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ATYPICAL PRESENTATIONS OF BULLOUS PEMPHIGOID- A CASE SERIES

AUTHORS: 1. Dr Sukanya Sivasubramaniam MBBS., JuniorResident, Dept. of Dermatology, Vinayaka Missions Medical college and hospital, Karaikal, Puducherry

2**. DR. V. Sivasubramanian, M.D., D.V.,** Professor and Head of department, Dept. of Dermatology, Vinayaka Missions Medical college and hospital, Karaikal, Puducherry

ABSTRACT:

Bullous pemphigoid is an acquired autoimmune blistering disorder, typically affects 70 years and older. It is characterized by "subepidermal bullae and deposition of complement and antibodies along the basement membrane zone". The classical presentation includes prodromal stage ,non bullous stage and bullous stage. But bullous pemphigoid is a "great mimicker", it shows polymorphic . The presence of bullae is probably not always necessary in defining BP because it is a polymorphic disease. Urticarial, erythematous, and eczematous patches, plaques that are targetoid, nodular, lichenoid, vesicular, or polycyclic lesions are further potential lesions. Unlike classical BP , in childhood and adolescent ,incidence rate is low, palmoplantar involvement is common, has good prognosis. Localized BP occurs 16% to 29% of all cases of bullous pemphigoid. Furthermore, it is becoming more and more clear that bullous pemphigoid diagnosis criteria should be developed globally, to enable diagnosis even when the clinical presentation of the patient is unusual. It is also essential to recognise atypical clinical signs and symptoms of bullous pemphigoid in order to start the right treatment as soon as feasible. Particularly because such kinds of BP have a lower response to medication and novel therapeutic approaches need to be used
. DIF of perilesional skin showing IgG or C3 deposits or both, and the detection of circulating antibodies against the two main antigens of BP, are the two cornerstones in the diagnosis, particularly when the clinical presentation is doubtful.

BACKGROUND:

Bullous pemphigoid is an acquired autoimmune blistering disorder, typically affects 70 years and older. It is characterized by "subepidermal bullae and deposition of complement and antibodies along the basement membrane zone". The target sites are major & minor bullous pemphigoid antigens(BP antigen

1&2) , which are lying in hemidesmosomes and lamina lucida. The classical presentation includes prodromal stage ,non bullous stage and bullous stage. But bullous pemphigoid is a "great mimicker", it shows polymorphic .Unlike classical BP , in childhood and adolescent ,incidence rate is low, palmoplantar involvement is common, has good prognosis. Localized BP occurs 16% to 29% of all cases of bullous pemphigoid.[1][2]

CASE PRESENTATION: [TABLE 1]

Case report 1

Ms A, aged 21 years ,college student presented with itchy fluid filled bulla all over the body [FIG 1] since 4 months, aggravated since 4 days, with few raw painful erosions over bilateral malar region, chin which heals with post inflammatory hyperpigmentation.No history of arthralgia, oral ulceration, photosensitivity. On examination, Nikolsky sign was negative and bulla spread sign was positive. Tzanck smear of bulla showed inflammatory cells predominantly eosinophils seen. Differential diagnosis are bullous pemphigoid , linear IgA bullous disorder.

Thyroid function tests were normal; anti-thyroid antibodies and Anti-nuclear antibodies (ANA) were negative. Skin biopsy from blister revealed "Subepidermal bulla with fibrin & eosinophils in blister cavity; superficial dermis showing edema ,perivascular eosinophil rich infiltrate".[FIG 2] Direct immunofluorescence assay of perilesional skin showed linear deposits of IgG and C3 along the basement membrane zone and salt spilt DIF showed IgG on epidermal side of spilt skin.[FIG 3] Clinical, histopathological, immunofluorescence findings were suggestive of Bullous pemphigoid in adolescent age group.

Patient was treated with oral prednisolone 0.75 mg/kg, oral tetracycline with nicotinamide and supportive care. She responded well to this regimen and disease was under control. No recurrence in 6 months follow-up period.

Case report 2

Mr B, aged 76 years, presented with itchy fluid filled bulla over both soles for past 10 days, few ruptured spontaneously to form erosions [FIG 4]. No history of physical, chemical or thermal injury. History of similar lesions on same site was present 6 months back and was resolved with topical medications. On examination, Nikolsky sign was negative and bulla spread sign was positive.

Tzanck smear showed no acantholytic cells. Differential diagnosis irritant contact dermatitis, frictional blister, mechanobullous disorder.

