Case Report

Clinical management of bullous pemphigoid—The importance of cytology in diagnosis

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Abstract

Bullous pemphigoid (BP) is a common immune-mediated blistering disorder with predominant skin involvement and occasionally oral manifestations. Vesiculobullous lesions of the oral mucosa present with similar clinical features, and hence arriving at a clinical diagnosis is aided by a valuable chairside investigation, exfoliative cytology. Cytology done in the present case ruled out pemphigus because of the absence of Tzanck cells in the smear. Biopsy and direct immunofluorescence further confirmed the diagnosis of BP. Treatment initiated with systemic steroids and immunomodulators, along with oral topical application of triamcinolone acetonide resulted in complete remission in 2 months. This case report highlights the role of cytology in the diagnosis of vesiculobullous lesions and management protocol for BP patients presenting with simultaneous skin and oral lesions.

Keywords: Bullous pemphigoid, cytology, immunomodulators, steroids

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INTRODUCTION

Bullous pemphigoid (BP) is one of the most frequently encountered autoimmune blistering disorders which is benign, self-limiting with periods of remission.[1] BP is usually common in elderly patients, especially with multiple comorbidities and has no sex predilection.[2] Oral mucosal involvement occurs in 10 to 45% of cases which consists of vesicles, erosions and ulcerations.[2] Cytology offers a reliable diagnostic tool as it can provide insight into diagnosis for the surgeon/physician, instead of invasive procedures like biopsy.[3] Over the past decade, cytology has been aiding in the screening of oral potentially malignant disorders for the presence of dysplasia and early diagnosis of oral squamous cell carcinoma (OSCC).[4] However, exfoliative cytology does play a pivotal role as a potent investigative tool in the diagnosis of blistering genodermatoses and viral lesions.[5] Definitive diagnosis of vesiculobullous lesions, especially subepithelial dermatoses is usually made by histopathological examination coupled with immunofluorescence. The current case report highlights a case of BP with mucocutaneous lesions, where cytology proved as a valuable adjunct to clinical diagnosis, thereby instilling prompt treatment with systemic steroids and immunomodulators leading to better treatment outcomes and long-term disease-free follow-up.

CASE HISTORY

A 70-year-old male patient reported the chief complaint of multiple oral ulcers for the past 3 months associated

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with a burning sensation. History revealed the occurrence of oral blisters which spontaneously ruptured and healed within a week; however, there was a simultaneous eruption of new blisters and oral ulcers. The patient noted pruritic erythematous patches, followed by the formation of blisters on the forehead and trunk concomitantly during the occurrence of oral lesions. Extra oral examination revealed, multiple erosions and depigmentation on his forehead and trunk. Intraoral examination revealed generalized erythematous gingiva with erosions, focal areas of desquamation and tissue tags with negative Nikolsky's sign [Figure 1a-c]. A provisional diagnosis of Pemphigus Vulgaris (PV) was considered and differential diagnosis included BP, benign mucous membrane pemphigoid, and dermatitis herpetiformis. After obtaining informed consent, exfoliative cytology was performed which revealed the absence of Tzanck cells with normal squamous epithelial cells and mixed inflammatory cells [Figure 2a]. Skin and oral biopsy was performed perilesional within 1 cm over the ruptured bullae and was evaluated for both histopathology and DIF. Histopathological evaluation revealed subepithelial bullous lesions with a dense and diffuse infiltrate of plasma cells admixed with lymphocytes and a few mast cells in the sub-epithelium [Figure 2b]. Direct immunofluorescence (DIF) revealed evidence of linear deposition of IgG and C3 along the dermo-epidermal junction (basement membrane zone) [Figure 2c]. Considering the clinical, histopathological and immunofluorescence features, final diagnosis was given as BP. The patient was prescribed Tab. Prednisolone 20 mg in two divided doses for 1 week, Tab. Methotrexate 10mg per week in two divided doses on a given day, Tab. Folvite 5 mg, once a day, for one week, except for the day when the patient was prescribed Methotrexate. The patient showed good symptomatic improvement and subsequently was advised to apply topical triamcinolone acetonide 0.1% for oral lesions, and clobetasol 0.05% ointment for the skin lesions twice daily. After 2 weeks, there was a 50% reduction in the severity. Methotrexate was withdrawn, and the patient was advised Tab. mycophenolate mofetil 500mg, once a day for 2 weeks and Tab. Fluconazole 150 mg, twice a week, along with tapering of Tab. Prednisolone to 5 mg once daily for 2 weeks. At one-month follow-up, 90% resolution of the lesions was observed. Two months later the patient reported with the appearance of erosions localized to buccal gingiva of 36,37, which showed healing within 1 week, after topical application of 0.1% triamcinolone acetonide [Figure 1d and e]. Currently, the patient is under follow-up and disease-free for 2 years.

