VOLUME - 12, ISSUE - 06, JUNE - 2023 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Medical Science

COINCIDENCE OF TRIGGERING FACTORS WITH VARIOUS PRESENTATIONS OF BULLOUS PEMPHIGOID.

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ABSTRACT Bullous pemphigoid (BP) is the most frequent autoimmune subepidermal blistering disease provoked by autoantibodies directed against two hemidesmosomal proteins: BP180 and BP230. Its pathogenesis depends on the interaction between predisposing factors, such as human leukocyte antigen (HLA) genes, comorbidities, aging, and trigger factors. Several trigger factors, such as drugs, thermal or electrical burns, surgical procedures, trauma, ultraviolet irradiation, radiotherapy, chemical preparations, transplants, and infections may induce or exacerbate BP disease. Identification of predisposing and trigger factors can increase the understanding of BP pathogenesis. Furthermore, an accurate anamnesis focused on the recognition of a possible trigger factor can improve prognosis by promptly removing it.

KEYWORDS : autoimmune bullous disease; bullous pemphigoid; etiopathogenesis; predisposing factors; trigger factors.

Bullous pemphigoid is the most common autoimmune dermatosis presenting with crops of tense pruritic blisters, often in older adults. Mucosal involvement may occur and a number of clinical subtypes exist. Autoantibodies are directed to components of the basement membrane, particularly the BP antigens BP180 and BP230. Male patients are more likely to have antibodies to BP 180, where as antibodies to B P 230 occur with equal frequency

The pathogenesis of BP is dependent upon the interaction between genetic predisposition, physiological skin alterations due to aging and specific triggers. Several triggers have already been reported to induce this disease and include drugs, thermal or electrical burns, surgical procedures, trauma, UV radiation, radiotherapy, chemicals and infections.

Data from the current literature support the hypothesis that alterations of the skin barrier associated with aging increase individual susceptibility to these aforementioned triggers. Consequently, this has been reported to lead to the attack of autoantibodies, demonstrating the predilection of BP for the elderly population.

Bullous pemphigoid (BP) rarely affects young people, with an incidence of less than 0.5 cases per million population below 50 years of age . A somewhat lower mean age of 64 years at disease onset was reported from China . It is an autoimmune vesiculobullous disorder that occurs due to antibodies against trans membrane protein BP 180 and hemidesmosomal protein BP 230, along with complement activation, mainly C3, and chemotaxis of neutrophils and eosinophils.

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MATERIALS AND METHOD

Between august 2017 to november 2022 100 patients were got admitted in melmaruvathur adhiparasakthi institute of medical science with the diagnosis of bullous pemphigoid.

Skin biopsy done and we collected data regarding age, sex , h/o drug intaken, exposure to radiation, h/o trauma, h/o burns, h/o phototherapy and herpes virus infection.

In these 100 cases 60 cases are males and 40 female cases.

No of patients	Male patients	Female patients
20-40	10	8
40-50	20	12
50-70	30	20

NO OF PATIENTS	H/O DRUG THERAPY	H/O PSORIASIS, DIABETES	·NO OF RADIATION
NO OF MALES -60	30	20	5
NO OF FEMALES-40	20	10	5

Triggering factors

Bullous pemphigoid usually appears randomly with no clear factors contributing to the onset of disease. Some cases may be triggered by:

- **Medications.** Prescription drugs that may cause bullous pemphigoid include etanercept (Enbrel), sulfasalazine (Azulfidine), furosemide (Lasix) captopril, losartan and pencillin.
- **Light and radiation.** Ultraviolet light therapy to treat certain skin conditions may trigger bullous pemphigoid, as can radiation therapy to treat cancer.
- **Medical conditions.** Disorders that may trigger bullous pemphigoid include psoriasis, lichen planus, diabetes, rheumatoid arthritis, ulcerative colitis and multiple sclerosis.

