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A CASE SERIES OF RARE VESICULOBULLOUS DERMATOSES FROM EASTERN INDIA

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Abstract
Diagnostic evaluation of vesiculobullous disorders and erosive skin dermatoses relies on amalgamation of clinical, histomorphological and direct immunofluorescence findings. Some classical findings as in pemphigus, bullous pemphigoid, viral dermatoses and others are well-characterized, some atypical dermatoses presenting in pediatric age group and some paraneoplastic vesiculobullous lesions are difficult to diagnose and impose a challenge to the histopathological findings. DIF is an important tool in the diagnosis of autoimmune blistering disease but a negative DIF finding in the challenging cases give an insight to the specific diagnosis. Histopathology remains the gold standard for diagnosing the diseases based on the level of cleft, inflammatory infiltrate and other changes. This case series explores three unique presentations of vesiculobullous and erosive dermatoses: a chronic relapsing disorder initially suspected to be bullous systemic lupus erythematosus (BSLE) but showing features of erythema multiforme; a rare pediatric case of lichen planus pemphigoides (LPP); and a classic presentation of necrolytic migratory erythema (NME) in a patient with a prior history of squamous cell carcinoma of the tongue.

Keywords: Lichen; Bullous; Necrolytic; Erythema; Pemphigoid

Introduction

Vesiculobullous lesions comprise a variety of clinical lesions showing overlap in many clinical features. Vesicle is defined as a fluid filled lesion less than 0.5 cm clinically and bulla is defined as a fluid filled lesion greater than 0.5 cm. The histopathology and immunofluorescence are an adjunct to diagnose a variety of vesiculobullous lesions. There are various causes of blistering dermatosis from autoimmune to drug induced to lichenoid to infective, metabolic and paraneoplastic pathogenesis. Histopathology remains gold standard for the diagnosis based on three important microscopic features based on plane of cleft, predominant inflammatory cell infiltration in the dermis and specific epidermal changes that are the clue to the diagnosis when immunofluorescence findings are non- contributory. The present case series highlights three atypical vesiculobullous presentation of some diseases.

Lichen planus pemphigoides is an extremely rare autoimmune blistering disorder with an estimated general incidence of 1 per 10,00,000 patients annually [1]. While it is rare in adults, it is rarer in children with very few cases reported till date [2].

Another case of a bullous systemic lupus erythematosus in a male. Systemic lupus erythematosus is a common autoimmune disease in females which is 10 times higher than in men [3]. According to a study, disease severity in SLE is higher in Asians as compared to other ethnic groups [4]. Bullous SLE is a subset of SLE with a blistering dermatosis and a rare phenomenon in males with few cited cases [5]. Necrolytic migratory erythema is a rare cutaneous disorder which is paraneoplastic presentation. It typically presents with glucagonoma [6]. Here, the patient with a known history of carcinoma oral cavity presents with blistering dermatoses.

Case 1:

A 9-year-old female presented with clear fluid filled blisters over left foot extending to lower legs, abdomen, chest and back for 30 days. Patient had history of reduced appetite and loss of weight. Blisters ruptured on its own leaving a painful scar with itching and little tendency to heal. Biopsy was sent from lesion over right leg with a clinical diagnosis of chronic bullous disorder of childhood or lichen planus pemphigoides of childhood or pemphigus vulgaris or bullous SLE.

On dermatology examination, multiple plaques were present over abdomen, chest, back and both arms with multiple superficial erosions on bilateral lower limbs largest of which measured 7x5 cm over left leg with foul smelling serosanguinous discharge. Palms, soles and oral mucosa were spared.

Laboratory investigation of complete blood count was with normal limit and Antineutrophilic antibody test with 1:80 initial dilution was negative. Urine routine microscopy showed presence of pseudohyphae of yeast. Tzanck smear showed anucleated cells and occasional neutrophils. No acantholytic cells, multinucleated giant cells and eosinophils were seen.

Histomorphology revealed amalgamation of two pathological processes with lichenoid features like orthokeratosis, hyperkeratosis, foci of wedge shaped hypergranulosis, saw tooth rete ridges, marked vacuolar degeneration of basal layer along with mononuclear infiltration in the dermo epidermal junction. A subepidermal bulla within which plasma protein, lymphocytes, a few polymorphs and eosinophils were seen (**Figure 1**). Direct immunofluorescence testing with IgG, IgM, IgA, C3 and fibrinogen were negative. Correlating histomorphological features and DIF findings, diagnosis of lichen planus pemphigoides of childhood was given.

