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CASE REPORT

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Lymphocytic infiltration as a marker of disease severity in patients with bullous pemphigoid—A case series

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Key Clinical Message

Patients of Bullous Pemphigoid with predominant lymphocytic inflammatory infiltrate on histopathology have a severe form of the disease requiring high doses of steroids along with an adjuvant immunosuppressant. Thus, the histopathological evaluation would predict the severity of Bullous Pemphigoid, especially in countries where ELISA and immunofluorescence are not readily available.

KEYWORDS

bullous pemphigoid, cellular infiltration, histopathology, lymphocyte, severity

1 | INTRODUCTION

Bullous Pemphigoid is the most common subepidermal autoimmune blistering disorder characterized by the presence of IgG autoantibodies directed against BP 180 and/or BP230.[1] The reported cumulative incidence of BP is 8.2 per million people with an incidence rate of 34.2 per million person-years.[2]

A conglomeration of genetic factors, environmental influences (UV radiation and trauma), and drugs have been recognized as risk factors for Bullous Pemphigoid. Activation of Toll-like Receptor (TLR), an imbalance between autoreactive T helper (Th) and T regulatory (Treg) cells, and stimulation of B cells produce autoantibody.[3] Autoantibodies result in complement activation, mast cell degranulation, recruitment of inflammatory cells, liberation of proteolytic enzymes, and interfere with the adhesion molecules.[1] Additionally, the Th17 pathway maintains the inflammatory cascade.[3]

Histopathological studies of skin lesions typically demonstrate a subepidermal blister with a variable degree of inflammatory cell infiltrate comprised of characteristically eosinophils, neutrophils, and lymphocytes.[4] Immunohistochemistry shows predominant CD68+ and CD3+ cells in subepidermal bullous lesions.[5] This is a case series including three patients of Bullous Pemphigoid that shows lymphocytic infiltrate as a marker of disease severity in BP.

2 | CASES PRESENTATION

Three of our patients with Bullous Pemphigoid (59 years male, 68 years female, and 75 years female) presented to our dermatology clinic with generalized itchy tensed vesicles and bulla over the erythematous skin, erosions, and crustings as shown in Figure 1A–F. One of the patients had oral mucosal involvement which is depicted in Figure 1G. The duration of the disease ranged from 6 months to 1 year. Nikolsky's sign and Asboe Hansen's sign were negative. Bullous Pemphigoid Disease Area Index (BPDAI) Severity scores were 48, 36, and 60 respectively. All three patients were treated at multiple centers with topical/oral medications however, the documents were unavailable. Patients