Skin biopsy of bulla showed "Subepidermal bulla with fibrin & eosinophils in blister cavity; ,perivascular eosinophil poor infiltrate". Clinical, histopathological findings were suggestive of Localized Bullous pemphigoid limited to soles.

Patient was started on oral antibiotics,topical steroids and supportive care. He responded well to this regimen and disease was under control. No recurrence in 6 months follow-up period.

Case report 3

Mr C, aged 62 years, housewife presented with fluid filled bulla over right nipple areolar region for past 4 days [FIG 5]. History of itching preceeding the onset of lesions. Bulla spread sign was positive. Tzanck smear showed eosinophils. Patient was screened for breast and other internal malignancies and found to be negative. She was diagnosed as Localized bullous pemphigoid in the breast. She received topical steroids,reacted favourably and was monitored for three months with no signs of relapse.

Case report 4

Mr D, aged 73 years farmer presented with spontaneously appearing bullous eruption localized to both thighs, and complaints of intense pruritus for 3 weeks duration. He also had vitiligo for past 7 years and recently was treated with topical PUVASOL [FIG 6].He developed blisters after 4 to 7 days of topical PUVASOL.

Routine haematological and biochemical tests showed normal values. Tzanck test showed few eosinophils and no acantholytic cells seen. Thyroid function tests were normal; anti-thyroid antibodies and Anti-nuclear antibodies (ANA) were negative. Skin biopsy from blister over normal skin revealed "Subepidermal bulla with eosinophils in blister cavity;perivascular eosinophil rich infiltrate" .He was diagnosed with Bullous pemphigoid induced by topical PUVASOL.

He was treated with oral prednisolone with withdrawal of topical PUVASOL. Remission of disease achieved within 2 to 3 weeks and vitiligo became stable.

Case report 5

Mrs E, aged 45 years housewife presented with vesicles over both arms for past 7 days [FIG 7]. She had intense pruritus. She had previous history of classical

bullous pemphigoid . Skin biopsy of vesicle showed " Subepidermal bullae with neutrophil and occasional eosinophil infiltration". Indirect immunofluorescence with salt spilt skin showed linear IgG deposition on epidermal side.She was diagnosed as Vesicular Bullous pemphigoid. Lesions controlled effectively with oral methylprednisolone(12mg/d) and dapson(50 mg/d), which was tapered without relapse.

Case report 6

Mrs F, aged 64 years farmer, presented with itchy fluid filled lesions all over body for for past 7 days. On examination ,few bulla in oral cavity was present [FIG 8]. On examination, Nikolsky sign was negative and bulla spread sign was positive. Tzanck smear of bulla showed inflammatory cells predominantly eosinophils seen. Differential diagnosis are bullous pemphigoid , linear IgA bullous disorder.

Skin biopsy from blister revealed "Subepidermal bulla with fibrin & eosinophils in blister cavity; superficial dermis showing edema ,perivascular eosinophil rich infiltrate". Direct immunofluorescence assay of perilesional skin showed linear deposits of IgG and C3 along the basement membrane zone and salt spilt DIF showed IgG on epidermal side of spilt skin. Clinical, histopathological, immunofluorescence findings were suggestive of Bullous pemphigoid. It is a rare case report because only 10 – 30 % cases of bullous pemphigoid have oral involvement.

Case report 7

Mrs G, aged 56 years , presented with bulla over lichenified papules and normal skin over bilateral legs for past 2 weeks [FIG 9]. Clinical and histopathological findings show findings of both lichen planus and bullous pemphigoid. Hence, she was diagnosed as Lichen Planus Pemphigoides. She was treated with oral prednisolone and topical medications and remission achieved in 10 days.

Case report 8

Mrs H, aged 53 years, presented with vesicles and bulla over both palmoplantar region associated with intense pruritus for past 1 week. Tzanck smear showed eosinophils. Skin biopsy of blister showed "Subepidermal bullae with neutrophil and occasional eosinophil infiltration".She was diagnosed with Dyshidrosiform Bullous pemphigoid and was treated with topical steroids.

Case report 9

Mr I, aged 70 years , presented with hyperkeratotic excoriated and pruritic nodules; blisters on pre-existing nodular lesions or on uninvolved skin over

bilateral legs for past 2 weeks. She showed mixed clinical features of both prurigo nodularis and bullous pemphigoid. Skin biopsy showed findings of prurigo nodularis and bullous pemphigoid. She was diagnosed with Pemphigoid Nodularis and was treated with oral & topical steroids.