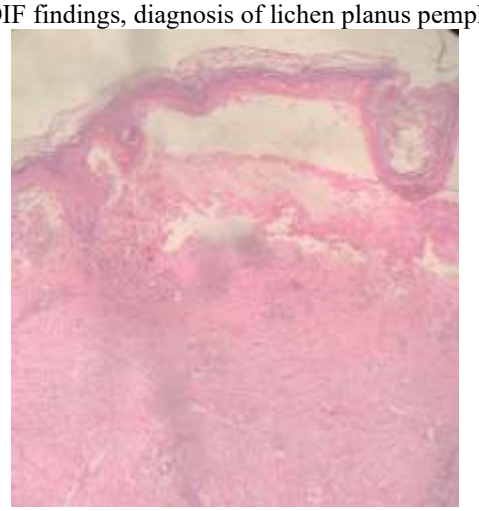


Figure 1: A subepidermal bulla in lichen planus pemphigoides of childhood within which plasma protein, lymphocytes, a few polymorphs and eosinophils were seen.

Patient was treated with steroids (Tablet Omnacortil 30 mg), antibiotics (Tablet clavam 625 mf), tab teczine 5 mg, Olesoft max lotion, Chitomesh SD cream and syrup calcimax. Follow-up was advised after one month.

Case 2: Chronic relapsing Erythema Multiforme mimicking Bullous SLE

A 21 years old male patient with a known history of cerebral palsy presented with a sudden erupting blister over dorsum of his hands and arms with difficulty in swallowing due to oral ulcers since a short duration of 4 days. Lesions healed with post-inflammatory scarring and some ruptured spontaneously. Patient had a 7-year history of similar episodic history of blistering responding well to antibiotics, especially linezolid, with flare-ups occurring upon discontinuation.

Clinical examination revealed well-defined hemorrhagic vesicle, bullae and crusted plaques over the extensor aspects of arms, back and oral erosions. A 4mm punch biopsy was taken from interdigital space of the right hand. On histopathology, crucial changes in epidermis and dermis were present. Epidermis exhibited irregular acanthosis, spongiosis and hyperkeratosis. One of the important findings were focal dyskeratosis and necrotic keratinocytes within the epidermis. Mild inflammation along the dermoepidermal junction with extension into perivascular and periappendageal region was seen in superficial dermis. DIF was uniformly negative for IgG, IgM, IgA, C3 and fibrinogen. Correlating histopathology and DIF findings, a descriptive diagnosis was given (**Figure 2**).

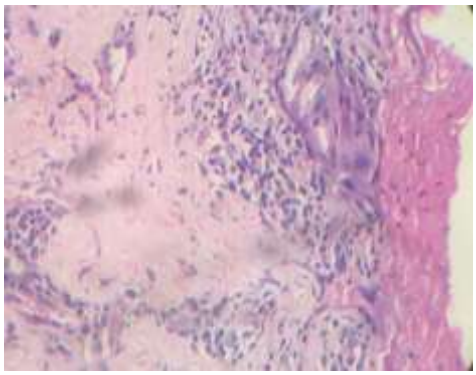


Figure 2: Mild inflammation along the dermoepidermal junction with extension into perivascular and periappendageal region was seen in superficial dermis.

Patient was treated with Clonate-F ointment local application, mucopain gel for oral cavity, T bact ointment for local application.

Case 3: Necrolytic Migratory Erythema (NME) in a patient with prior tongue malignancy.

A 68 years old male patient presented with a generalized blistering and erosive eruption. Notable past history includes squamous cell carcinoma of tongue two years ago. Wide local excision and modified radical neck dissection was done.

The dermatological presentation at present raised suspicion for Bazex syndrome, paraneoplastic pemphigus and necrolytic migratory erythema. A 4 mm punch biopsy from the chest revealed diagnostic epidermal alterations.