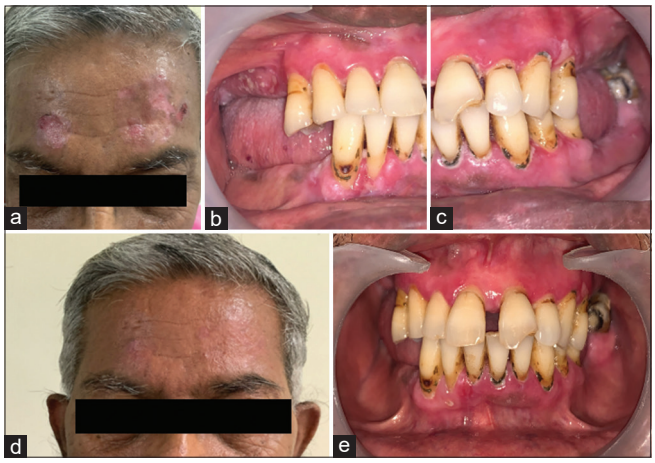

Figure 1: (a) Multiple ruptured bullae with erosion and depigmentation on his forehead, (b and c) Sloughing of epithelium with tissue tags, loss of stippling and generalized desquamation of the gingiva; (d) Complete resolution of lesion noted in the forehead, (e) Complete resolution of the oral lesions

DISCUSSION

Autoimmune bullous disorders (ABDs) encompass two major groups of diseases, namely 'pemphigus diseases' (PDs) and 'ABDs of the pemphigoid type' based on the level at which blistering occurs. BP is classified under subepithelial blistering, which is caused by the production of autoantibodies against proteins namely BP180/collagen XVII and BP230/dystonin in the basement membrane.[6] Clinically, BP is associated with a non-bullous prodromal phase characterized by pruritic, erythematous patches followed by tense bullae on an erythematous base not associated with scarring on healing. The present case also had a severe pruritic prodromal episode followed by bullous eruption, with simultaneous presentation of oral and skin lesions. Cytology, especially plays a vital role in the diagnosis of clinically similarly appearing vesiculobullous lesions and has been recommended as the first line of investigation and as an adjunct to histopathological examination.[7] Cytology was negative for Tzanck cells in the current case, thus helping in ruling out pemphigus vulgaris (PV). A study done to assess the diagnostic value (sensitivity and specificity) of Tzanck smear in vesiculobullous and viral lesions, demonstrated BP to show 90.9% negative results compared to 28% in PV, thereby revealing its valuable potential in differentiating PV from BP. Hence, Tzanck smear, though a relatively older investigative tool, remains a simple, rapid, inexpensive and patient-friendly test for genodermatoses.[5]

Histopathology of skin and oral biopsy revealed subepithelial bulla with dense inflammatory infiltrate. DIF has been considered to be the most reliable and sensitive test for BP which revealed IgG and/or C3 along the dermo-epidermal junction in our case, which is by