Case report 10
Mrs J, aged 77 years, presented with blister, erosions, crusting along with erythroderma all over body for past 12 days. Mucous membrane was not involved. She developed these lesions after intake of ibuprofen for myalgia. Skin biopsy of bulla showed "Subepidermal cleft with prominent eosinophil infiltration in upper dermis". She was diagnosed with Erythrodermic Bullous pemphigoid. She was started with methylprednisolone(1000mg/day) for 3 days followed by oral steroid and supportive therapy.

DISCUSSION:
Eighty percent of subepidermal bullous dermatoses are caused by bullous pemphigoid (BP). It frequently manifests as tense bullous eruptions with generalised pruritus. A group of 4 clinical predictors for BP that were all statistically significant are 1) No atrophic scarring 2) Lack of involvement of the head and neck 3) No mucosal involvement 4) being older than 70 years old. With a positive predictive value of 95%, a sensitivity of 90%, and a specificity of 83%, the diagnosis of BP was made possible by the presence of three of the four important clinical criteria. Bullous pemphigoid can be difficult to diagnose when the clinical appearance is misleading because clinical presentation is unquestionably the first sign the clinician uses to aid in the diagnosis.

IgG autoantibodies are formed against BMZ antigens of 180 kDa and 230 kDa, collagen XVII, COL17 or BPAg2, and BPAg1, respectively, in the etiopathogenesis of BP. The most important antigenic determinant is BP180, while BP230 seems to be more concerned with cytoskeletal activity and dermoepidermal transition signals. Recent research has shown that mast cells and IgE are involved in the growth of BP lesions.

The association of malignancies with BP is likely to be related to the incidence of both diseases in the elderly, although some reports have suggested an increase in the frequency of certain cancers, such as those in the digestive tract, lung, and bladder and lymphoproliferative diseases. [2][5][6]
BP is rarely described in patients with inflammatory or autoimmune diseases. In certain patients, it appears to be triggered by trauma, burns, radiotherapy, or irradiation by ultraviolet rays. BP has also been observed in association with psoriasis and lichen planus. [7]
In some patients, systemic medications may lead to the development of BP, including diuretics (furosemide), antibiotics (amoxicillin, ciprofloxacin),

potassium iodide, and captopril. The mechanism by which drugs induce BP has not been determined. [8]

Of greater interest, BP has been associated with neurological diseases, such as dementia, stroke, multiple sclerosis, epilepsy, and Parkinson disease, but the underlying pathophysiological mechanism is not completely understood. It is possible that the BP antigens BPA1 and BPA2 act as autoreactive antigens in the central nervous system and in tegument.[9- 13]

Classical BP presents in 3 phases: PRODROMAL PHASE - pruritis (mild to intractable) ; NON-BULLOUS PHASE - urticaria like or dermatitic rash , lasting for 1-3 weeks & several months respectively; BULLOUS PHASE - Widespread tense vesicles & bullae (1-3 cm or larger), exudate- clear or haemorrhagic, base- normal or erythematous or urticarial with intense pruritus. The distribution of the lesions is frequently symmetrical, with the chest and limb flexures predominating. Localized BP is rare. Between 10% and 30% of affected people have oral involvement. Rarely anogenital areas, throat, oesophagus, eyes, or nose affected.

Although not pathognomonic, histological findings are strongly indicative of BP. Eosinophilic spongiosis, subepidermal clefts, and/or an eosinophil infiltrate in the upper dermis lining the dermal-epidermal junction. In subepidermal bullae, the absence of acantholysis, and a superficial dermal infiltrate primarily with eosinophils and few neutrophils or lympho-monocytes are characteristics of the histologic changes in established lesions, neutrophil-predominant lesions may also exist.[1][15]

Since DIF is positive in almost all patients, it is the most reliable diagnostic criterion[16].In the basement membrane zone of the perilesional skin, DIF reveals a continuous linear deposition of IgG (70–90% of patients), C3 (90–100% of patients), or both (BMZ). This pattern can also be seen in epidermolysis bullosa acquisita and cicatricial pemphigoid (CP) (EBA). The salt-split skin test can be used to distinguish between BP and various disorders. In patients with bullous pemphigoid, DIF on the patient's autologous skin following treatment with 1 mol/L NaCl displays IgG on the blister roof (epidermal side of split skin), but in CP and EBA, the IgG localises to the blister floor (dermal side of split skin).

