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Facts and Treatment of Bullous Pemphigoid: A Review

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Abstract

Bullous pemphigoid (a type of pemphigoid) is an autoimmune pruritic skin disease that typically occurs in people aged over 60, that may involve the formation of blisters (bullae) in the space between the epidermal and dermal skin layers. It is classified as a type II hypersensitivity reaction, which involves formation of anti-hemidesmosome antibodies, causing a loss of keratinocytes to basement membrane adhesion. Pemphigus and bullous pemphigoid are autoantibody-mediated blistering skin diseases. In pemphigus, keratinocytes in epidermis and mucous membranes lose cell-cell adhesion, and in pemphigoid, the basal keratinocytes lose adhesion to the basement membrane. Pemphigus lesions are mediated directly by the autoantibodies, whereas the autoantibodies in pemphigoid fix complement and mediate inflammation. In both diseases, the autoantigens have been cloned and characterized; pemphigus antigens are desmogleins (cell adhesion molecules in desmosomes), and pemphigoid antigens are found in hemidesmosomes (which mediate adhesion to the basement membrane). This knowledge has enabled diagnostic testing for these diseases by enzyme-linked immunosorbent assays and dissection of various pathophysiological mechanisms, including direct inhibition of cell adhesion, antibody-induced internalization of antigen, and cell signaling. Understanding these mechanisms of disease has led to rational targeted therapeutic strategies.

Keywords: *Autoimmune, Autoantibody, Blistering of Skin.*

1. Introduction

Bullous pemphigoid is a rare skin condition that mainly affects older people. It usually starts with an itchy, raised rash. As the condition develops, large blisters can form on the skin. It may last a few years and sometimes causes serious problems, but treatment can help manage the condition in most cases.

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Bullous pemphigoid (a type of pemphigoid) is an autoimmune pruritic skin disease which typically occurs in people aged over 60, that may involve the formation of blisters (bullae) in the space between the epidermal and dermal skin layers. It is classified as a type II hypersensitivity reaction, which involves formation of anti-hemidesmosome antibodies, causing a loss of keratinocytes to basement membrane adhesion.

Bullous pemphigoid is a rare and chronic autoimmune disorder characterised by large sub-epidermal blisters called bullae, that predominantly involves the skin and less commonly the mucous membranes.[1] It is the most common type of the pemphigoid group, representing 80% of sub-epidermal immunobullous cases. It is more commonly known as *cutaneous pemphigoid*.

Etiology

In most cases of bullous pemphigoid, no clear precipitating factors are identified.[2] Potential precipitating events that have been reported include exposure to ultraviolet light and radiation therapy. Onset of pemphigoid has also been associated with certain drugs, including furosemide, nonsteroidal anti-inflammatory agents, DPP-4 inhibitors, captopril, penicillamine, and antibiotics.[3]

Pathophysiology

The pathogenetic mechanism of blister formation is known, the trigger to the formation of the antibodies to the hemidesmosome antigens is still unknown. Most of the bullous pemphigoid cases are due to autoantibodies (mostly IgG) directed at antigens (BP180 and BP230) arranged at the dermal-epidermal junction. However, most commonly, drug can be one of the causes of bullous pemphigoid, such as thiazide diuretics, antibiotics (e.g., penicillins, vancomycin), nonsteroidal anti-inflammatory drugs (NSAIDs) and angiotensin-converting enzyme (ACE) inhibitors (e.g., captopril) and possibly angiotensin receptor blockers (ARBs, e.g., valsartan).

The implicated drugs include penicillin derivatives, sulfasalazine, ibuprofen, phenacetin, enalapril, captopril, lisinopril, gabapentin, novoscabin, levobunolol ophthalmic solution, tetracoq, influenza, tetanus, and other vaccinations, a homeopathy regimen, nifedipine, 5-aminosalicylic acid, doxazosin, serratiopeptidase, losartan, cephalexin, bumetanide, fluoxetine, chloroquine, antipsychotic drugs, enoxaparin, ciprofloxacin, furosemide (frusemide), neuroleptics, penicillamine, gliptin plus metformin, intravenous iodine, etanercept, levofloxacin, and topical fluorouracil. Influenza vaccination does not appear to be an important trigger for bullous pemphigoid. Trauma, burns, lymphedema, phototherapy, and radiation have been implicated in a very small number of cases.[4]

The bullae are formed by an immune reaction, initiated by the formation of IgG autoantibodies targeting dystonin, also called bullous pemphigoid antigen 1, and or type XVII collagen, also called bullous pemphigoid antigen 2,[5] which is a component of hemidesmosomes. A different form of dystonin is associated with neuropathy. Following antibody targeting, a cascade of immunomodulators results in a variable surge of immune cells, including neutrophils, lymphocytes and eosinophils coming to the affected area. Unclear events subsequently result in a separation along the dermoepidermal junction and eventually stretch bullae.

