinson's disease, dementia, and cardiovascular and pulmonary diseases were considered comorbid conditions as well as etiological factors. The advanced age of the patients of our study may explain this high occurrence of comorbidities.

Parasitic delusions can be associated with substance abuse of many types. Cocaine, methamphetamine, methylphenidate hydrochloride and alcohol are notorious substances, abuse of which may cause tactile hallucination giving a sensation of parasitic crawling.[25] In our study, 4 patients had a history of substance abuse to one or more agents including alcohol, cannabis and amphetamine.

Conclusion

Establishing an effective liaison among different disciplines is very crucial for early diagnosis and management of delusional parasitosis. As most of the patients of DP seek health care from dermatologists, early diagnosis and referral to a psychiatrist can help to reduce the psychiatric disease burden as well as prevent scarring and other cutaneous morbidities.

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Original Article:

Clinical spectrum of Muco-cutaneous manifestations of HIV infected patients, during attending Anti-Retroviral Therapy (ART) center, BSMMU

Mariam Akther Bannya[1], Lubna Khondker[2]

1. MD Resident, Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
2. Associate Professor, Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

Abstract

Background: Mucocutaneous manifestations are one of the most important clinical markers and may be the first clue of HIV infection and disease progression. A wide range of infectious, noninfectious, and neoplastic skin lesions develop during the course of the disease. These mucocutaneous manifestations may indicate the worsening of immune status. **Objective:** To explore the mucocutaneous manifestations among HIV patients of Bangladesh. **Methods and Materials:** A cross sectional study was conducted during the period of January 2020 to June 2021. Ninety-Seven HIV patients attending in at Anti-Retroviral Therapy (ART)center of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh were enrolled in this study based on exclusion and inclusion criteria. Mucocutaneous manifestations of all the patients were clinically diagnosed. Consecutive type of sampling technique was applied to collect the sample from the study population. **Results:** Majority of the patients belonged to the age group between 31- 40 years (37.1 %) and most of the patients were male 61 (62.8 %). Most common infectious mucocutaneous manifestations were fungal infection in 71(73.2%) followed by parasitic infections in 13(13.4%), bacterial infection in 5(5.2%), viral infections in 3 (3.1%) and among the fungal infections Tinea Corporis 40 (41.2%) was most common, followed by Tinea Cruris, Oral candidasis 10(10.3%) each and among the noninfectious manifestations Seborrhoic Dermatitis 16 (16.5%) was the most common. Conclusion: Most common mucocutaneous manifestations were fungal infection (Tinea corporis, Tinea cruris, Oral candidiasis) followed by Seborreic Dermatitis and Scabies.

Key words: Muco-cutaneous manifestations of HIV, infectious mucocutaneous manifestations of HIV, non-infectious mucocutaneous manifestations of HIV.

Introduction

Human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) is a spectrum of conditions caused by infection with the human immunodeficiency virus.[1] Human immunodeficiency virus (HIV) infection was first described in North America in 1981, rapidly followed by a worldwide epidemic.[2,3]

HIV is transmitted by sexual contact, by exposure to blood (e.g. injection drug use, occupational exposure in health-care workers) and blood products, or to infants of HIV-infected mothers (who may be infected in utero, perinatally or via breastfeeding).[4] Worldwide, the major route of transmission is heterosexual. After mucosal exposure, HIV is transported via dendritic cells to the lymph nodes, where infection becomes established. This is followed by viraemia and dissemination to lymphoid organs, which are the main sites of viral replication.[3,4] A huge number of HIV patients are living throughout the world. It is stated that around 37.6 million people were living with HIV among them around 27.4 million people were accessing antiretroviral therapy and 6,90,000 people died from AIDS related illness in 2020.5,6 In

Corresponding author
Dr Lubna Khondker, Associate Professor, Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

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Bangladesh estimated people living with HIV is 14,000. Approximately 1600 people were newly infected with HIV and 580 people died due to AIDS related illness in Bangladesh in 2018.[7]

More than 90% of HIV infected patients show at least one mucocutaneous manifestation during the course of their disease.[8,9] Skin manifestations not only act as markers but also reflect the underlying immune status and help to determine the stage of the disease.10 Skin conditions may indicate progression of HIV disease and they can be disabling, disfiguring, or even life-threatening.[11] Many skin diseases can be considered as HIV indicators, disease stage marker and antiretroviral therapy efficacy.[12,13] Some dermatological manifestations are good markers of HIV infection such as generalized prurigo and herpes zoster of the young adult, oral hairy leukoplakia other have a prognostic value such as Kaposi sarcoma.[14,15] Oral hairy leukoplakia are good indicators of the diagnosis, stage and prognosis of HIV infection.[16,17]

HIV contributes significantly to patient morbidity in terms of quality of life and may also reflect the progress of HIV disease.[18] If CD4 T cell count >500 cell/mm3, the common mucocutaneous manifestations are Acute retroviral syndrome, Herpes zoster infection (non-disseminated), Seborrheic dermatitis.[19,20] If CD4 T cell count 200-500 cells/mm3, the common mucocutaneous manifestations are recurrent or persistent Dermatophyte infections, Oral candidiasis, Oral hairy leukoplakia, Disseminated Herpes Zoster infection etc.[21,22] If CD4 T cell count <200 cells/mm3, the common mucocutaneous manifestations are Bacillary angiomatosis, Cutaneous Miliary Tuberculosis, Hyperkeratotic scabies, Eosinophilic folliculitis, Herpes simplex virus infection (>1 month's duration), Idiopathic pruritus, Invasive fungal infections, Papular pruritic eruption etc.[21-23] In current world, with advancement of treatment of HIV, patients' life expectancy increasing due to dramatic decline in immunodeficiency related events and death.[15]

Materials & Methods

A cross sectional study was conducted at Anti-Retroviral Therapy (ART)center of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. This study was conducted during the period of January 2020 to June 2021. Data were collected from adult HIV infected patients attending at ART center at Bangabandhu Sheikh Mujib Medical University. Adults living with HIV, Aged ≥18 years, patients with mucocutaneous finding were the study population. Consecutive type of sampling technique was applied to collect the sample from the study population during the study period. Semi-structured questionnaire was the research instrument. Mucocutaneous manifestations of all the patients were clinically diagnosed. Ethical clearance for the study was taken from the Institutional Review Board(IRB) of BSMMU. Permission for the study was taken from ART center, BSMMU from where study subjects were selected. All the subjects were thoroughly appraised about the nature, purpose and implications of the study, as well as entire spectrum of benefits and risks of the study. His/her privacy were ensured, and information did not be disclosed to any source. Subjects were assured about the confidentiality of data and freedom to withdrawn them from the study anytime. Informed written consent of all the subjects was taken. Patients' identity did not disclosed while analyzing the results of this study. Data was analyzed and calculated using the Statistical Package for Social Sciences (SPSS version 26). Continuous variables were reported as the mean ± standard deviation. Absolute and relative frequency of mucocutaneous manifestation was computed.

Result

This cross-sectional study was conducted in the Department of Dermatology and Venereology and ART centre, Bangabandhu Sheikh Mujib Medical University, during the period of January 2020 to June 2021. A total of ninety-seven HIV patients were included in this study. The observations and results were as follows:

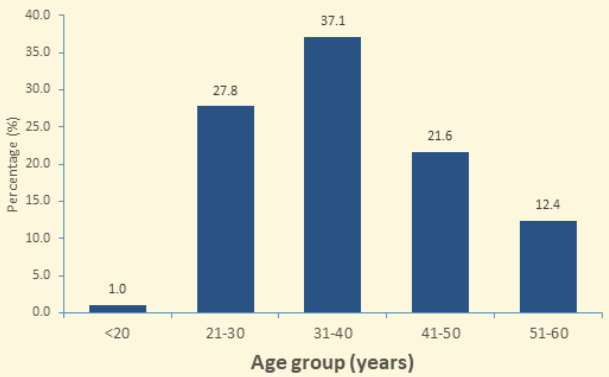

fig 1. Age distribution of the study patients

Figure1 showed that majority of the patients belonged to the age group between 31- 40 years (37.1 %) followed by 21-30 years (27.8%), 41-50 years (21.6%), 51-60 years (12.4%) and <20 years (1%).