A majority of patients (60–80%) can have circulating IgG autoantibodies, which typically bind to the epidermal side of salt-split normal human skin, according to indirect immunofluorescence (IIF) investigations . Circulating autoantibodies can be detected by enzyme-linked immunosorbent assay (ELISA) with sensitivity up to 100%, utilising the NC16A domain and other extracellular regions of BP180 or BP230. ELISA has largely taken the role of immunoblot

and immunoprecipitation procedures today, which are still useful but difficult to use for regular testing.[1]

Clinical features, histopathological findings, presence of antibodies against the BP180 peptide as determined by an enzyme-linked immunosorbent assay, and, more critically, direct immunofluorescence (DIF) and indirect immunofluorescence (IIF) findings by microscopy are used to make the diagnosis of BP. In the majority of cases, immunofluorescence is both necessary and sufficient for classifying subepidermal bullous dermatoses correctly. The exact immunopathological characteristics of the classic form of BP exist in all cases of atypical BP, allowing for the final correct diagnosis.

CONCLUSION :

The presence of bullae is probably not always necessary in defining BP because it is a polymorphic disease. Urticarial, erythematous, and eczematous patches, plaques that are targetoid, nodular, lichenoid, vesicular, or polycyclic lesions are further potential lesions. BP is typically broad but can occasionally stay isolated. We only partially accept with the term "cutaneous pemphigoid" as mucosal involvement, even though it may be present in the majority of cases (10–30%) and in youngsters, is more common. It is the only sign of the disease in 50% of patients.[17]

Furthermore, it is becoming more and more clear that bullous pemphigoid diagnosis criteria should be developed globally, to enable diagnosis even when the clinical presentation of the patient is unusual[14][16][18][19]. It is also essential to recognise atypical clinical signs and symptoms of bullous pemphigoid in order to start the right treatment as soon as feasible. Particularly because such kinds of BP have a lower response to medication and novel therapeutic approaches need to be used

. DIF of perilesional skin showing IgG or C3 deposits or both, and the detection of circulating antibodies against the two main antigens of BP, are the two cornerstones in the diagnosis, particularly when the clinical presentation is doubtful.

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TABLE 1:ATYPICAL PRESENTATIONS OF BULLOUS PEMPHIGOID

Atypical manifestation	Types of lesions	Distribution
Adolescent BP	Typical bulla lesions	Face, extremities,trunk
Localized BP limited to soles	Bulla , erosions	Bilateral soles
Localized BP in the breast	Bulla	Right nipple areolar region
BP induced by topical PUVASOL	Vesicles, bulla, depigmented patches	Bilateral thighs
Vesicular BP	Vesicles	Bilateral arms
BP with oral involvement.	Bulla, erosion	Oral mucosa

Lichen Planus Pemphigoides	Bulla,vesicles,lichenified papules and plaques	Bilateral legs
Dyshidrosiform BP	Vesicles	Bilateral palmoplantar region
Pemphigoid Nodularis	hyperkeratotic excoriated and pruritic nodules; bulla	Bilateral legs
Erythrodermic BP	Bulla, erythroderma	All over body