The pathophysiology of bullous pemphigoid consists of two major components, which are immunologic and inflammatory. In the immunologic component, autoantibodies act against the hemidesmosomal bullous pemphigoid antigens BP230 (BPAg1) and BP 180 (BPAg2 or type XVII collagen) which are located at the lamina lucida of the basement membrane zone. These antigens play an important role in the adhesion complexes that promote epithelial-stromal adhesion. The predominant subclass of antibodies that acts against the antigens is IgG4. IgG1 and IgG2 antibodies are less frequently detected compared to IgG4 antibodies, while IgG3 antibodies are usually absent. When the autoantibodies bind specifically to the target antigens, the complement system and mast cells are activated, thereby representing the inflammatory component. Inflammatory cells such as neutrophils and eosinophils are then attracted to the affected area. They are postulated to release proteolytic enzymes which degrade the hemidesmosomal proteins, resulting in blister formation.[6]

Other potential contributory factors including genetic factors, environmental exposures to infections and drugs as well as the phenomenon of epitope spreading are also known to cause bullous pemphigoid.

Signs and symptoms

Clinically, the earliest lesions may appear as a hives-like red raised rash, but could also appear dermatitic, targetoid, lichenoid, nodular, or even without a rash (essential pruritus). Tense bullae eventually erupt, most commonly at the inner thighs and upper arms, but the trunk and extremities are frequently both involved. Any part of the skin surface can be involved. Oral lesions are present in a minority of cases. The disease may be acute, but can last from months to years with periods of exacerbation and remission.

Several other skin diseases may have similar symptoms. However, milia are more common with epidermolysis bullosa acquisita, because of the deeper antigenic targets. A more ring-like configuration with a central depression or centrally collapsed bullae may indicate linear IgA disease. Nikolsky's sign is negative, unlike pemphigus vulgaris, where it is positive.

Diagnosis

Diagnosis consist of at least 2 positive results out of 3 criteria (2-out-of-3 rule): (1) pruritus and/or predominant cutaneous blisters, (2) linear IgG and/or C3c deposits (in an n- serrated pattern) by direct immunofluorescence microscopy (DIF) on a skin biopsy specimen, and (3) positive epidermal side staining by indirect immunofluorescence microscopy on human salt-split skin (IIF SSS) on a serum sample.[7] Routine H&E staining or ELISA tests do not add value to initial diagnosis.

Clinical assessment

For patients greater than 70 years old.

- Blistering skin disease characterized by the presence of tense blisters and erosions that occur without another identifiable cause and rarely on mucosa.
- Unexplained pruritus, pruritic eczematous eruptions, or urticarial plaques

Histopathology

Lesional tissue, preferably of an intact vesicle or the edge of an intact bulla is obtained using punch biopsy for Haemotoxylin and Eosin (H&E) staining.

Typical histopathologic findings include:

- Sub-epidermal split with numerous eosinophils within the cleft.
- A superficial dermal inflammatory cell infiltrate of variable intensity with lymphocytes, eosinophils, and neutrophils.
- Eosinophlic spongiosis (Specifically in early lesion or may be seen in clinically erythematous skin surrounding the blister)

Direct immunofluorescence

Direct immunofluorescence (DIF) studies involve directly detecting tissue bound antibodies. Biopsy specimens for DIF should be taken from perilesional skin instead of lesional skin for H&E histopathologic evaluation. DIF specimens should be placed in Michel's solution or Zeuss transport media instead of formalin.

DIF of bullous pemphigoid will show the presence of fine, continuous and linear deposits of IgG and/or C3 along the epidermal basement membrane. Other classes of immunoglobulins such as IgM and IgA are present in approximately 20% of cases and usually are less intense. In some cases, with the deposits of IgA, patient may have oral lesion. At early stages of the disease, only C3 may be present.[8]

Indirect immunofluorescence

Indirect immunofluorescence is used to detect circulating antibodies targeting the antigens at the basement membrane zone in patients with pemphigoid. In this procedure, patient's serum is collected and overlaid on salt-split normal human skin and incubated. Following this, the specimen will be stained for fluorescent detection of antibodies.