Histopathology examination revealed epidermis showing hyperkeratosis and parakeratosis. A defining feature was the presence of marked thinning of the epidermis combined with abrupt necrosis of the upper layers of the stratum spinosum. Keratinocyte degeneration was prominent, hydropic swelling, cytoplasmic eosinophilia and nuclear pyknosis was seen. Superficial epidermis showed an intraepidermal pustule formation containing neutrophils reflecting neutrophilic chemotaxis (**Figure 3**). Underlying dermis demonstrated a moderate perivascular lymphohistiocytic infiltrate with focal melanin incontinence. DIF was negative for all major immunoreactants.

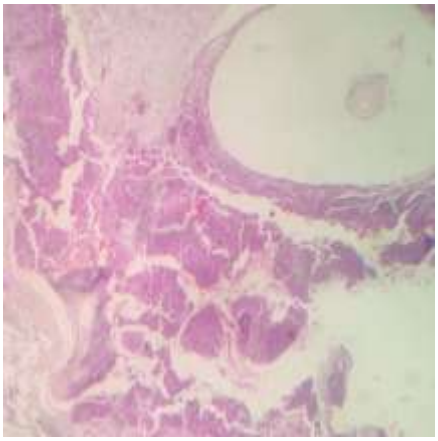


Figure 3: Superficial epidermis showed an intraepidermal pustule formation containing neutrophils reflecting neutrophilic chemotaxis.

Patient was treated with Tablet Augmentin 625 mg thrice daily, tablet TRD-MD 50 mg thrice daily, tablet Tazloc 40 mg, betadiene oral mouth wash and rest all other symptomatic treatment tablets were continued.

Discussion

All the three cases relied on histology diagnosis and DIF negative was not a diagnostic dead end but a support to the diagnosis. The first case Lichen planus pemphigoides (LPP) is by definition an autoimmune subepidermal blistering disease in which IgG and/or C3 is deposited along the basement membrane zone. DIF is a supportive investigation to distinguish between LPP and bullous lichen planus, in which the subepidermal cleft is a consequence of severe basal vacuolar damage and immunoreactants at the basement membrane zone are absent [2,7,8]. The histopathology beautifully captures this duality: the lichenoid interface dermatitis causing basal cell damage, juxtaposed against a tense subepidermal split rich in eosinophils. It represents a true overlap condition where lichen planus lesions develop concurrent with or are followed by subepidermal blistering. The pathogenesis is believed to involve epitope spreading, wherein the basal layer destruction in lichen planus exposes hidden hemidesmosomal antigens (such as BP180), triggering a secondary autoantibody response. While DIF is typically positive for linear IgG and C3 in LPP, the negative DIF in this instance makes the striking histomorphological evidence, the saw-tooth rete ridges and wedge-shaped hypergranulosis combined with subepidermal separation absolutely critical for diagnosis. Morphology described like wedge shaped hypergranulosis, saw tooth appearance of rete ridges, marked basal vacuolar degeneration and band like mononuclear infiltrate and a subepidermal bulla is that of lichen planus with blister formation. With all DIF parameters negative, diagnosis bullous disease of childhood is a defensive diagnosis and not lichen planus pemphigoides. Chronic bullous disease of childhood requires linear IgA at the basement membrane zone and its absence excludes it. LPP and chronic bullous disorder of childhood are managed as autoimmune blistering disease with prolonged immunosuppression or dapsone. Bullous lichen planus is a self-limiting lichenoid dermatosis in which the therapeutic emphasis and prognostic counselling differ substantially. Although DIF can show false negative result from lower leg site, negative panel in this scenario is suggestive of but not conclusive. Correct management would have been repeat DIF from perilesional trunk site after steroid withdrawl. This case is reported for its extreme rarity in a 9-year-old child and its severe, widespread clinical presentation.

Biopsy for first case was taken during an active flare, 15 days after all treatment had stopped, from upper limb site. Bullous SLE, Epidermolysis bullosa acquisita, childhood bullous pemphigoid were the differentials. All three are DIF positive disorders. Reaction pattern with an interface dermatitis with dyskeratotic cells and necrotic keratinocytes, with the infiltrate extending both perivascularly and periappendageally is shown. Erythema multiforme is characteristically a superificial perivascular process whereas fixed drug eruption typically shows a heavier superficial and deep infiltrate with peiradnexal extension, eosinophils, neutrophils and dermal melanophages [10,11]. A seven-year history of recurrent corps resolving with post-inflammatory hyperpigmentation and no scarring, mucosal erosions at multiple sites, repeated temporal association with fixed

drug eruption is the more suitable diagnosis. Levocetrizine is one of the agents this patient received, is itself a reported cause of generalized bullous fixed drug eruption [12]. Advice for repeat representative biopsy is appropriate as the submitted tissue had no bulla.