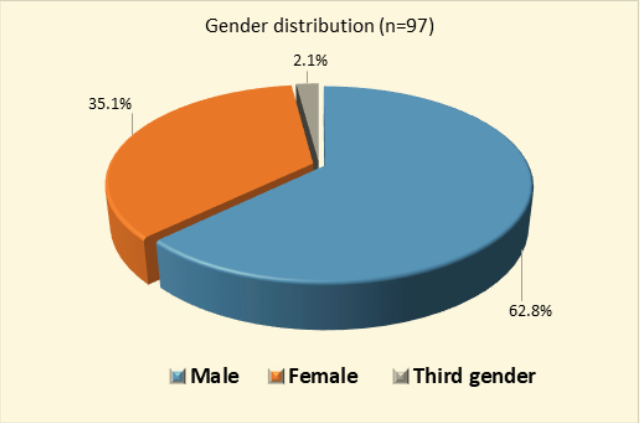

fig 2. Pie diagram showing the gender distribution of the study patients

Figure 2 showed that most of the patients were male 61 (62.8 %) followed by female 34 (35.1 %) and third gender 2 (2.1%).

Table-I: Distribution of HIV patients among infectious mucocutaneous manifestations (n=97)

Mucocutaneous manifestation in HIV patients	No. of disease (%)
Fungal infection	71 (73.2%)
Tinea Corporis	40 (41.2%)
Tinea Cruris	10 (10.3%)
Tinea pedis	2 (2.1%)
Onychomycosis	4 (4.1%)
Pityriasis Versicolor	5 (5.2%)
Oral candidiasis	10 (10.3%)
Viral infection	3(3.1%)
Herpe simplex	1 (1.0%)
Wart	2 (2.1%)
Parasitic	13 (13.4%)
Scabies	13 (13.4%)
Bacterial	5(5.2%)
Paronychia	3 (3.1%)
Folliculitis	2 (2.1%)

Table I: Showed most common infectious mucocutaneous manifestations were fungal infection in 71(73.2%) followed by parasitic infections in 13(13.4%), bacterial infection in 5(5.2%), viral infections in 3 (3.1%). Among the fungal infections Tinea Corporis 40 (41.2%) were more common, followed by Tinea Cruris, Oral candidasis 10(10.3%) each, Pityriasis Versicolor 5(5.2%) and Onychomycosis 4 (4.1%).

Table-II: Distribution of HIV patients among non-infectious type mucocutaneous manifestation (n=97)

Mucocutaneous manifestation in HIV patients (non-infectious)	No. of disease (%)
Seborrhoic Dermatitis	16 (16.5%)
Eczema	1 (1.0%)
Acne	2 (2.1%)
Melanonychia	5 (5.2%)
Aphthous stomatitis	2 (2.1%)
Cheilitis	2 (2.1%)
Oral pigmentation	1 (1.0%)
Alopacia	2 (2.1%)

Table II: Showed among the noninfectious manifestations Seborrhoic Dermatitis 16 (16.5%) were the most common followed by Melanonychia in 5(5.2%), Acne in 2(2.1%), Aphthous stomatitis 2(2.1%), Cheilitis 2(2.1%), Oral pigmentation in 1(1.0%) and Eczema 1(1.0%).

Discussion

This cross-sectional study was conducted with ninety-seven patients attending in the ART center, Bangabandhu Sheikh Mujib Medical University, from January 2020 to June 2021 to find out the pattern of mucocutaneous manifestations of HIV infected patients at Bangladesh.

Majority of the patients in this study, belonged to the age group between 31- 40 years (37.1%) whereas Khat et al. reported majority of the patients (42%) belonged to the age group between 31-40 years, Chandrakala et al. reported majority of the patients (36%) were in the age group of 31-40years.[24,25] Malkud et al. reported majority of the patients 43.3% were in the age group of 30-39 years. Kore et al. reported majority of the patients (49.7%) were in the age group of 31-40 years.[26,27] Singh et al. reported higher prevalence age group of 30-39.[28] These findings were almost similar to the current study.

Most of the patients in this study were male 62.9 % followed by female 34 35.1 % and third gender 2.1%. Vijaya et al. reported 63 were male, 60 were female and third gender 2 were enrolled to their study.[29] Malkud et al. 2016 reported male (68.3%) predominant.[26] Kore et al. 2013, reported male (66.8%) predominant.[27] These findings were almost similar to the current study where male patients were predominant.

Common fungal infections were Tinea Corporis 41.2% followed by Tinea cruris 10.3% and Tinea pedis 2.1%. Khat et al. reported the most common fungal

infection was dermatophytosis (59.1%). The presentation of dermatophytosis was very much similar to non HIV patients and hot climate in this region had claimed to higher prevalence of Dermatophytosis in immunosuppression condition.[24] Similar result was found in the study of Kore et al. 2013, where statistically significant association found between immunological stage of HIV infections and Dermatophytosis (p<0.008).[27]

Oral candidiasis was found in 10.3% cases in this study. Similar result found in the study of Boushab et al. where oral candidiasis 11.6%.[30] Ashrisf et al. reported Oral Candidiasis in 16%.[31] Halder et al. reported Oral candidiasis 17% cases.[32] These findings were almost similar to the current study. In this study, Pityriasis Versicolor was found 5.2%, similar result found in the study of Vijaya et al. reported six cases of Pityriasis Versicolor infection among 125 patients and Khat et al. reported Pityriasis Versicolor 2.3%.[29,24] Onychomycosis 4.1% was found in this study, similar result was found in the study Rajput et al. where onychomycosis reported in 3.8% cases.[10]

In this study one case of Herpes simplex virus infection was found, similar result was found in the study of Vijaya et al. reported one case of Herpes simplex virus infection among 125 patients.[29] Khat et al. reported Herpes Simplex Virus infection 3.8%, which is slightly higher than this study.[24] In this study, wart 2.1% was found. Khat et al. reported wart 5.4%.[24] In this study, Scabies 13.4% was found in immunocompetent patient (CD4 count above 500). No Crusted Scabies was found in this study because this occurred in immunosuppression condition. Malkud, et al., reported Scabies in 11.6% among 120 HIV patients.[26] Similar result was found in the study of Khat et al., where Scabies was statistically significant (p<0.012).[24]

Seborrheic Dermatitis 16.5% was the most common noninfectious manifestations encountered in this study. Similar result was found in the study of Kore et al. found Seborrheic Dermatitis 22% patient among 352 patients.[27] Shikur et al. found 11% Seborrheic Dermatitis patients among 572 patients.[33] Williams et al. reported Seborrheic Dermatitis in 30.6% among 36 patients.[34] In this study, Melanonychia was found 5.2% cases Khat et al. reported melanonychia in 6.9% patients among the 130 patients.[24]

Conclusion

Most common mucocutaneous manifestations were fungal infection (Tinea corporis, Tinea cruris and Oral candidiasis) followed by Seborreic Dermatitis and Scabies. Further studies are recommended to include large number of patients with a multi centered evaluation.

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Review Article:

Scabies,how difficult to treat- A systematic review

Jesmin Akter Leena1[1]

1. Assistant Professor, Dept. of Dermatology, Sir Salimullah Medical College, Dhaka, Bangladesh.

Abstract

Background: Scabies is a neglected tropical disease that continues to have global impacts and long-term health consequences in all nations regardless ofsocial and economic status.Treatment failure is an important factor concerning the increase in scabies incidence over the last decade. Here, we present an updatedreview of scabies by focusing on the challenges and difficulties in treatment that prevent the efforts foradequate control of the disease. **Methods:**The Cochrane Database of Systematic Reviews, MEDLINE, SCOPUS, Google Scholar, PubMed, and MEDLINE were all used in a systematic search. We incorporated case-control studies, prospective or retrospective cohorts, randomized and quasi-randomized trials, longitudinal (one-arm) observational studies, and case series that were published in the previous ten years. Our search terms included "vaccine," "mass drug administration," "scabies," "Sarcoptes scabiei var. hominis," "treatment," "management," "research updates," and "outcomes." Studies that discussed treatment resistance, failure, and difficulties in treating scabies were included. To gather information on global scabies control initiatives, obstacles, and experiences, as well as knowledge gaps, needs assessments, and recommendations for the future, a literature search was conducted. The papers that were included were only published in English. **Results:** For the systematic review, a total of 26 studies met the eligibility requirements. Drug resistance, application errors (especially with topical agents), neglecting repeated treatments, insufficient compliance, reinfestation due to insufficient decontamination of the patient's environment, failing to treat contacts concurrently, and not providing written information about necessary measures are among the established reasons why treating scabies can be challenging. **Conclusion:** Scabies is a highly contagious parasitic cutaneous disease that is stigmatizing and debilitating. Increased awareness, accurate diagnosis, prompt treatment, and selecting the right treatment options are essential for the effectivecontrol of scabies and for the prevention of the spread of the disease. **Abbreviation:** NTD, MDT, IACS

Key words: Scabies, treatment, failure, challenges.