In bullous pemphigoid, circulating IgG targeting the basement membrane, mainly BP180 and BP230 hemidesmosomal proteins are detectable in 60-80% of patients. IgA and IgE classes can also be detected, but less frequently.

Enzyme-linked immunosorbent assay (ELISA)

ELISA for bullous pemphigoid is commercially available to test for circulating Ig against NC16A domain of BP180 and BP230, known as bullous pemphigoid antigen 2 [BPAg2] and bullous pemphigoid antigen 1 [BPAg1] respectively. Antibodies to BP180NC16A domain is useful for the diagnosis of bullous pemphigoid as it has a sensitivity of 89% and specificity of 98%.

Detection of BP180 and/or BP230 antibodies in serum does not give a confirmative diagnosis of bullous pemphigoid. A study has reported that 7% were tested positive for one or both autoantibodies in one series of 337 people without bullous pemphigoid. ELISA findings should be correlated with DIF to reduce the risk of misdiagnosis.

Treatment
The treatment for bullous pemphigoid includes:

1. Corticosteroids
i. Topical Corticosteroids
ii. Systemic corticosteroids

2. Glucocorticoid-sparing drugs
i. Immunosuppressive drugs
ii. Anti-inflammatory drugs

3. Biologic therapy
i. Intravenous immunoglobulin
ii. Rituximab

Treatments include topical steroids such as clobetasol, and halobetasol which in some studies have proven to be equally effective as systemic, or pill, therapy and somewhat safer.[9] However, in difficult-to-manage or widespread cases, systemic prednisone and powerful steroid-free immunosuppressant medications[10], such as methotrexate, azathioprine or mycophenolate mofetil, may be appropriate. Some of these medications have the potential for severe adverse effects such as kidney and liver damage, increased susceptibility to infections, and bone marrow suppression. Antibiotics such as tetracycline or erythromycin may also control the disease, particularly in patients who cannot use corticosteroids.

The anti-CD20 monoclonal antibody rituximab has been found to be effective in treating some otherwise refractory cases of pemphigoid. A 2010 meta-analysis of 10 randomized controlled trials showed that oral steroids and potent topical steroids are effective treatments, although their use may be limited by side-effects, while lower doses of topical steroids are safe and effective for treatment of moderate bullous pemphigoid.
IgA-mediated pemphigoid can often be difficult to treat even with usually effective medications such as rituximab.

Among all, topical or systemic corticosteroids are considered as the first line therapy in controlling bullous pemphigoid. Other drugs and immunomodulatory therapies are often used as adjunct to minimize the adverse effect of long-term use of corticosteroids and improve the healing of the disease.

There are several factors that have to be taken into account when choosing the therapies given to the patient: (a) patient's age (b) underlying disease such as hypertension, diabetes mellitus and other cardiovascular disease (c) side effect with the use of drugs (d) patient's ability to compliant to the therapy (d) severity and extent of disease (e) cost of drugs.

Corticosteroids
High potency topical corticosteroid is preferred as the first line treatment due to its efficacy and fewer systemic adverse effects when compared to systemic corticosteroids. Studies have shown that patients with extensive bullous pemphigoid (defined as >10 new bullae per day) treated with topical corticosteroids (Topical Clobetasol Propionate 0.05% cream) had better clinical outcomes than patients with extensive bullae pemphigoid who were treated with systemic glucocorticoid therapy (Prednisone). Systemic glucocorticoids can be used for patients when there are factors that make the use of topical corticosteroids not feasible, such as elderly patient inability to apply the cream on their own, cost or patient's own preference.

Topical Corticosteroids
Topical Clobetasol Propionate 0.05% cream is usually used and applied twice daily. A study by Joly et al. demonstrated that the use of 10 to 20g of Clobetasol Propionate per day for moderate disease and 20

to 30g per day for extensive disease until 15 days after disease control, then tapered to discontinuation over four months was as effective as the standard regime (40g per day tapered slowly over 12 months).