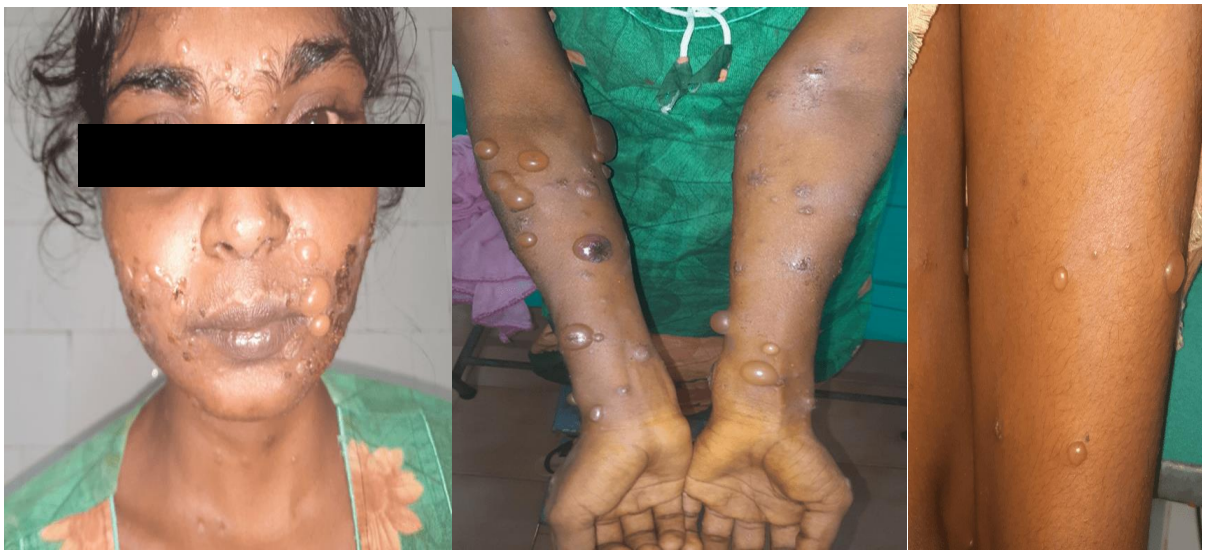

FIG 1: ADOLESCENT BP

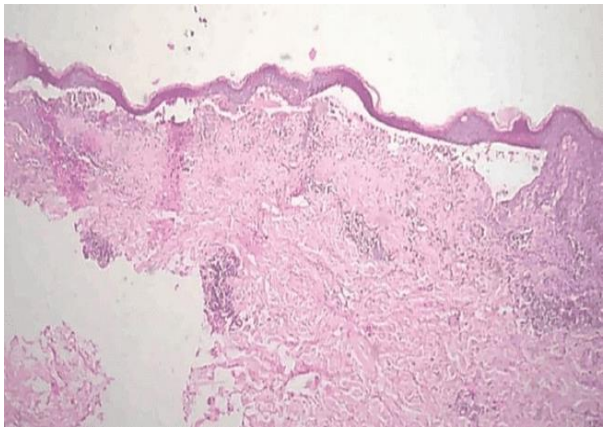

FIG 2: HPE OF ADOLESCENT BP

"Subepidermal bulla with fibrin & eosinophils in blister cavity; superficial dermis showing edema ,perivascular eosinophil rich infiltrate"..

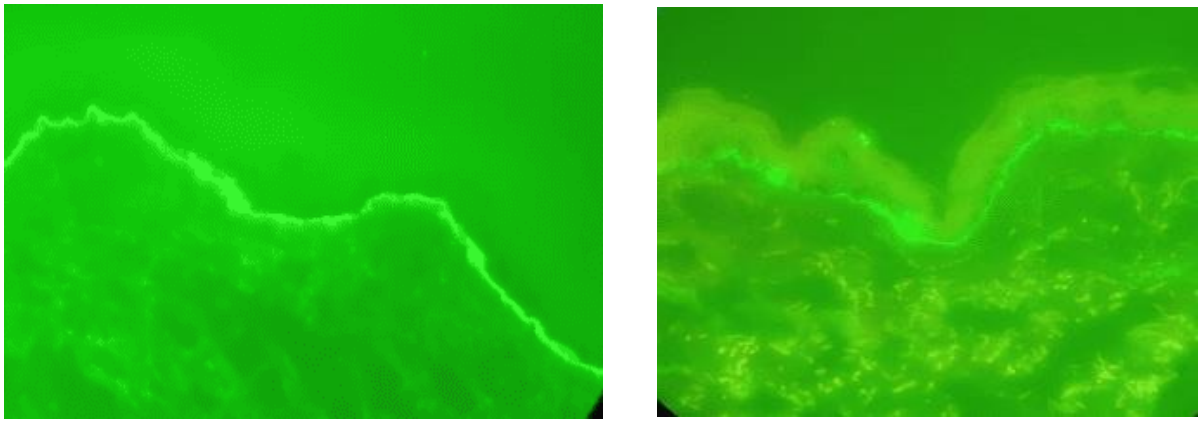

FIG 3: DIF OF ADOLSECNT BP showing "linear deposits of IgG and C3 along the basement membrane zone"