Introduction

Scabies affects 200 million individuals worldwide, according to estimates. In 2017, scabies was added to the list of tropical illnesses that the World Health Organization considers to be among the most neglected in the world, indicating the need for more comprehensive research to determine the disease burden and for widespread disease control measures[1]. The origin of this extremely contagious skin infection is the Sarcoptes scabiei (S scabiei) var. hominis mite, a restricted ectoparasite that resides in the epidermis and manifests as generalized pruritus.[2-4] Greek words "sarx" (which means "flesh") and "koptein" (which means "to smite or to cut") are the source of the name "Sarcoptes". The Latin verb "scabere," which means "to scratch," is the source of the name "Scabiei."[5] The mites that cause scabies can spread both directly and indirectly, affecting multiple family members simultaneously.[6] It is also recognized

Corresponding author
Dr. Jesmin Akter Leena, Assistant Professor, Dept. of Dermatology, Sir Salimullah Medical College, Dhaka, Bangladesh. email: jesminleena912@gmail.com

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that scabies is a sexually transmitted infection.[7] The risk of scabies transmission is increased by the length and frequency of direct skin-to-skin contact, as well as by the amount of mites on the skin.[8] Effectively treating the patient and taking all necessary precautions to prevent the disease from spreading to other people are the main objectives of scabies therapy.

Up to 30% of cases may result in treatment failure, which is thought to be a significant contributing cause to the rising scabies incidence that has lately been documented in affluent nations.[9-12] It has been proposed that factors such as drug resistance, treatment choice, exposure to future transmission events, and host immunological condition are predictors of treatment failure.[13,14] Studies, however, have not undergone a systematic evaluation and are quite varied. The frequency of scabies that is resistant to therapy for different medications is also poorly documented. Moreover, a thorough analysis of the variables linked to treatment failure has not been done. To ascertain the challenges associated with treating scabies, we therefore carried out a comprehensive evaluation of observational studies and randomized clinical trials.

The goal of this article is to provide an overview of the difficulties in managing the illness with the resources at hand and stopping its spread.

Method

Search strategy:Five electronic databases—PubMed, Google Scholar, Cochrane Database of Systematic Reviews, MEDLINE, and SCOPUS—were thoroughly searched. The pertinent studies that have been published in the past 10 years have been chosen. We measured at least one of our outcomes of interest (i.e., treatment failure, reinfestation, retreatment/recurrence, persistent itching, susceptibility to scabies mites, or risk factors for treatment failure) using randomized and quasi-randomized trials, prospective or retrospective cohorts, case-control studies, longitudinal (one-arm) observational studies, and case series. The original search plan was developed on PubMed and subsequently modified to fit the included databases' formats. To incorporate the various keywords into the search method, the Boolean operators "OR" and "AND" were employed.Articles resulting from these searches and relevant references cited in those articles were reviewed. The most relevant articles were included in this review. Keywords in our search included “scabies”, “Sarcoptes scabiei var. hominis”, “treatment”, “management”, “research updates”, “mass drug administration”, “vaccine” “challenges” and“outcomes”.

Inclusion and exclusion criteria:Only human studies were eligible for inclusion. A literature search yielded 196 initial hits; after screening following the defined inclusion and exclusion criteria, 26 studies were selected for this review. Finalinclusion was subjectively restricted to 26major medical and epidemiological articles basedon their relevance to the study objectives and aims. A systematic literature searchwas performed givingpreference to review articles, large epidemiologicalfield studies, and articles that comprehensively and/orappropriately covered the topics of interest and helpedexplain the significance of the issues this article covers. Studies that discussed treatment resistance, failure, and difficulties in treating scabies were included. The papers that were included were only published in English.

Articles that only discussed scabies guidelines or protocols in a specific nation or institution, or that presented a case study of a single patient or an outbreak of scabies in a single institution, were also disqualified. Excluded from consideration were any research that listed scabies among a variety of illnesses, indications, causes, or coexisting conditions. To find any manuscripts that the search strategy missed, reviewers' reference lists were examined.

Data extraction: The literature search aimed to retrieve information on control efforts, challenges, experiences, knowledge gaps, and needs assessments and recommendations for the futurein the field of global scabies control. We intended to compile data from multiple articles regarding the same study to ensure complete data extraction. The identified papers were first searched for duplicates then the remaining papers had their titles screened to allow for the quick elimination of studies that did not fit the inclusion Criteria.All titles and abstracts identified were screened for relevance and resolved the queries. Then full texts of papers assessed to be relevant were reviewed.

Quality assessment: We used the Cochrane Collaboration’s tool for assessing the risk of bias. Studies were assessed independently by two investigators in multiple domains of bias, including selection, performance, detection, attrition, and reporting. We also assessed the response or participation rate in the study, the quality of the scabies assessment (as described in the study report), and the statistical analysis of the results.

Compliance with Ethics Guidelines

This article does not include any research that we have done using humans or animals; instead, it is based on earlier investigations.

Scabies epidemiology: According to the most recent estimates, 150–200 persons worldwide contract scabies annually, with Asia, Oceania, and Latin America having the highest rates of scabies cases15. Young children who live in crowded conditions in impoverished populations are more frequently at risk16. Since scabies is contagious, people who live with patients may often become infected. There is an increased risk of scabies and associated breakouts for those who live in crowded housing situations or in clustered communities. Scabies is endemic in areas with few resources, where poverty and overcrowding are more prevalent. The mite can spread widely in households where there is inadequate access to treatment and high population density. When people who reside in these endemic areas seek treatment, they frequently return to rapid re-infestation.[17]

Scabies mites

Sarcoptes scabiei var hominis, an obligate human parasite,is a member of the family Sarcoptidae, which belongsto the order Astigmata, in thesubclass Acari, class Arachnida.The parasite is white-brownin colour and has 4 pairs of legs.The size of female mites is roughly double that of male mites, measuring 0.3 × 0.4 mm.[18] Male mites that land on human skin look for unfertilized female mites, mate on the skin's surface, and promptly perish after mating.[19-21] With their powerful mandibles, fertilized female mites excavate tunnel-like burrows in the stratum corneum. The release of proteolytic enzymes, which break down the stratum corneum, speeds up this process, which typically takes 20 to 30 minutes.[19-21] They keep on burrowing at a rate of 0.5 to 5mm per day for the rest of their life which is approximately 4to 8 weeks.[19-21] Fertilized female mites lay 0 to 4 eggs perday for an average of 40 to 50 eggs during theirlifetime.[20,21] The eggs are deposited in the burrowed tunnel andhatch in 2 to 5 days19. The larvae burrow into the intactstratum corneum tomake short borrows where they molt intonymphs, mature into adults in 10 to 17 days, and emergeonto the skin surface.[20] Mites can crawl at a rate of 2.5 cm/minute onwarm skin but are unable to jump or fly[19,20] At normal room temperature and with a relativehumidity of 40 to 80%, scabies mites can survive outsidethe human body for 24 to 36 hours.[22] Scabies mites are resistant to alcohol and soap23. On average, fewer than 10% of the eggs will develop intoadult mites.[20] With classicscabies, the average burden on anormal host is 10 to 15 live adult mites at any given time.[19,22] In temperate climates, the incidenceis higher in fall and winter than in summer.[19] Predisposingfactors include poorhygiene, malnutrition, poverty,overcrowding, homelessness, reduced access to healthcare, indiscriminate sexual contact, dementia, poor sensoryperception, and immunodeficiency. Community-wide outbreaks have occurred inhospitals, child-care settings, nursing care homes, and long-term care facilities.[24] Scabies is common in developingcountries.[25] The risk of transmission increases with the durationand frequency of direct skin-to-skin contact as well asthe number of scabies mites on the skin.[21]

Scabies diagnosis

The International Alliance for the Control of Scabies (IACS) was founded in 2012, and its members produced scabies diagnosis criteria in 2018 and 2020, respectively. In a Delphi consensus survey, a group of 34 international experts originally developed the IACS criteria.[26] Three levels of certainty were suggested for the diagnosis: clinical, confirmed, or suspected scabies.

The 2020 International Alliance for the Control of Scabies (IACS) has summarized its diagnostic criteria for scabies.[27]

A: Confirmed Scabies

A1: Mites, eggs, or faeces on light microscopy of skin samples

A2: Mites, eggs, or faeces on the individual using a high-powered imaging device

A3: Mite visualized on the individual using dermoscopy

B: Clinical Scabies

B1: Scabies burrows

B2: Typical lesions affecting male genitalia

B3: Typical lesions in a typical distribution and two history features

C: Suspected Scabies

C1: Typical lesions in a typical distribution and one history feature

C2: Atypical lesions or atypical distribution and two history features

H: History Features
H1: Pruritus
H2: Close contact with an individual who has had itch or typical lesions in a typical distribution.