Systemic corticosteroids

Prednisone is usually used to treat bullous pemphigoid. The dose varies between 0.2 and 0.5 mg/kg/day and will continue until active inflammation, new blister formation, pruritus has stopped for at least 2 weeks. The dose is then slowly tapered over the months. Initially, prednisolone can be reduced by relatively large amounts (approximately 10 mg) and smaller amount (2.5–5 mg) subsequently. Should the patient develop flare up of the lesion, the dose should be increased to the previous level or higher and maintained longer before further, slower tapering.[11]

Glucocorticoid sparing drugs

For patients who require high dose of corticosteroids for clearing or maintenance, glucocorticoid sparing agents such as immunosuppressive drugs and anti-inflammatory drugs can be used as an adjunct therapy to reduce the systemic side effects of corticosteroids. Patients who have comorbidities and contraindications for corticosteroids may also consider these glucocorticoid sparing agents.

Immunosuppressant drug

Immunosuppressant drugs include azathioprine (1–3 mg/kg/day in two equally divided doses), mycophenolate mofetil (1000–3000 mg/day or 40 mg/kg/day in two divided doses), and methotrexate (10–15 mg/week).

Anti-inflammatory drugs

Tetracycline antibiotics are often used in combination of nicotinamide to treat bullous pemphigoid. For the administration of drugs, tetracycline is prescribed as 500 mg four times daily, doxycycline and minocycline as 100 mg twice daily and nicotinamide, 500 mg 4 times daily. Dapsone is also shown to be effective in treating bullous pemphigoid. However, the efficacy of dapsone is limited. Dapsone is usually commenced at a low dose of 25 to 50 mg/day and increase by 25 mg every week until the condition improves. Maximum dose that can be prescribed is 250 mg/day.[12]

Biologic therapy

For refractory disease, biologic therapies such as intravenous immunoglobulin and Rituximab should be considered. [13]

References

1. Cozzani E, Gasparini G, Burlando M, Drago F, Parodi A (May 2015). "Atypical presentations of bullous pemphigoid: Clinical and immunopathological aspects". Autoimmunity Reviews. 14 (5): 438–45
2. Longo, D (2012). Harrison's Principles of Internal Medicine. McGraw-Hill Medical. p. 427.
3. Culton DA, Liu Z, Diaz LA (17 October 2007). "Chapter 54. Bullous Pemphigoid". In Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ (eds.). Fitzpatrick's Dermatology In General Medicine, Two Volumes (7th ed.). Mcgraw-hill.
4. Seshadri, Divya (2013). "Acantholysis revisited: Back to basics". Indian J Dermatol Venereol Leprol. 79 (1): 120–6.
5. Online Mendelian Inheritance in Man (OMIM): COLLAGEN, TYPE XVII, ALPHA-1; COL17A1 - 113811.
6. Online Mendelian Inheritance in Man (OMIM): DYSTONIN; DST - 113810.
7. Bullous Pemphigoid." Quick Answers to Medical Diagnosis and Therapy". Retrieved 2012-07-21.
8. Giang, Jenny; Seelen, Marc A. J.; van Doorn, Martijn B. A.; Rissmann, Robert; Prens, Errol P.; Damman, Jeffrey (2018). "Complement Activation in Inflammatory Skin Diseases". Frontiers in Immunology. 9: 639.
9. Meijer JM, Diercks GF, de Lang EW, Pas HH, Jonkman MF (December 2018). "Assessment of diagnostic strategy for early recognition of bullous and nonbullous variants of pemphigoid". JAMA Dermatol. 155 (2): 158–165.

10. Wojnarowska F, Kirtschig G, Highet AS, Venning VA, Khumalo NP (August 2002). "Guidelines for the management of bullous pemphigoid". The British Journal of Dermatology. 147 (2): 214–21.
11. Kirtschig G, Middleton P, Bennett C, Murrell DF, Wojnarowska F, Khumalo NP (October 2010). "Interventions for bullous pemphigoid". The Cochrane Database of Systematic Reviews. 2010 (10): CD002292.
12. Lamberts A, Euverman HI, Terra JB, Jonkman MF, Horváth B (2018). "Effectiveness and Safety of Rituximab in Recalcitrant Pemphigoid Diseases". Frontiers in Immunology. 9: 248.
13. He Y, Shimoda M, June 2015. "Persistence of Autoreactive IgA-Secreting B Cells Despite Multiple Immunosuppressive Medications Including Rituximab". JAMA Dermatology. 151 (6): 646–50.