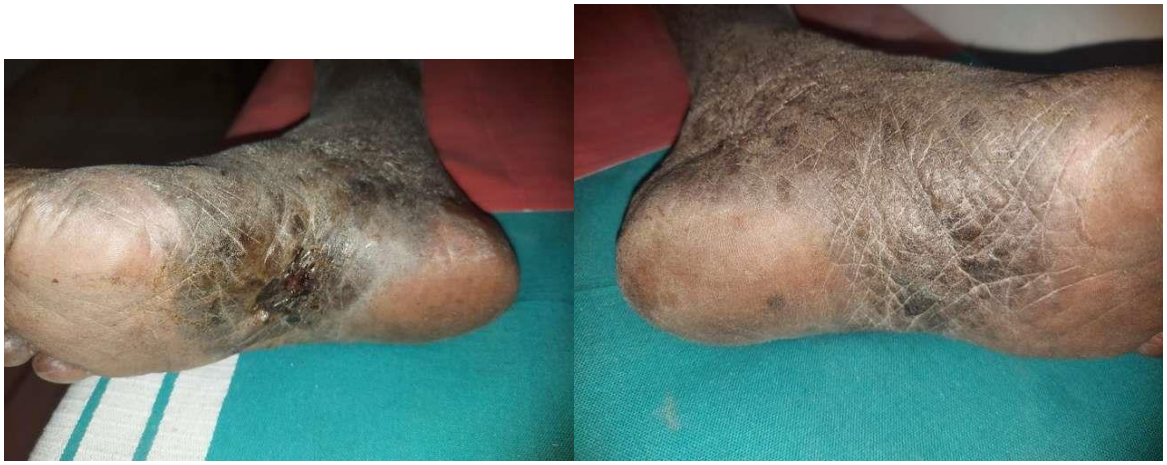

FIG 4: Localized Bullous pemphigoid limited to soles

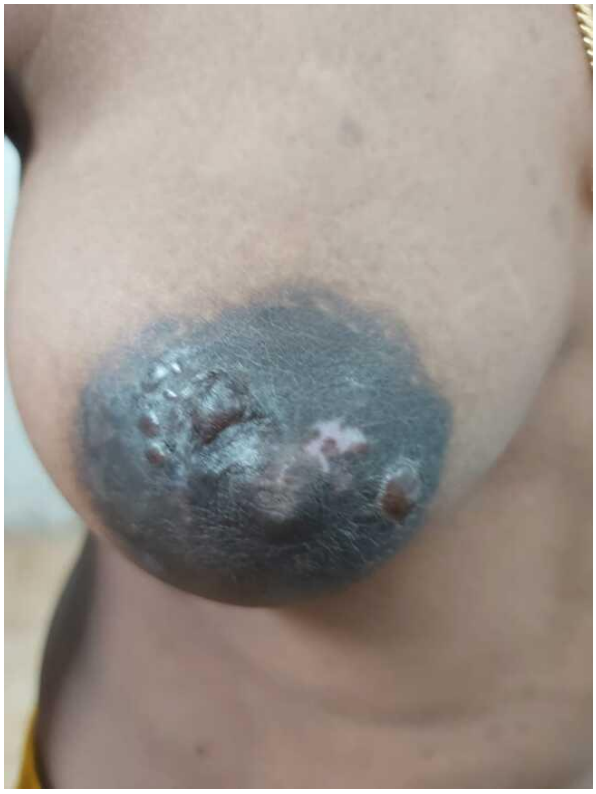

FIG 5: Localized bullous pemphigoid in the breast