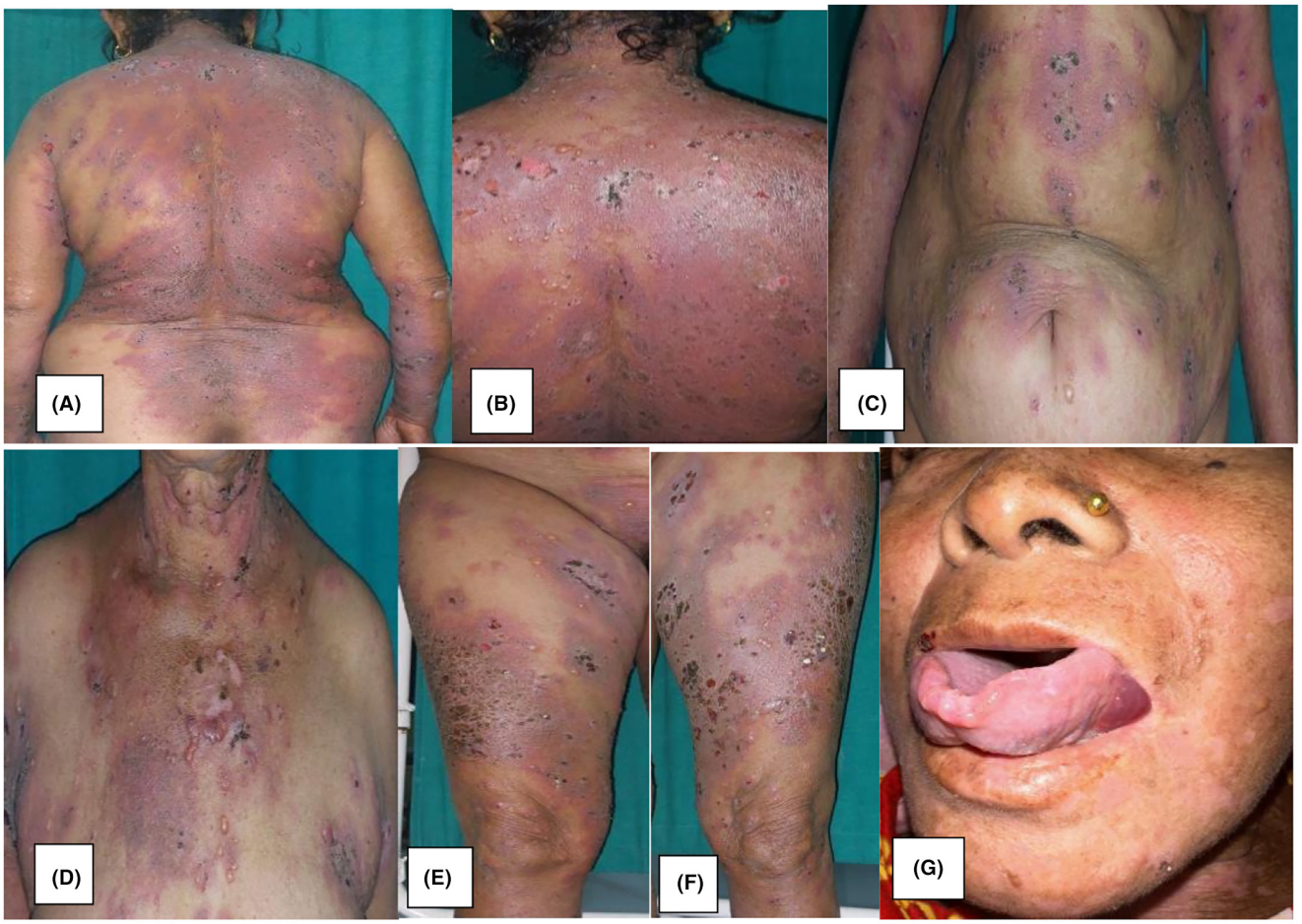

FIGURE 1 Bullous pemphigoid. (A–F) A 75-year-old female patient with multiple itchy tensed vesicles and bulla on the erythematous skin with areas of erosion and crustings on the anterior and posterior trunk, and thighs bilateral. (G) Solitary hemorrhagic bullae on the lateral aspect of the tongue in the same patient.

showed only mild improvement with the treatment and similar morphology lesions continued to appear.

3 | METHODS

Tzanck smear was performed which revealed mixed inflammatory cells that is, neutrophils, eosinophils and lymphocytes without acantholytic cells (Figure 2). At our center, excisional skin biopsy of the tensed vesicle from all three patients revealed subepidermal clefting and predominant lymphocytic infiltrate in papillary dermis on histopathology as shown in Figure 3A,B. Direct immunofluorescence, Anti BP180, and Anti BP230 antibodies were not performed due to lack of availability at our center.

All three patients were initially treated with the recommended dose of oral prednisolone 0.5 mg/kg/day.[6]

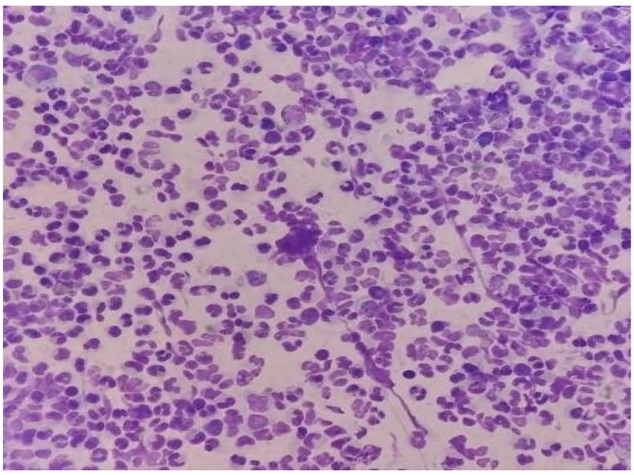

FIGURE 2 Tzanck smear showed mixed inflammatory cells (neutrophils, eosinophils, and lymphocytes) without any acantholytic cells (10× view).

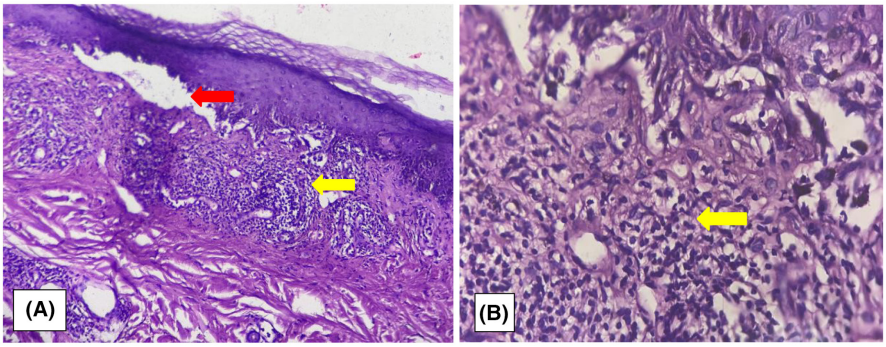

FIGURE 3 (A, B) Skin biopsy of the same patient shows subepidermal cleft (red arrow) with predominant lymphocytic infiltration in the papillary dermis (yellow arrow) on Hematoxylin and Eosin staining (10× view) and (40× view) respectively.