No of cases	nasal, oral, and genital mucosal erosions with widespread vesiculobullous eruptions following the intake of losartan	intense itching, followed by extensive urticarial plaques and papulonodular lesions after the ingestion of captopril,
Males- 40-50 age group	5	2
Females50-60 age group	5	4

No of patients	No of males	No of females
Complaints of blisters and itching	30	14
Complaints of drug eruptions	20	16
Complaints of verrucous vegetating lesions in groins	10	10

Bullous pemphigoid (BUL-us PEM-fih-goid) is a rare skin condition that causes large, fluid-filled blisters. They develop on areas of skin that often flex — such as the lower abdomen, upper thighs or armpits. Bullous pemphigoid is most common in older adults. Rarely it is presented in younger patients.

In bullous pemphigoid, the immune system produces antibodies to the fibers that connect the outer layer of skin (epidermis) and the next layer of skin (dermis). These antibodies trigger inflammation that produces the blisters and itching of bullous pemphigoid.

Various presentations	No of cases in males	No of cases in females
Bullous pemphigoid	16	10
Epidermolysis bullosa acquista	10	12
Bullous lupus erythematosus	20	10
Toxic epidermo necrolysis	14	8

NO OF PATIENTS	H/O DRUG THERAPY	H/O PSORIASIS,DIABETES	NO OF RADIATION
NO OF MALES - 60	30	20	5
NO OF FEMALES-40	20	10	5

No of cases with associated malignancy	Melanoma	Small cell ca of lung
Males 50-60 age group	8	10
Females 50-60 age group	10	7

No of cases	Associated withThermal burns
Males age group 20 -40	5
Females age group 20-40	7

Histopathological examination ;

Bullous pemphigoid is a unilocular subepidermal blister, eosinophils being the predominant cell in the dermis and blister cavity. Lumen of the blister

Contains eosinophils – there are relatively few eosinophils in the dermis. There are numerous eosinophils in the upper dermis at the edge of the blister. In addition to eosinophils , neutrophils and lymphocytes are also seen. Eosinophilic spongiosis also present in some cases.

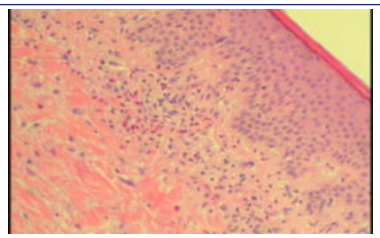
Vesicular pemphigoid; There is a small sub epidermal blister. Pemphigoid vegetans; sub epidermal blister with prominent acanthosis of epidermis.

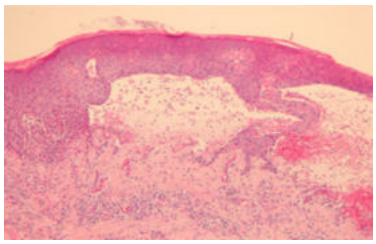
Pemphigoid nodularis; acanthosis , overlying hyperkeratosis and mild papillomatosis.

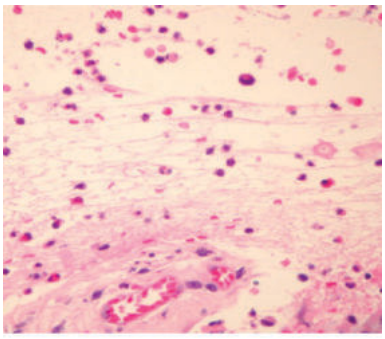
Prodromal lesions of bullous pemphigoid- show edema of the papillary dermis and superficial and mid- dermal perivascular infiltrate with numerous eosinophils, occasional lymphocytes and rare neutrophils. Eosinophils line up along the basement membrane is present in some cases.