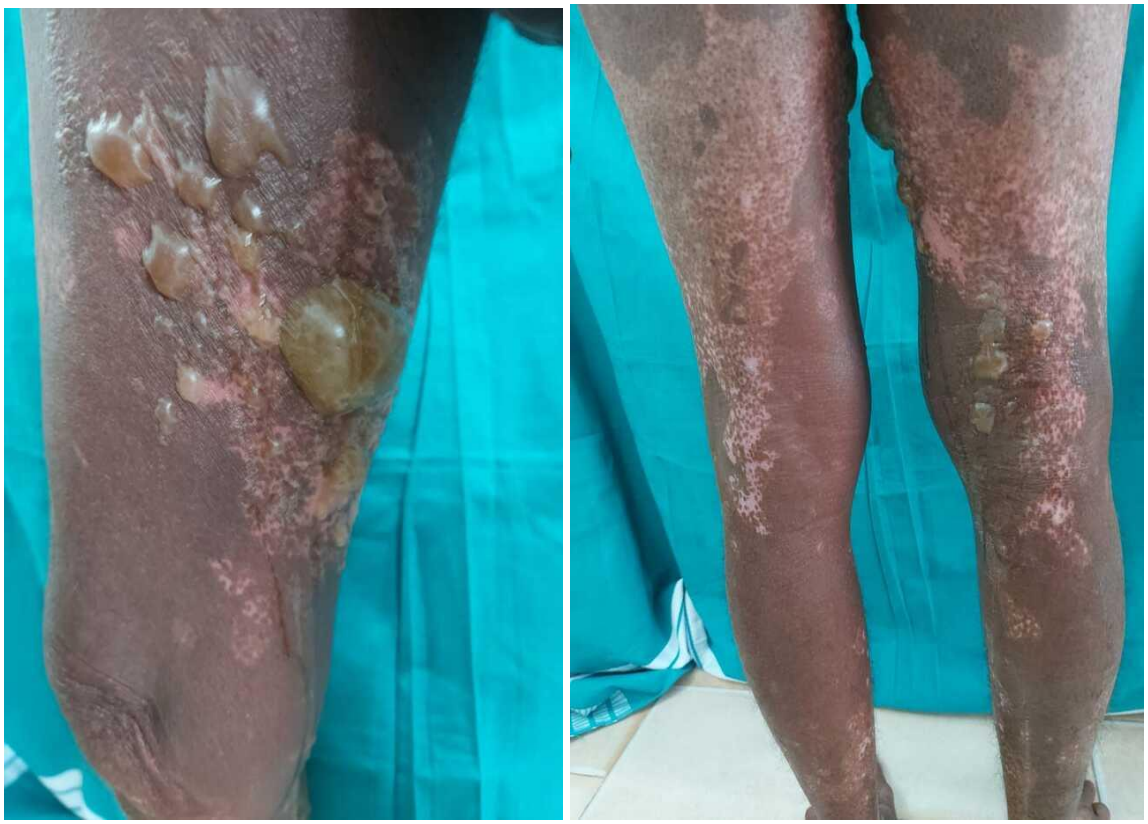

FIG 6: Bullous pemphigoid induced by topical PUVASOL

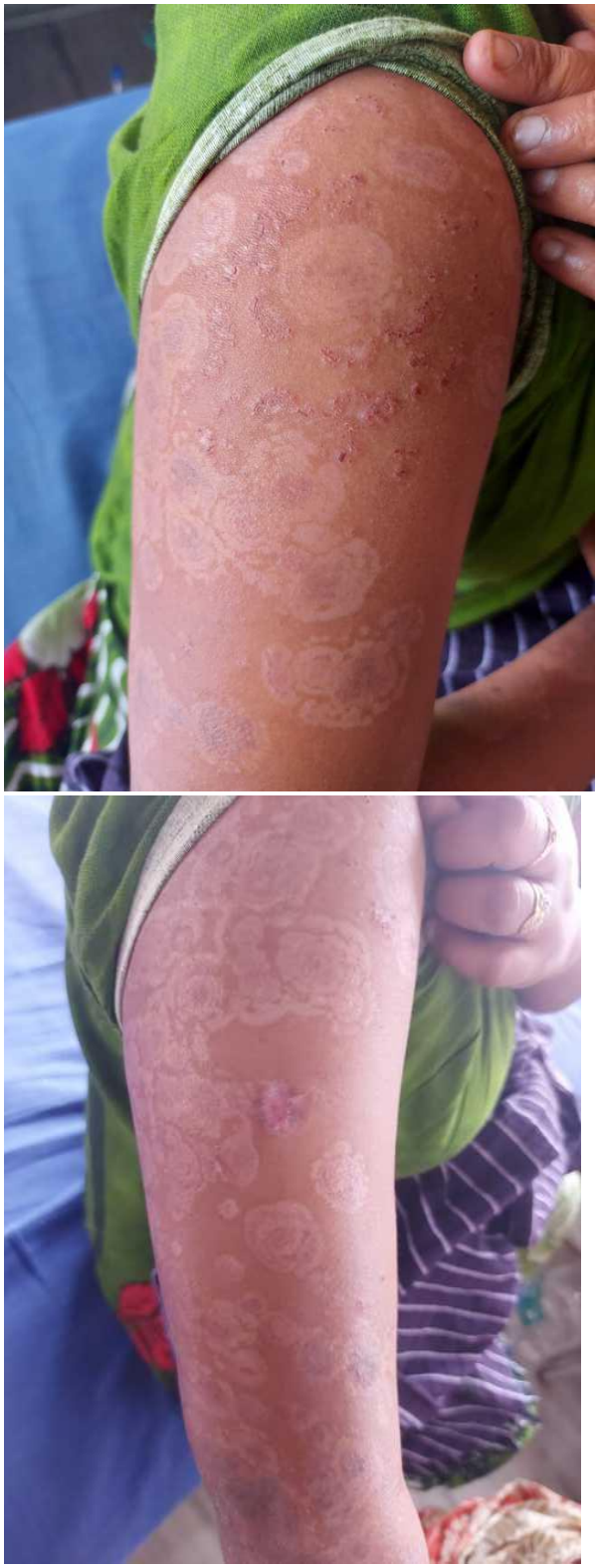

FIG 7: Vesicular Bullous Pemphigoid