The diagnostic criteria have limitations in that it does not include the diagnosis of variant or atypical presentations of scabies, such as bullous scabies, crusted scabies, scabies in immunocompromised individuals, or scabies in the elderly, intellectually disabled, or bedridden individuals. Consequently, clinical judgment remains imperative in the diagnosis of scabies. There are currently no easily accessible laboratory tests to confirm scabies. Rather, the "gold standard" is to use a microscope to see mites, eggs, or feces. The justification for a novel, trustworthy technique to diagnose scabies is supported by the fact that microscopy detection rates range from 10 to 70%.[28] The need for intrusive skin scrapings has been eliminated by dermatoscopes, however, dermoscopy still requires an operator. Dermatoscopes arenot affordable in all regions, cannot visualize feces or eggs, and are harder to detect mites in darker skin types.[27]

Treatment of scabies

For scabies, several approved therapies exist. There are topical (such as lindane, permethrin, sulfur-containing treatments, crotamiton, malathion, and benzyl benzoate) as well as oral (such as ivermectin, thiabendazole, and flubendazole) remedies available. In several jurisdictions, oral ivermectin has not been authorized for the treatment of scabies, and it is not readily available. The standard treatments are topical and usually need to be applied all over the body for eight to twelve hours. After seven to fourteen days, a second application is advised. The ideal course of treatment is not universally agreed upon, and suggestions made in one country may not be suitable in another. To prevent infestation, every close personal contact of the patient should receive treatment at the same time. According to the 2017 European Guidelines for the Treatment of Scabies, topical therapy should be used on all skin areas including the skin beneath the ends of the nails.[29]
Itching is a common side effect following scabies treatment, and it can last for two to four weeks. Emollients should be applied often to relieve post-treatment itching. Oral antihistamines and low-dose topical corticosteroids may also be utilized in some circumstances.[29] Two weeks following the last scabicide treatment, a microscopic examination is advised to evaluate the efficacy of the treatment.[29] It can take up to six weeks following the end of treatment for symptoms and indicators of hypersensitivity to go away, thus it is best to wait until then to determine treatment failure.
To achieve treatment success, not only is ordering the proper scabicide needed, butthe washing of clothing, bedding, towels, and other items is needed; these items should bemachine washed (at least at 500C), drycleaned, or sealed and stored in a plastic bag for 1 week.[29]

Challenges related to therapy

It has been difficult to treat children since, for a long time, there was no clear protocol for treating scabies in children, and did not result in a full recovery.[30] As of right now, the guidelines specify which precise acaricides to use and at what doses for newborns and older children. Children as young as two months old are permitted to use permethrin. Children under the weight of 15 kg should not be administered ivermectin.[29] Because there was insufficient information on the adverse effects of the available acaricides, the treatment of pregnant women was also controversial for a long time. Permethrin, benzyl benzoate, and sulfur are suggested as safe therapeutic alternatives in pregnancy by the most recent treatment guidelines.[29]
Inadequate drug administration, length of treatment, wrong dosage, or drug resistance are among the possible causes of treatment failure for Sarcoptes, as reported in the literature. In multicenter research comprising 112 patients, Aussy et al. found that the reason for therapy failure was a single dose of ivermectin (as opposed to two intakes) and topical benzyl benzoate alone.[31] However, Sunderkötter et al. clarified that failing permethrin treatment could be brought on by insufficient exposure to this acaricide.[32] Additionally, Isogai et al. clarified that subungual debris and nails might harbour Sarcoptes mites and eggs.[33] Furthermore, the overall state of the patient (such as immunosuppression) may impact the course of therapy, necessitating the use of multiple acaricides or extending its duration.[34] Research has indicated that in impoverished areas, living in close quarters with high population density, having frequent physical contact, sharing clothes, bedding, and other items, and having inadequate shelter are the primary community-level risk factors for scabies infestation and severe infection.[39,40]

New Treatment Options for Scabies

New studies are being conducted because new scabicides are needed that are more effective against eggs and have a half-life that extends to the entire 14-day life cycle of the mite. Moxidectin is also being studied as an oral alternative to ivermectin. Ivermectin and moxidectin are members of the same family. It is noteworthy that this medication has a substantially longer half-life in plasma and the skin than ivermectin, as well as quick absorption and wide distribution37. Because of this pharmacological feature, it could be able to treat the scabies mite during its whole life cycle. In a preliminary study using an experimental pig model for scabies, a single oral dose of moxidectin proved to be more successful than the traditional two doses of ivermectin. In Australia and France, a multinational clinical phase II trial aims to develop moxidectin as a novel single-dose scabies treatment (NCT03905265).[43]

Higher doses of ivermectin are an intriguing alternative that is presently being researched for the treatment of scabies44. There's a growing theory that a greater ivermectin dosage might be required to treat the parasite infection. When this idea was first brought up concerning head lice infestation, research revealed that a twofold dose of 0.4 mg/kg ivermectin was roughly 95–100% effective45. The efficacy of ivermectin given orally as the higher double dose of 0.4 mg/kg with the conventional treatment dose of 0.2 mg/kg, given three times seven days apart (on D0, D7, and D14), is being compared in a randomized controlled clinical trial approved by the French Ministry of Health. Both arms are supplemented with daily application of emollient therapy and topical5% permethrin on D0 and D7 (GALECRUSTED, NCT02841215).[46]

The value of pets as "family members" has steadily increased in recent years. Studies in this regard have demonstrated the efficacy of treating fluralaner topically and orally. Chitin, a vital part of the exoskeleton of arthropods, including the scabies mite, is blocked from being synthesized by fluazuron. It does not work against adult mites; instead, it stops the development of new larvae inside the eggs. A single dose of the innovative medication fluralaner, which is safe, efficacious, and maintains results for twelve weeks after treatment, can be used to treat canine sarcoptic mange.[38]

Mass drug administration

Treatment for scabies is typically directed at the patient and their household contacts in nations where the disease is infrequent. It has been discovered that treating the entire population at once is more successful when scabies become endemic.[41] This is known as mass drug administration, and it can be applied nationally or in places where people are confined, such as jails, hospitals, nursing homes, and schools.[42] Oral, topical, or systemic medicine may be used in MDA.

Nevertheless, there is still debate regarding the use of oral ivermectin in MDA.[47] Firstly, there are some countries where the medicine is not approved for the treatment of scabies, and it has been connected to certain safety issues with pregnant women and children under the age of five.[47] Second, similar to topical medications, resistance may arise with protracted, recurrent regimens of oral ivermectin.[48,49] Third, there is evidence from certain studies that ivermectin does not work as well as topical agents.[50,51]

Vaccines

In endemic locations and for cases of crusted scabies, vaccinations are anticipated to be a viable means of preventing the development of scabies.[35] It is common for a second scabies infestation to be less severe than the first, and numerous accounts exist of animals developing immunity following a prior infestation. As a result, a vaccination might work. Recent advances in our understanding of the interplay between Sarcoptes and the immune system of the infected individual should have a positive impact on efforts to develop a vaccine. With increased host antibody levels and fewer mites after infection, immunity develops quickly.[36] Mice and rabbits were used in an animal model to test an anti-mite vaccine; nevertheless, more trials are required.

What actions are necessary to effectively control scabies?

Plans for further research and other requirements:

The literature on scabies still has a lot of significant gaps.[52] The initial areas of concern concerning therapy are safety and the limitations of the therapeutic choices that are now accessible. There are issues with ivermectin and other medications in young children and during pregnancy, and more research is needed on ivermectin dose optimization. The emergence of mite generations resistant to various scabicidal medications, the most effective treatment for crusted scabies, and the poor efficacy of current treatments in preventing relapses all require more research. The development of vaccines

is the last field still awaiting advancement. Guidelines for the best therapeutic approaches should also be developed to address consequences such as secondary bacterial infections, inflammatory skin reactions, and other issues.We should support comparative research to evaluate novel medications. To determine if MDA is a successful community-wide scabies control strategy, more research is required. Additional thought must be given to the economic impact of scabies to calculate its direct and indirect costs.[53] It is also necessary to map the prevalence of disease in neglected areas, such as impoverished populations in Africa.[54] Furthermore, financial agencies should refocus their efforts on scabies because it is a disease mostly affecting the impoverished. Financing for research on population-based tools, diagnostics, and therapy should be prioritized.