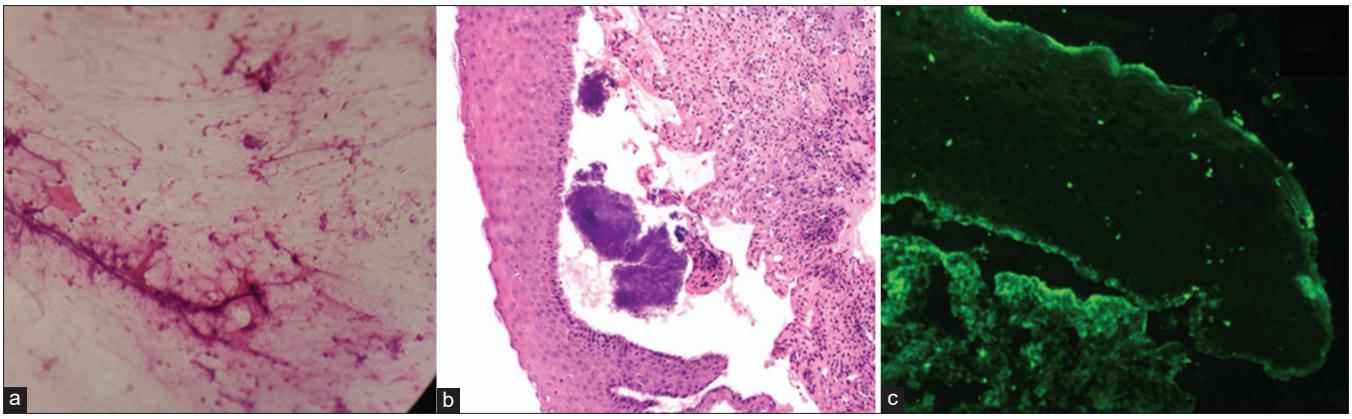

Figure 2: (a) Exfoliative cytology revealed the absence of Tzanck cells with normal squamous epithelial cells and mixed inflammatory cells; (b) Subepithelial cleft with a dense and diffuse infiltrate of plasma cells admixed with lymphocytes and few mast cells in the entire sub-epithelium (H&E stain, ×100); (c) Immunofluorescence revealed linear deposition of IgG and C3 along the basement membrane

the literature.[7] DIF has served to be extremely useful and has remained the gold standard for the definitive diagnosis of vesiculobullous lesions, especially since most of these lesions have similar clinical presentations. Thus, DIF is a valuable aid along with exfoliative cytology and histopathological examination to make the definitive diagnosis and for devising the management protocol.[8] The clinical examination, exfoliative cytology findings, histopathological examination and DIF helped us to arrive at a conclusive diagnosis.

Despite steroids being the mainstay of treatment, steroid-sparing drugs such as methotrexate, azathioprine, cyclophosphamide, cyclosporine and mycophenolate mofetil have also been employed in the treatment of BP. Methotrexate and mycophenolate mofetil used in the current case have shown better efficacy due to their anti-inflammatory effects and good safety profile, respectively.[9,10] The present case showed a good clinical response to a combination of steroids and immunomodulators. Systemic steroids form the mainstay treatment for PV, combined with immunosuppressants, such as azathioprine, mycophenolate mofetil and the anti-CD20 monoclonal antibody rituximab, to reduce the steroid dosage and their associated side effects. However, steroid-sparing agents along with topical corticosteroids hold the first line of therapy, especially for localized and milder forms of BP.[7] In the present case, with the aid of exfoliative cytology results, treatment with methotrexate (immunosuppressant) was initiated during the early clinical course, along with short-term systemic steroids, and topical corticosteroids, thereby resulting in complete resolution of lesions with disease-free follow-up for 2 years. The current case report is unique of its kind as it takes the clinical importance of employing a simple chair-side investigative procedure of exfoliative cytology during routine clinical practice for formulating a management strategy, thereby reducing the morbidity associated with BP and improving treatment outcomes. The patient not only became symptomatically better within 2 weeks but also demonstrated excellent treatment response to immunosuppressants within one month after initiation of treatment.

CONCLUSION

The current case highlights the valuable role of a chairside investigation, exfoliative cytology in the diagnosis of vesiculobullous lesions. DIF poses to be the gold standard in differentiating the subepithelial dermatoses. Prompt treatment with short-term systemic steroids, topical steroids, and immunomodulators resulted in complete remission with disease-free status at two years follow-up.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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