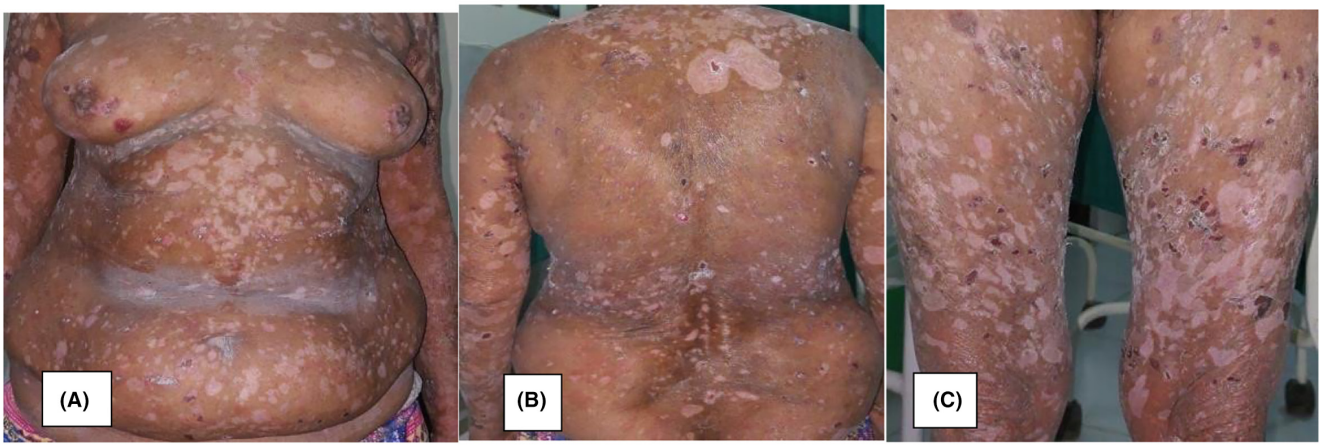

FIGURE 4 (A–C) Healing of vesicles and bulla with hypopigmented scaly macules and patches in the same patient in follow-up.

However, lesions did not improve in 3 weeks rather new lesions appeared. The dose of prednisolone was increased to 1 mg/kg/day however, there was no improvement. As recommended, Methotrexate (7.5 mg/week) was added.[6] The initial low dose of steroid was increased to a high dose based on the body weight followed by adjuvant methotrexate uniformly in all three cases.

4 | RESULTS

After 3 weeks of high-dose prednisolone and adjuvant methotrexate, old lesions started healing and new lesions did not appear. Prednisolone was tapered and methotrexate was discontinued upon clinical improvement. In all these patients, the disease is under control with only low-dose prednisolone in subsequent follow-ups (Figure 4). Thus, the predominant lymphocytic infiltrate in Bullous Pemphigoid predicts the severity of the disease, and this group of patients requires high-dose steroids along with adjuvant immunosuppressants for optimum management.

5 | DISCUSSION

Bullous Pemphigoid is an antibody-mediated subepidermal blistering disorder common in the elderly. The nature of inflammatory infiltrate in Bullous Pemphigoid plays an important role in identifying the phenotype of the disease and this was observed in retrospective analysis in our patients. All three patients had predominant lymphocytic infiltration in the papillary dermis and required high doses of oral prednisolone (1 mg/kg/day) and adjuvant immunosuppressants for optimum disease control.

Although the role of autoreactive B and T lymphocytes in the pathogenesis of Bullous Pemphigoid is clearly known, there is a paucity of literature showing the relation between predominant lymphocytic infiltrate and the phenotype of BP.

The severe phenotype of Bullous Pemphigoid observed in our study might be explained by the activation of autoreactive B lymphocytes which rely on autoreactive T-helper (Th) cells. An epitope on a Bullous Pemphigoid Antigen 180/230 is recognized by the surface immunoglobulin on a B cell and the antigen is internalized and degraded. Peptides derived from the antigen are returned to

the B-cell surface bound to MHC class II molecules. These complexes are recognized by helper T cells, which activate the B cells to produce antibodies against the antigen via secretion of IL-4 and CD40 (present on T cell) and CD40L (present on B cell) interaction.[7]

The finding was supported by Staner S et al. who reported significantly higher mean levels of erosion/blister (p 0.046), urticaria/erythema (p 0.007) and pruritus (p 0.040) BPDAI in 71 Bullous Pemphigoid patients with predominant lymphocytic infiltration.[8]

6 | LIMITATIONS

This is a single center-based retrospective observation that draws the attention of practicing dermatologists for the management of patients with Bullous Pemphigoid however, a multicentric study is required to draw a definite inference. The study lacked evaluation of antibody titers since immunofluorescence and enzyme-linked immunosorbent assay (ELISA) are not available at our center.

AUTHOR CONTRIBUTIONS

Mahesh Mathur: Conceptualization; formal analysis; supervision; writing – original draft; writing – review and editing. **Neha Thakur:** Conceptualization; investigation; methodology; supervision. **Gautam Das:** Conceptualization; investigation; methodology; visualization. **Supriya Paudel:** Data curation; supervision; visualization. **Sunil Jaiswal:** Conceptualization; data curation; formal analysis; writing – original draft; writing – review and editing.

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None.

CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in repository name, doi, reference number.

ETHICS STATEMENT

The patient in this manuscript has given written informed consent for the use of their case details (including photographs) for publication.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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