Biopsy from second case with clinical impression and differential diagnosis included bullous SLE, childhood bullous pemphigoid and epidermolysis bullosa acquisita. However, histopathology showed features favoring Erythema Multiforme. Presence of necrotic keratinocytes with superficial perivascular lymphocytic infiltrate and vacuolar interface changes seen in biopsy were suggestive. Negative DIF rule out autoimmune blistering disease including bullous SLE. Erythema multiforme is usually acute and self-limiting. This case is presented for uniqueness in relapsing after 7 years. The response to antibiotic treatment suggests an underlying recurrent infectious trigger or a chronic bullous fixed drug eruption, making the pathological identification of keratinocyte necrosis the linchpin of diagnosis.

Case three demonstrates a negative DIF excluding one paraneoplastic possibility while supporting another. Histopathology of upper epidermal pallor, necrosis and subcorneal pustulation without extensive full thickness necrosis is seen in toxic epidermal necrolysis. Upper necrolytic epidermis transition to lower normal epidermis was the hallmark feature. NME is the cutaneous manifestation of alpha-cell pancreatic tumor glucagonoma. This case is unique as patient has a known case of oral squamous cell carcinoma. NME occurring as a manifestation apart from glucagonoma is known as pseudoglucagonoma syndrome due to internal malignancy, hepatic dysfunction and profound nutritional deficiencies (e.g. zinc or amino acid deficiency). Surgery and reliance on subsequent tube feeding with a previous history of squamous cell carcinoma and head and neck surgery may represent a paraneoplastic phenomenon or a severe nutritional deficiency. Histological confirmation is vital in this case.

Morphology described as parakeratosis, abrupt necrosis of the upper stratum spinosum with an underlying viable epidermis, hydropic degeneration of keratinocyte , pyknosis, a neutrophilic intraepidermal pustule and superficial perivascular inflammation with melanin incontinence is the classical picture of necrolytic migratory erythema, in which necrolysis of the upper spinosum layer, epidermal pallor, confluent parakeratosis and subcorneal or intraepidermal pustulation are the recognized features [13]. Negativity for IgG and C3 argues strongly against bullous pemphigoid and absence of bulla is itself consistent. In paraneoplastic pemphigus, DIF is only 27-41% sensitive, indirect immunofluorescence would be needed before that entity can be dismissed [14]. It is the hallmark of glucagonoma syndrome, but in the absence of glucagon secreting tumor, pseudoglucagonoma syndrome in chronic pancreatitis, hepatic cirrhosis, malabsorption, celiac disease, hypoproteinemia and deficiencies of zinc and essential fatty acids and small cell lung carcinoma is considered [15]. Patient had oral squamous cell carcinoma with prolonged enteral feeding, a substrate for hypoproteinemia and micronutrient deficiency that underlie the necrolytic reaction pattern. Serum glucagon, zinc, albumin, amino acid profile, liver function and imaging to exclude pancreatic primary and recurrence of primary tumor. To our knowledge, NME following treated oral cavity squamous cell carcinoma is not well described.

Limitations: This being a small, retrospective study without antigen specific serology, salt-split skin, IIF or immunoblot, without repeat biopsy of case 1 and 2. Clinical photographs or long-term follow-up in the above cases are lacking. Case 2 DIF was performed when the patient had started on corticosteroid therapy and from a suboptimal site. Diagnosis in these cases are not immunological proven rather clinicopathological reconstrucions.

Conclusion

Vesiculobullous lesions with DIF negative findings are a result not the absence of one. Biopsy site, specimen adequacy and treatment status reclassified all three of these patients away from autoimmune blistering diseases and towards drug-induced interface reaction, a lichenoid bullous dermatosis and a metabolic paraneoplastic necrolytic erythema respectively.

Declaration

The authors disclose that there is no conflict of interest.

Acknowledgement

None.

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