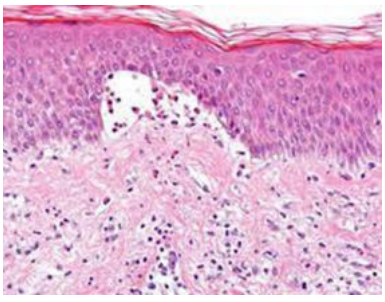
Bullous pemphigoid lesions

Focal eosinophilic spongiosis, numerous dermal eosinophils and eosinophils lined up along the basement membrane. Elevated IgE and peripheral blood eosinophilia.







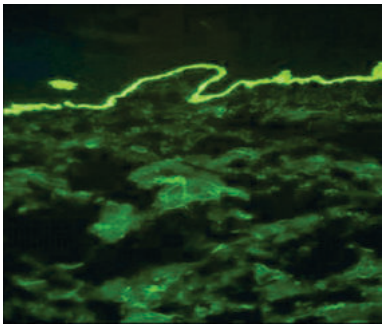


Laboratory

- Enzyme linked immunosorbent assay (ELISA):
- NC16A domain of BPAG2: sensitivity = 84%, specificity = 98%
- BPAG1: sensitivity = 48%, specificity = 94%.

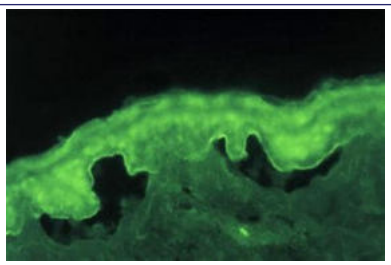
Direct immunofluorescence

Direct immunofluorescence shows a linear , homogenous deposition of IgG and or C3 along the Basement membrane zone of the skin around the lesion.



Indirect immunofluorescence in bullous pemphigoid.

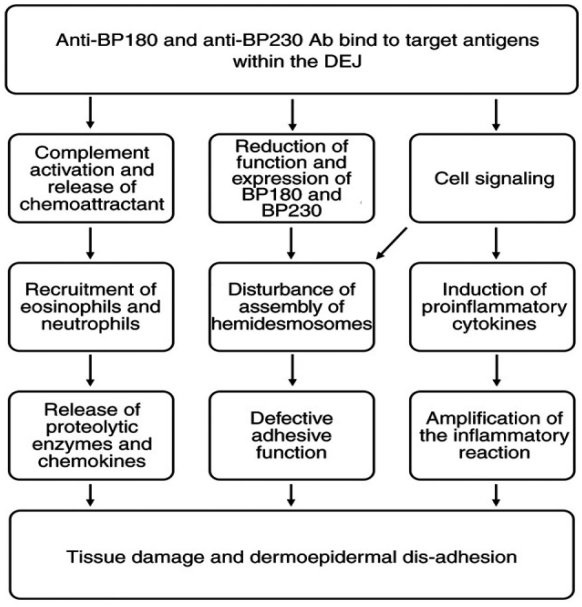
IDIF studies document the presence of IgG circulating autoantibodies in the patient's serum that target the skin basement membrane component. Seventy percent of patients with bullous pemphigoid have circulating autoantibodies that bind to split skin.



DISCUSSION;

One of most common skin infections in world wide is bullous pemphigoid. Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disorder, representing 80% of subepidermal immunobullous cases. Bullous pemphigoid most commonly affects elderly patients between the ages of 60 to 80 years.

Bullous pemphigoid (BP) is the most common subepidermal autoimmune vesiculobullous disorder. It mainly affects the elderly, with a mean age at presentation of 69 to 83 years and an incidence of 7 to 43 per million population in European studies. Bullous pemphigoid (BP) is rarely encountered in young people, with an incidence rate of less than 0.5 cases per million population in individuals less than 50 years.



Bullous pemphigoid in young individuals is an infrequent entity with less than 0.5 per million population . Genetic and environmental factors can contribute to triggering bullous pemphigoid. This subepidermal blistering disorder can also be induced by certain drugs such as antihypertensives (captopril, enalapril, losartan, and beta blockers), furosemide, spironolactone, and antibiotics like ampicillin, cephalexin, and ciprofloxacin. Patients with drug-induced BP have a younger age of onset ..