A hopeful start toward scabies control was made in 2020 when scabies was added to the new WHO roadmap for neglected tropical diseases 2021–2030, taking into account the needs previously mentioned.[55] Scabies control, not eradication, is the goal of this strategy. A measure of advancement towards the roadmap's scabies control objective will be the count of nations that have integrated scabies control into their universal health care program. It is anticipated that this indicator will rise from the baseline value of zero in 2020 to 25 (13%) in 2023, 50 (26%) in 2025, and 194 (100%) countries in 2030.The WHO states that the roadmap is intended to serve as a call to action for various nations, funders, policymakers, researchers, and disease experts to work together and connect their plans and strategies to create coordinated efforts toward the control and eradication of NTDs, and consequently lessen the suffering of impoverished populations affected by them. It is believed that drawing attention to scabies in this manner will concern everyone worried about the urgent need to further investigate and coordinate activities aimed at eradicating this illness.

Conclusion

Standardizing treatment guidelines for scabies is one of the measures that have been used. In endemic areas, mass drug administration is a campaign intended for both prevention and treatment. The present medications used to treat scabies are unfortunately not working as well as they once did, thus new treatments must be found. New acaricides are being created for this reason to improve therapeutic choices that will benefit the patient and successfully treat this illness. Additionally, prevention is required before contracting scabies, particularly for those residing in endemic areas. Regretfully, efforts to develop a vaccination that works have not yet been successful. Drug resistance, mistakes made when applying medication (especially topical treatments), missing follow-up treatments, low compliance, reinfestation due to insufficient environment decontamination, treating contacts at the same time, and not providing written instructions about necessary precautions are all known reasons why treating scabies can be challenging.

Controlling scabies worldwide is now possible, despite the present obstacles. Scabies global control appears to be a worthwhile, realistic goal that may be accomplished in the not-too-distant future with persistent interventions, ongoing resources, genuine commitment and support, and a focus on the targets and indicators identified in the WHO roadmap for NTD 2021–2030.

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Conflict of interest

The authors declare no conflict of interest, financial orotherwise.

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Case Report:

Cutaneous Polyarteritis Nodosa without any subcutaneous nodules but with Pyoderma Gangrenosum like ulcers: A Rare Case Report

Lubna Khondker[1], Pranam Swapan Dash[2], Wasi Deen Ahmed[3].

1. Associate Professor, Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
2. Medical Officer, Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
3. MD Resident, Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

Abstract

Cutaneous Polyarteritis Nodosa (cPAN) is a rare form of vasculitis of medium and small sized vessel of unknown etiology, first described by Kussmaul and Maier in 1866. The average age of onset is approximately 50 years. In both adults and children, males appear to be more commonly affected than females. cPAN is characterized by disease affecting primarily the skin without any major organ involvement. cPAN is demonstrated purpura, ulcerations, and tender recurrent subcutaneous nodules on the lower extremities as well as postinflammatory hyperpigmentation. Systemic symptoms may include fever, rash, joint pain and myopathy. Diagnosis is confirmed by histopathologic evidence of necrotizing inflammation of the medium and small-sized arteries. Treatment for cPAN includes the use of topical or intralesional corticosteroids for limited disease, systemic corticosteroids for extensive disease, and nonsteroidal anti-inflammatory drugs for symptomatic relief. cPAN is difficult to control and often requires longer courses of prednisone and steroid-sparing agents such as colchicine. Untreated polyarteritis nodosa has a poor prognosis, with a 5-year survival of 13%. Treatment improves this substantially, with current 5-year survival rates of approximately 80%. Subcutaneous nodules precede skin ulceration in a case of cPAN in 80% of times. But here we are presenting a case of cPAN who was admitted into Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University with multiple sharply marginated hyper pigmented painful plaques over the left thigh with elevated vesicular margin and surrounding erythematous halo, without any subcutaneous nodules and with multiple pyoderma gangrenosum-like ulcers with necrotic slough with perilesional erythematous halo. Although only 20% of cPAN cases present without any subcutaneous nodules, and even fewer present with pyoderma gangrenosum like ulceration, this case report will reveal the rare possibility of presenting both and therefore will warrant the clinical suspicion of cPAN in case of lower limb ulcerations in a young lady.

Key words: Cutaneous Polyarteritis Nodosa(cPAN), subcutaneous nodules, Pyoderma Gangrenosum like ulcer in PAN.

Introduction

PAN is necrotising arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules, and not associated with Anti-Neutrophil Cytoplasmic aAntibodies (ANCAs).[1] It can affect any organ but, for unknown reasons, it spares the pulmonary and glomerular arteries.[2] A less severe form called cutaneous polyarteritis nodosa (cPAN) has also been described. Its features include tender subcutaneous nodules, livedo reticularis, cutaneous ulcers, and necrosis.[3] It is often associated with streptococcal infection.[4] Hepatitis B infection is an important cause of secondary polyarteritis nodosa.[5,6] Peripheral nerves and skin are the most frequently affected tissues. The skin can demonstrate a range of lesions, including purpura, livedoid, subcutaneous nodules, and necrotic ulcers.[2] Neurologically, mononeuritis multiplex is the most common presentation.

Corresponding author
Dr Lubna Khondker, Associate Professor, Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

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Involvement of the gastrointestinal tract, kidneys, heart, and central nervous system is associated with a higher mortality.[7] If there is renal involvement, patients may present with hypertension or acute kidney injury. Gastrointestinal symptoms occur in 14-65% of patients and postprandial abdominal pain from ischaemia is the most common symptom.[8]

Diagnosis of polyarteritis nodosa requires the integration of clinical, biopsy, and angiographic findings. According to the ACR criteria, polyarteritis nodosa can be diagnosed in a patient with vasculitis if three or more of the following features are present:6 weight loss greater than 4 kg, livedo reticularis, testicular pain or tenderness, myalgias, mononeuropathy or polyneuropathy, new-onset diastolic blood pressure greater than 90 mm Hg, renal dysfunction (blood urea greater than 14.3 mmol/L or creatinine greater than 133 µmol/L), evidence of hepatitis B infection, arteriogram showing the arteries that are dilated or constricted by the blood vessel inflammation and on biopsy, presence of granulocyte or mixed leukocyte infiltrate in the wall of a small or medium-sized artery. ANCAs are negative in PAN, and a positive ANCA in the context of necrotising vasculitis strongly suggests microscopic polyangiitis, granulomatosis with polyangiitis, or Churg-Strauss syndrome.[5] Inflammatory markers (including ESR and CRP) are elevated. Biopsy of small arteries will show evidence of necrotising inflammation.[6,9] Arteriography shows microaneurysms in the small-sized and medium-sized arteries.[10] FDG-PET/CT (Fluorodeoxyglucose positron emission tomography-computed tomography) is emerging as a potentially useful non-invasive imaging technique for diagnosis.[11] In cutaneous polyarteritis nodosa:3 Mild cases may require only non-steroidal anti-inflammatory drugs (NSAIDs) or colchicine. Prednisolone 30 mg daily or less is often effective in more severe cases but a dosage of 1 mg/kg/day may be required. Unfortunately, exacerbations occur with the tapering of the corticosteroids and adverse effects limit their long-term use. Immunosuppressive agents are frequently effective in cPAN resistant to high-dose corticosteroids.

Case report

A 23-year-old woman got admitted into Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University with multiple sharply marginated hyper pigmented painful plaques over the left thigh. She gave a history of similar lesions on left arm three years back which ultimately ulcerated and healed subsequently leaving a scar after treatment with Prednisolone and Azathioprine for 6 months. She remained symptom-free for next three years without any medication. Review of systems was significant for myalgia, fatigue and unintentional weight loss. She denied any atypical limb pain, leg cramps, joint pain, photosensitivity, wrist or foot drop or any other skin lesions.

Physical examination on admission found a normotensive, afebrile woman in no acute distress, and there were multiple sharply marginated hyper pigmented tender plaques over the left thigh with elevated vesicular margin and surrounding erythematous halo. On 7th day of admission, the plaques on the thigh turned into deep tender ulcers with undermined edge covered with necrotic slough with perilesional erythematous halo. Evaluation of conjunctivae and sclera were normal.

