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COMPREHENSIVE REVIEW OF BULLOUS PEMPHIGOID: PATHOGENESIS, CLINICAL MANIFESTATIONS AND MANAGEMENT STRATEGIES

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ABSTRACT Bullous pemphigoid (BP) is the most prevalent autoimmune blistering disease, primarily affecting the elderly, with an incidence ranging from 2 to 42 cases per million annually and a global prevalence of 49 to 169 cases per million. BP is characterized by subepidermal blister formation due to autoantibodies targeting hemidesmosomal proteins, notably BP180 and BP230. Classification includes typical BP and mucous membrane pemphigoid, among others. Pathogenesis involves autoantibody production targeting hemidesmosomal proteins, complement activation, and inflammatory cell recruitment. Clinical manifestations include itching, erythema, urticarial plaques, and tense bullae, with mucous membrane involvement less common. Diagnosis relies on clinical, histological, and immunological findings. Management includes systemic corticosteroids, immunosuppressive agents, and biologic therapies, along with supportive care.

KEYWORDS : Pemphigus, Bullous Dermatoses, Immunoglobulin G, Oral Mucosa.

INTRODUCTION

Bullous pemphigoid (BP) is a rare autoimmune blistering skin disorder that primarily affects the elderly. It is characterized by the formation of large, tense blisters on the skin and mucous membranes, often accompanied by itching. The exact cause of BP is unknown, but it is thought to be related to an autoimmune response targeting the proteins that help attach the epidermis to the dermis. Despite advances in understanding and management, challenges remain in the diagnosis and treatment of BP. Clinicians must balance the use of potent immunosuppressive therapies with the potential for adverse effects, especially in older patients who may have comorbidities. Additionally, further research is needed to elucidate the underlying mechanisms of BP and to develop more targeted and effective treatments (1).

In this narrative review, we aim to provide a comprehensive overview of the current understanding of BP, including its epidemiology, pathophysiology, clinical presentation, diagnosis, and treatment options.

METHODS

This narrative review on bullous pemphigoid, a comprehensive search was conducted in electronic databases including PubMed, Embase, and Cochrane Library. The search strategy utilized a combination of Medical Subject Headings (MeSH) terms and keywords related to bullous pemphigoid, such as "bullous pemphigoid," "autoimmune blistering disease," and "pemphigoid."

After removing duplicates, the titles and abstracts of the identified articles were screened for relevance. Full-text articles were then reviewed to determine their eligibility for inclusion. A total of 15 references were included in this narrative review based on their relevance and contribution to the understanding of bullous pemphigoid.

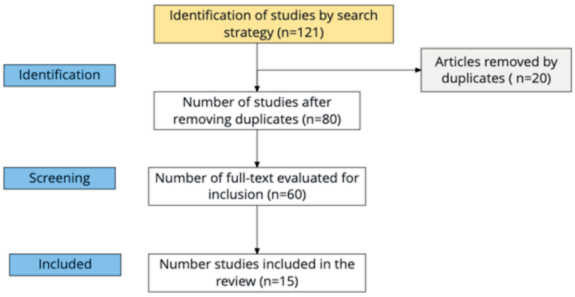

Figure 1. PRISMA.

Epidemiology and Classification

Bullous pemphigoid (BP) is the most common autoimmune blistering disease, predominantly affecting the elderly population, with an annual incidence ranging from 2 to 42 cases per million worldwide. The incidence increases with age, peaking in the seventh and eighth decades of life, with a slight predominance in females (2).

BP is characterized by subepidermal blister formation due to autoantibodies targeting hemidesmosomal proteins, particularly BP180 and BP230. The classification of BP includes several subtypes based on clinical and immunological features. These subtypes include typical BP, characterized by tense bullae on erythematous or normal skin, and mucous membrane pemphigoid, which primarily affects mucous membranes. Other variants include localized, drug-induced, and childhood BP (3).

Pathogenesis

The pathogenesis of bullous pemphigoid (BP) is complex and involves a cascade of events leading to autoantibody production and subsequent blister formation. BP is characterized by the presence of autoantibodies targeting two main components of the hemidesmosome: BP180 (also known as type XVII collagen) and BP230 (also known as BPAG1). These autoantibodies are predominantly of the IgG class, particularly IgG4 subclass, and are directed against the NC16A domain of BP180 and the N-terminus of BP230 (3).