Bullous pemphigoid occurs when your immune system attacks a thin layer of tissue below your outer layer of skin. The reason for this abnormal immune response is unknown, although it sometimes can be triggered by taking certain medications.

Few cases of bullous pemphigoid in young individuals have been documented in the literature. In a case series of 100 patients, 2 young patients presented with intense itching, followed by extensive urticarial plaques and papulonodular lesions after the ingestion of captopril, 5 young patients developed nasal, oral, and genital mucosal erosions with widespread vesiculobullous eruptions following the intake of losartan. Most of the cases had elevated serum IgE with peripheral eosinophilia and were treated successfully with a combination of dapsone and systemic corticosteroids, along with discontinuation of the drug.

The pathomechanism includes autoantibodies against BP180 and BP230 antigens, which are components of the dermo-epidermal junction .Anti-BP180 autoantibodies of various immunoglobulin isotypes and IgG subclasses are present in bullous pemphigoid sera, with IgG being predominant, followed by IgE. Serum levels of anti-BP180-NC16A IgG and IgE correlate well with disease activity in bullous pemphigoid.

BP lesions mostly present over flexors and abdomen as tense blisters on the urticarial base, with negative Nikolsky's sign. Most patients experience prodromal symptoms of pruritus and urticarial lesions weeks or months before the eruption of blisters ;. Mucous membranes also affected. However, there are certain clinical variants: Classic, localized, pemphigoid vegetans, dyshidrosiform, pigmented, nodular, papular, erythrodermic, toxic epidermal necrolysis-like, etc. . The classic form of BP is characterized by large, tense blisters on normal skin or on an erythematous base with lesions most commonly on flexural surfaces, the lower abdomen, and thighs, although they may occur anywhere, as in our patients. . Localized BP is an unusual variant with less than 10 cases reported in young people so far , with the most common site being lower limbs or over surgical/burn/trauma scar, radiation therapy, and phototherapy site . The bullae are typically filled with serous fluid but may be hemorrhagic with a positive bulla spread sign and negative Nikolsky's sign. EBA is another subepidermal immunobullous disorder, which predominantly presents in elderly males as tense bullae over the sites of friction and trauma. The investigations confirming the diagnosis of BP in our patients included biopsy from intact blister for histopathological examination and perilesional biopsy for direct immunofluorescence studies.

Histopathology findings in BP are subepidermal blisters, and inflammatory infiltrates consisting of neutrophils, eosinophils, and lymphocytes/macrophages. Direct immunofluorescence shows linear IgG and C3 deposition in the basement membrane, often with elevated IgE and peripheral eosinophilia . The salt split technique also differentiates BP, epidermolysis bullosa acquisita, and bullous lupus erythematosus. It is performed by incubating punch biopsy specimens in 5 mL NaCl (1 mol/L) at 4°C for 24 hours, followed by separating the epidermis from the dermis using fine forceps . Bullous pemphigoid (BP) demonstrates roof pattern (autoantibody deposition on the epidermal side of the cleavage as major target antigens located in the upper portion of lamina lucida), while floor pattern is observed in epidermolysis bullosa acquisita.

The primary treatment modalities are topical steroids for mild disease and oral steroids along with other anti-inflammatory drugs (doxycycline, dapsone, and nicotinamide) for moderate to severe disease, in addition to supportive treatment like antihistaminics and antibiotics. Immunosuppressants, like azathioprine, mycophenolate mofetil, and methotrexate, and biologics, like rituximab and omalizumab, are usually reserved for severe or recalcitrant disease.

Bullous pemphigoid often goes away on its own in a few months, but may take as many as five years to resolve. Treatment usually helps heal the blisters and ease any itching. It may include corticosteroid medications, such as prednisone, and other drugs that suppress the immune system. Bullous pemphigoid can be life-threatening, especially for older people who are already in poor health

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