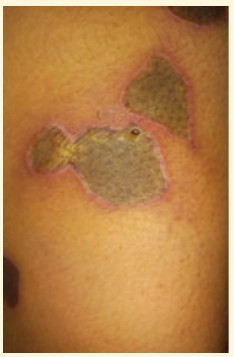

Figure A

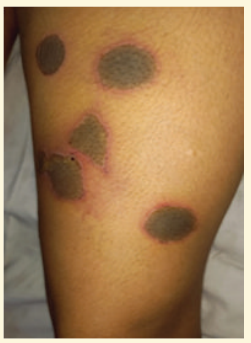

Figure B

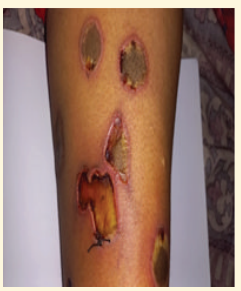

Figure C

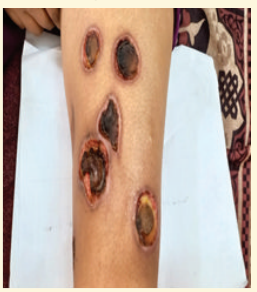

Figure D

Figure A and B: Erythematous Plaques during admission
Figure C: 7 days after admission
Figure D: 10 days after admission

Her complete blood count, C-reactive protein and comprehensive metabolic profile were all within normal limits. Hepatitis B and C panel were found negative. Wound swab culture obtained from ulcer revealed infection with Staphlycoccus aureus. A deep punch biopsy was obtained from the margin of an ulcer which revealed dense infiltration of lymphocytes in the reticular dermis and the subcutis with fibrinoid necrosis in the thick walled

medium-sized arteries. Based on histopathology and absence of systemic involvement, a diagnosis of cPAN was made. After addressing the infection with oral antibiotics, she was then started on Oral Prednisolone 1mg/KG/day and Methotrexate 15mg weekly. After 1 month of treatment with Prednisolone @1mg/kg/day, the ulcers show signs of healing as evidenced by appearance of granulation tissue with healthy ulcer margins.

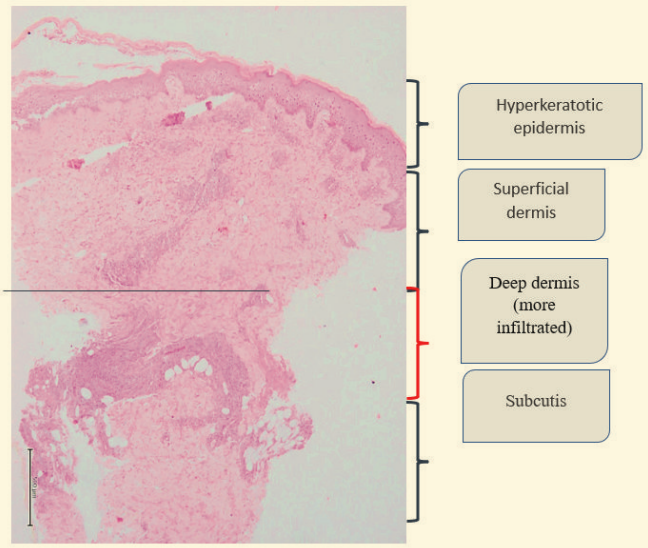

Figure E: Showing different layers of skin histopathology obtained from punch biopsy

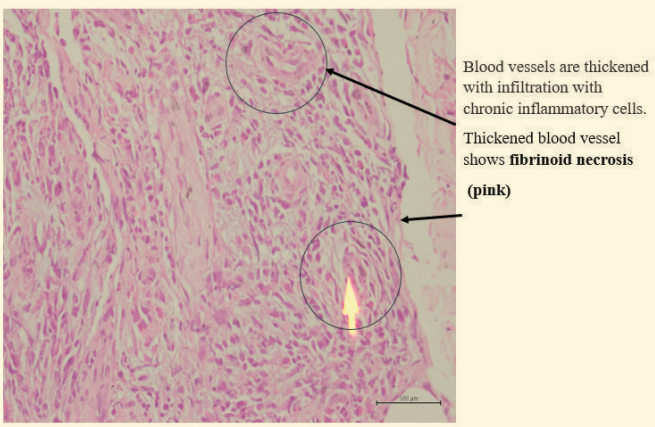

Figure F: Showing histopathological features of cPAN from the punch biopsy

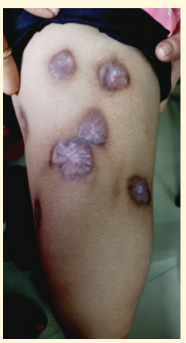

Figure G

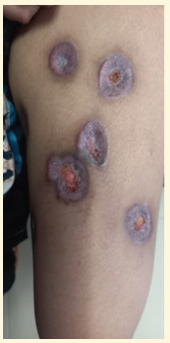

Figure H

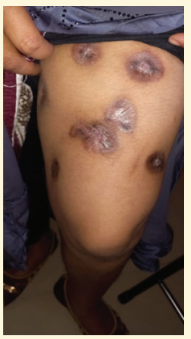

Figure I

Figure G: 1 month after starting Prednisolone
Figure H: 2 months after starting Prednisolone
Figure I: 4 months after starting Prednisolone

Discussion

Pineider J et al reported a case similar to our reported case except age and presence of painful black nodules of the patient. A 49-year-old white female smoker with a history of intravenous drug use and chronic hepatitis B complicated by early cirrhosis presented with painful ulcers on her right third finger and right second toe. She reported a 4-year history of recurrent spontaneous, painful black nodules, which ulcerated and then healed with scarring. She had been treated with multiple rounds of oral and intravenous antibiotics for presumed infections without resolution. Her liver transaminase levels were slightly elevated consistent with her known liver cirrhosis, but otherwise her comprehensive metabolic profile and complete blood count values were within normal limits. Magnetic resonance imaging of the right hand showed nonspecific arthritis of the third proximal interphalangeal joint without evidence of septic arthritis or osteomyelitis. Magnetic resonance imaging of the right foot showed mild skin irregularity over the second toe, interpreted as focal cellulitis. A punch biopsy was obtained from a purpuric papule on her right third finger. The day after biopsy, there was profound pathergy, creating a pyoderma gangrenosum-like lesion. Histopathology testing found a dense neutrophilic dermatitis with vasculitis, and near-complete obliteration of a medium-sized arteriole in the reticular dermis. Based on histopathology, lack of criteria to meet diagnosis for Behcet disease (BD) and absence of systemic involvement, a diagnosis of cPAN was made.[12] To the best of our knowledge, there is only one prior case reported in which a patient in whom pyoderma gangrenosum was initially diagnosed and was later

found to have systemic PAN after biopsy.[13]

Although usually cutaneous PAN presents with tender subcutaneous nodule on the background of livedo racemose and atrophic blanche-like lesions,14 our patient didn't show any of these signs. Rather she presented with Pyoderma Gangrenosum like deep, tender ulcers with erythematous halo. She also had negative P-ANCA, consistent with 80-90% of the patients of cPAN. We diagnosed the case ultimately based on the histopathological findings of dense lymphocytic infiltration with fibrinoid necrosis of the medium sized vessels in the reticular dermis and subcutis. There have been very few case reports where the initial clinical diagnosis of Pyoderma Gangrenosum (PG) was ruled out only after doing a histopathological analysis revealing features of PAN. cPAN patients who have elevated C-Reactive Protein and pretreatment ulcers have higher chances of relapse.[4] Delayed diagnosis and the inability to reduce severity of the flares resulted in prolonged skin, soft tissue, and joint damage leading to amputation of the affected digit. Therefore, early recognition is critical to control symptoms and prevent prolonged patient morbidity.

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Case report:

Noonan Syndrome with Multiple Lentigines: A rare Hereditary Multisystem Disorder

Md. Mostaque Mahmud[1], Iftekhar Ahmed[2], Mohammad Mahmudur Rahman[3]

1. Associate Professor, Dermatology & Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka
2. Ex-Assistant Professor, Dermatology & Venereology, Sir Salimullah Medical College
3. Assistant Professor, East West Medical College, Dhaka

Abstract

Noonan syndrome with multiple lentigines (NSML) is a rare hereditary disorder that was previously known as LEOPARD syndrome. We present a 24-year-old woman with hundreds of lentigines all over her body, wide-apart eyes, deafness, and an inability to talk since her childhood. Her hearing test revealed sensorineural deafness. She had a concentric type of cardiomyopathy in the echocardiographic report. Clinically she was labeled as Noonan syndrome with multiple lentigines. She had presented with greying of scalp hairs, which was a unique feature of such a case. Around 200 NSML cases were found worldwide. To the best of our knowledge, this is the first case of a patient with NSML presenting with grey hair.