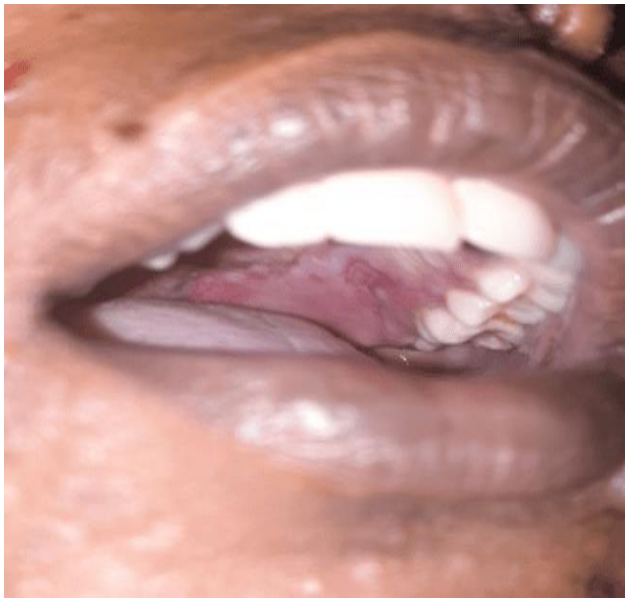

FIG 8: Bullous Pemphigoid involving oral mucosa

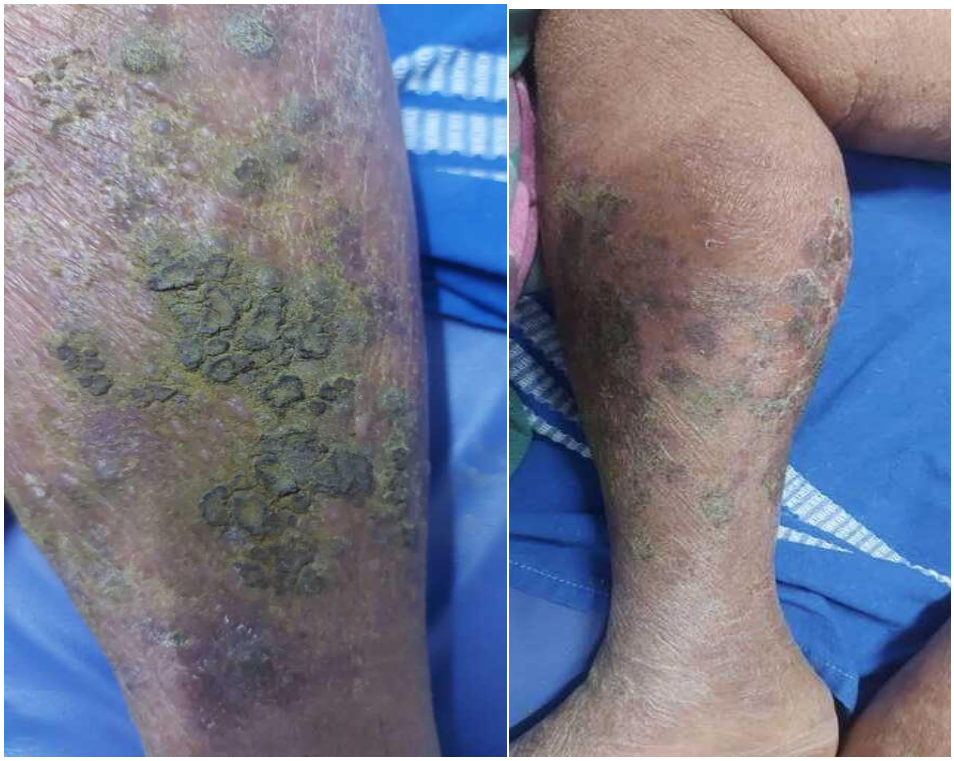

FIG 9: Lichen Planus Pemphigoides