Key words: Noonan syndrome with multiple lentigines, LEOPARD syndrome

Introduction

Noonan syndrome with multiple lentigines (NSML) previously known as LEOPARD syndrome (LS), is a rare autosomal condition with an unknown prevalence. LEOPARD is an acronym that stands for lentigines on the skin (L), electrocardiographic conduction defects (E), ocular hypertelorism (O), pulmonary stenosis (P), abnormal genitalia (A), retarded development (R), and deafness (D).[1,2] Mutations of the PTPN11 (90%), RAF1, BRAF, and MAP2K1 genes cause this syndrome. Noonan syndrome is an autosomal dominant condition similar to NSML.[3,4,5]

Several clinical findings of Noonan Syndrome overlap those of NSML, like facial anomalies, some congenital heart defects, sensorineural deafness, and growth retardation The leading causes of pediatric intracerebral haemorrhage (ICH) are arteriovenous malformations, hematologic abnormalities, and brain tumours.[6] NSML has no specific treatment option. Cardiovascular intervention and supportive measures can help the patients to continue a near-normal lifestyle.[7]

There is no single treatment for NSML. Some symptoms may require more regular follow up with different specialists than others. For example, hearing loss is usually followed closely and managed by an audiologist. Specific options for care may also depend on age. Regular follow-up can help inform appropriate screening and testing for health issues that may support a person with NSML.[8] Early intervention programs are useful to help the developmental differences in children with NSML. The life expectancy might differ among the people affected with NSML. Congenital heart defects can be a cause of shortened life span. Although some children may have more serious health complications, most children will meet almost all developmental milestones.[9]

Case report

A 24-year-old woman presented with hundreds of lentigines all over her body since early childhood. All of her dark spots were increasing in number, size, and pigmentation slowly day by day. The spots were asymptomatic and uniformly coloured. She had hearing loss and an inability to speak. Her hearing test revealed bilateral sensorineural deafness. Her eyes were wide apart (hypertelorism) but no visual

Corresponding author
Dr. Md. Mostaque Mahmud, Room-310, Block-C, Bangabandhu Sheikh Mujib Medical University, Mobile-01711100552, E-mail: drmstq@yahoo.com
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impairment. Her parents noticed her shortness of breath and chest discomfort on vigorous exertion. There was a concentric type of cardiomyopathy in her echocardiographic report. All her family members were in good health. She comes from a non-consanguineous parent. Clinically she was labeled as Noonan syndrome with multiple lentigines. She had presented with greying of scalp hairs and that was a unique feature of such a case. She was visited at the Dermatology OPD of BSMMU in 2023. Consent was taken from the patient and her guardians for case report and photograph.

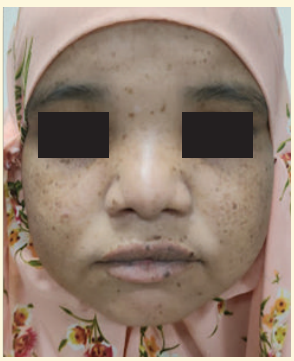

fig 1. Patients with multiple lentigines on the face with hypertelorism

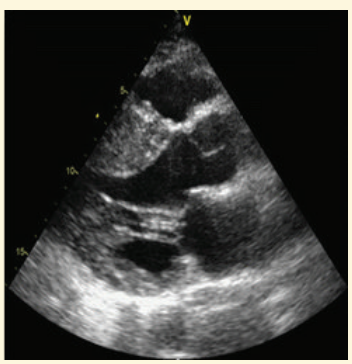

fig 2. Concentric cardiomyopathy on echocardiographic report

Discussion

There are various systemic presentations in NSML. Multiple dispersed flat, black-brown macules (lentigines), mostly on the face, neck, and upper part of the trunk sparing the mucosal surfaces. Lentigines usually appear at the age of four to five years and then increase up to thousands by puberty. Café au lait macules are observed in up to 70%-80% of affected individuals, usually preceding the appearance of lentigines. Skin hyperelasticity or lax skin has also been found in some cases. Neurofibromas have been observed in a few cases.[10] Approximately 85% of affected individuals have congenital heart defects similar to those observed in Noonan syndrome (NS). Hypertrophic cardiomyopathy is a common defect that is detected in 70% of individuals with heart disease. Pulmonary valve stenosis is described in approximately 25% of cases EKG abnormalities, with hypertrophic cardiomyopathy and conduction defects (23%).[11,12] In the present case a concentric type of cardiomyopathy was detected in echocardiography. Dysmorphic facial features are similar to those seen in Noonan syndrome. Inverted triangular-shaped faces, down-slanted palpebral fissures, widely spaced eyes (hypertelorism) and low-set and posteriorly rotated ears are the common presenting features of the face. A short neck with excess nuchal skin and a low-set posterior hairline is also described in some cases.[13,14] This patient has widely parted eyes but the ear and neck were normal. Sensorineural hearing loss is present in approximately 20% of persons with NSML.[15] Sensorineural deafness was detected in this case.

Pectus anomalies are present in 50% or more of affected individuals. Cryptorchidism, unilateral or bilateral, hypospadias, urinary tract defects, and ovarian abnormalities are observed infrequently.[16,17] Hypotonia is common in newborns and is associated with delayed psychomotor development.[18] But that feature was absent in the present case.

Gene mapping at least PTPNII was necessary to support the diagnosis but that was not possible for this case. Greying of hair is a new feature that was not listed before this case. There is no treatment option for NSML. We delivered details information about that syndrome to the patient attendance and suggested her to notice us about any discomfort or new features.

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Case report:

Olmsted Syndrome a Rare Type of Mutilating Palmoplantar Keratoderma: A Case Report

AKM Rejaul Haque[1], ATM Asaduzzaman[2] , Sharmin Begum[3]

1.Associate Professor, Department of Dermatology & Venereology, BSMMU, Dhaka
2.Professor, Department of Dermatology & Venereology, BSMMU, Dhaka
3. Assistant Professor, Department of Dermatology & Venereology, BSMMU, Dhaka

Abstract

Olmsted syndrome is a rare genetic disease characterized by mutilating transgradient palmoplantar keratoderma (PPK) associated with periorificial keratotic plaques. Its starts in the neonatal period or in childhood. The disease has a slow but progressive and extremely disabling course. We present a case with clinically and pathologically confirmed Olmsted syndrome. This case report is an important one for its rarity and disability.

Key words: JAK inhibitors, Alopecia Areata

Introduction

Olmsted syndrome is a rare type of palmoplantar keratoderma that shows marked clinical and genetic heterogencity. Mutilating palmoplantar keratoderma and periorificial keratotic plaque define this disease. The keratotic plaques observed on the skin appear as a result of overexpression of keratin 5 & 14.[1] The finding of Ki -67 immunostaining of suprabasal keratinocyte supports the notion that Olmsted syndrome is a hyperproliferative disorder[2]. Genetic linkage analysis added this disease to the list of skin channelopathies. Gain of function mutation in TRPV[3] gene give rise to AD, AR variants of Olmsted syndrome[3]. Stimulation of TRPV3 in keratinocytes causes keratotic plaques that characterized Olmsted syndrome. Sporadic cases by denovo mutation in TRPV3 thermosensitive cation channel may occur. On contrary XR variant of Olmsted syndrome is a result of specific mutation in MBTPS2 associated with alopecia universalis & nail dystrophy. Very rarely XD cases are also reported[4]. This report documents a further case of this syndrome.

Case report

A 3 year 10 months old boy was presented with painful pruritic palmoplantar keratoderma associated with periorificial and intertriginous keratotic erythematous scaly plaques. There were limitation of movement of fingers of the hands. He was born at term . There was no history of consanguineous marriage. The patient has one elder sister,she was at 9 years old & healthy. According to the statement of parent, the disease was started when the baby was about 10 days old. Initially the patient developed some papules & vesicles in the groin, axilla, and antecubital area. Soon after a few days vesicles become ruptured leaving a moist eroded surface. At this time, after consultation with a local physician, his mother applied some topical medications but the result was unsatisfactory. In course of time, papules became larger and coalesce

Corresponding author
Dr. AKM Rejaul Haque, Associate Professor, Department of Dematology and Venereology, Bangabandhu Sheikh Mujib Meical University, Shahbagh, Dhaka Bangladesh. email: reja8507haq@gmail.com

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to form erythematous keratotic scaly plaques. Gradually keratotic lesions developed around the nose, mouth, eye, ear, front and back of the neck, and perianal areas. He developed thick horny plaques in the palm & soles associated with erythema & scales at the age of 3 months. At the age of 1 year, the mother noticed scaly crusted plaques with non-scarring alopecia in the center of the scalp. The nails became thickened and discoloured at the age of 3 years.

Examination of skin revealed bilateral symmetrical diffuse palmoplantar keratoderma. The lesions were yellowish-brown in color and extended to the dorsum of both hands & feet. There were fixed flexion contracture on the distal phalanges. But, there were no constriction bands or pseudo ainhum around the digits. No evidence of auto-amputation was found. The nails were thickened, rough, dystrophic, discoloured with subungual hyperkeratosis. Both palmar & plantar lesions were hyperhydrotic & malodorous. Well-defined erythematous scaly hyperkeratotic plaques were seen around the mouth, ear, nose, anus. There were also hyperkeratotic areas noted in intertriginous areas like groin, axilla, antecubital area, popliteal fossa, front and back side of neck & flank. Scaly and crusty lesions were found in the scalp associated with central non scarring alopecia. Hairs in other areas were normal.

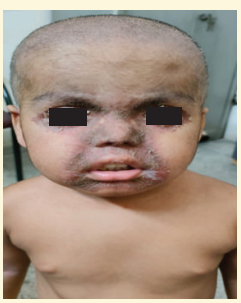

Fig 1. Well-defined erythematous scaly hyperkeratotic plaques were seen around the mouth, ear, nose

Fig 2. Hyperkeratotic fissured plaques on palms

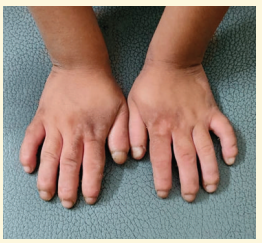

Fig 3. Keratoderma extending over dorsal aspect of hands

Odontological examination revealed leukokeratosis of buccal mucosa. Teeth were normal. Ophthalmological and Otological examination revealed no abnormality. On general examination, the child was undernourished, other findings were non-contributory.

Laboratory findings including Complete Blood Picture, Serum Albumin, Serum Zinc, Serum Alkaline Phosphatase,Total Protein, FT4,TSH,Urine routine Examination were normal. Skin scrapping & Nail shaving for fungal microscopic examination & culture was negative for fungi. Histopathological study showed psoriasiform hyperplasia, thick granular layer, alternating parakeratosis and hyperkeratosis, and acanthosis in the epidermis. Dermis reveals moderate infiltration of chronic inflammatory cells (Mast cells mixed with lymphocytes). No fungus or granuloma was seen.

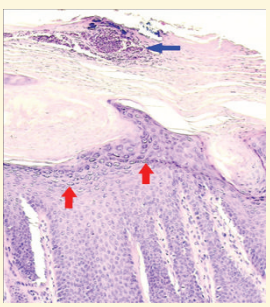

Fig 4. Red arrow-Thick granular layer,
Blue arrow-Polymorphs in thick stratum corneum H&E

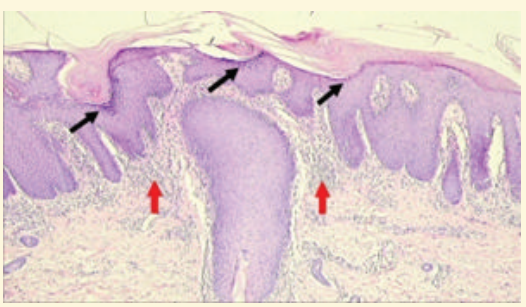

Fig 5. Black arrow- Thick granular layer ,
Red arrow -Chronic inflammatory cells in dermis H&E

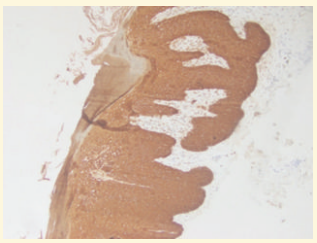

Fig 6. Pancytokeratin AE1/AE3 positive in all layers of epidermis including basal layer

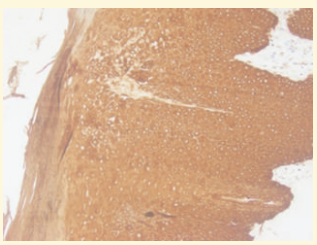

Fig 7. Pancytokeratin AE1/AE3 positive in all layers of epidermis including basal layer

Discussion

In 1927, H.C. Olmsted reported the first case of Olmsted syndrome, a 5-year-old Italian American boy with congenital PPK with periorificial hyperkeratosis. There was no such type of lesion seen previously[5]. To date, there have been 106 cases of Olmsted syndrome reported (up to June 2019)[6].

This is another case of Olmsted syndrome where lesions start in the neonatal period. The disease has a slow but progressive and extremely disabling course.

Major clinical manifestations include palmoplantar keratoderma and periorificial hyperkeratosis.

Clinical manifestations include other than two major ones are.

Hair: Diffuse, universal or patchy alopecia. In our context, there was patchy alopecia of scalp hair.Hypotrichosis, sparse, thinning, curly, wooly, coarse, dry, or easily broken hair also noted.[7]

Nail: Nail abnormalities including dystrophic, lusterless, onychogryphosis, leukonychia, irregular curvatures, subungual hyperkeratosis.[8]

Oral cavity: Leukokeratosis of tongue, palate, buccal mucosa.[9]

Teeth: Edentulous maxilla, premature loss of teeth, absence of premoler teeth, reduced masticatory ability.

Growth (Physical &mental): Delayed physical development ,Short stature, Mental retardation.

Malignancy: SCC, Malignant melanoma ,Adenocarcinoma of lung in one case.

Hearing: High tone loss hearing,Congenital deaf-mutism.

Recurrent infections: Bacterial /candidial infection in keratotic areas.[10]

Eye: Corneal opacity, dystrophy, epithetial dystrophy.[11]

Bone: Osteoporosis, Osteolysis of hand and feet.[12]

Others: Joint laxity, Primary sclerosing cholangitis, Erythromelalgia, Thrombocytosis, Non-Mutilating PPK.[13]

The summary of the clinical manifestations of Olmsted syndrome and similarities in the present case is as follows

1 Early age of onset	+
2 Short Stature	+
3 Delayed social age	+/-
4 Delayed bone age	+/-
5 Alopecia	+
6 Joint laxity	-
7 Auditory disturbance	-
8 Leukokeratosis of tongue	+
9 Hyperkeratosis of	+
Palm	+
Soles	+
Periorificial	+
Intertriginous area	+
10 Contracture of fingers	+
11 Dystrophic nail	+
12 Corneal opacity	-
13 Hyperhidrosis	+
14 Teeth abnormalities	-
15 Malignant potential	Negative until now
16 Infection in keratotie areas	+

Histopathological features of keratoderma of palms & soles are not diagnostic. They consist of psoriasiform hyperplasia, thick granular layer, hyperkeratosis,and parakeratosis. The involved epidermis shows acanthosis and papillomatosis. Dermis shows infiltration of chronic inflammatory cells with an increased number of mast cells.[14] Similar non-specific features have been found in biopsies taken from keratoderma of palm & souls in our case.

Cytokeratins have been identified as abnormal in the skin affected by keratoderma. Keratoderma in Olmsted syndrome remains in an immature, proliferative state.[15] The failure to differentiate to mature keratinocytes is responsible for the excessive deposition of acidic keratin 5 & 14, which is detected

by monoclonal antikeratin Ab AE1.[16] Cytokeratin AE1 immunostaining is noted through the entire thickness of the epidermis (normally this cytokine only stains the basal layer of the epidermis). Cytokeratin 10 is stained in the upper layer of the epidermis. Further immunohistochemical studies with Ki 67 marker demonstrated hyperproliferative activity involving basal & suprabasal keratinocytes in Olmsted syndrome.

The ultrastructural study was not informative, where electron microscopy of palmar keratoderma showed nonspecific defective keratinization, and KHG was decreased or absent.

Olmsted syndrome has to be differentiated from other severe forms of PPK such as Vohwinkel syndrome, Mal de Maleda syndrome, tyrosinemia type II, Pachyonychia congenita, Clouston syndrome, Haim-Munk syndrome in addition to inverse psoriasis, chronic mucocutaneous candidiasis, acrodermatitis enteropathica. Nutritional deficiencies that mimic Olmsted syndrome are essential fatty acid deficiency, multiple carboxylase deficiency, and PEM, but these are not keratrodematous disorders. Acrodermatitis enteropathica was excluded by measurement by zinc level which shows improvement with zinc therapy. Candida organisms are invariably confined to statum corneum and are demonstrable in scrappings, nall shaving & culture. Thus, the full-blown Olmsted syndrome with its typical association of mutilating bilateral PPK and periorificial keratotic plaque is distinctive enough to lead to the correct diagnosis.

Conclusion

Olmsted syndrome is a rare disease. As because histopathological, Immunohistochemical and Electron microscopy findings are not specific and molecular genetics are not readily available and yet to be explored we believe that, the diagnosis of Olmsted syndrome remains essentially clinical and must include the two major ones.

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