The initial step in BP pathogenesis is believed to be the binding of these autoantibodies to their respective antigens in the basal membrane zone (BMZ) of the skin. This binding triggers a series of events, including complement activation, recruitment of inflammatory cells, and release of inflammatory mediators. Complement activation leads to the formation of membrane attack complexes, resulting in direct damage to the basement membrane and keratinocytes. The recruitment of inflammatory cells, such as neutrophils, eosinophils, and mast cells, further amplifies the inflammatory response. These cells release various pro-inflammatory cytokines, chemokines, and proteases, which contribute to tissue damage and blister formation. In addition, the activation of mast cells can lead to the release of histamine, which contributes to the pruritus commonly seen in BP (4).

The final result of these processes is the formation of subepidermal blisters, characterized by a separation between the epidermis and dermis. The blister fluid contains a

mixture of inflammatory cells, antibodies, complement proteins, and proteases, further contributing to tissue damage and inflammation (5).

Clinical Manifestations

The clinical presentation of BP can vary widely but typically begins with the gradual onset of itching, erythema, and urticarial plaques. These early symptoms may precede the development of bullae by weeks to months. The bullae are typically large, tense, and located on erythematous or normal-appearing skin. They may rupture easily, leaving erosions and crusts. In severe cases, widespread involvement can lead to significant morbidity and mortality (5,6).

Mucous membrane involvement is less common in BP compared to other autoimmune blistering disorders, such as pemphigus vulgaris. However, when mucosal surfaces are affected, erosions and ulcerations can occur in the oral cavity, conjunctiva, and genitalia. This can lead to pain, difficulty eating, and impaired vision (6).

Diagnosis

The diagnosis of BP is based on a combination of clinical, histological, and immunological findings. A skin biopsy of a blister or urticarial plaque is essential for histological examination, which typically reveals subepidermal blistering with a dense inflammatory infiltrate composed mainly of eosinophils. Direct immunofluorescence (DIF) microscopy of perilesional skin demonstrates linear deposition of IgG and C3 along the basement membrane zone, a hallmark of BP (6,7).

Indirect immunofluorescence (IIF) testing on serum can detect circulating autoantibodies against BP180 and BP230. Enzyme-linked immunosorbent assays (ELISAs) are also used to detect serum antibodies to these antigens, with high sensitivity and specificity. Serological testing is particularly useful in cases where biopsy findings are inconclusive or unavailable (7).

Differential Diagnosis

Distinguishing BP from other blistering disorders, such as pemphigus vulgaris, epidermolysis bullosa acquisita, and linear IgA bullous dermatosis, is crucial due to differences in management and prognosis. Pemphigus vulgaris, for example, typically presents with intraepidermal blistering and is associated with mucosal involvement, while epidermolysis bullosa acquisita is characterized by subepidermal blistering and scarring (8).

Management and prognosis

The primary goals of treatment for pemphigus vulgaris are to control the disease activity, promote healing of existing lesions, prevent new blister formation, and improve quality of life. The initial treatment typically involves the use of systemic corticosteroids, such as prednisone, to suppress the autoimmune response and reduce inflammation. Corticosteroids are usually started at high doses and then gradually tapered to the lowest effective dose to maintain disease control (9,10).

In addition to corticosteroids, immunosuppressive agents may be used as steroid-sparing agents to reduce the long-term side effects of corticosteroid therapy. Azathioprine, mycophenolate mofetil, and methotrexate are commonly used immunosuppressive agents in the treatment of pemphigus vulgaris. These medications work by suppressing the activity of the immune system and reducing the production of autoantibodies. In recent years, biologic therapies have emerged as promising treatments for pemphigus vulgaris. Rituximab, a monoclonal antibody that targets CD20-positive B cells, has been shown to be effective in inducing remission in patients with refractory disease or those who are unable to tolerate conventional therapies. Rituximab is typically administered as a series of infusions over several weeks or months (10).

In addition to pharmacological therapy, supportive care is an important aspect of the management of pemphigus vulgaris. This may include wound care, pain management, and nutritional support to promote healing and prevent complications. Patients with pemphigus vulgaris should also receive regular monitoring for disease activity and side effects of treatment (11,12).

The prognosis of pemphigus vulgaris has improved significantly in recent years with advances in treatment. However, the disease is still associated with a significant morbidity and mortality, particularly in older patients and those with severe disease. Early diagnosis and initiation of treatment are key factors in improving outcomes for patients with pemphigus vulgaris (12).

The management of refractory disease in bullous pemphigoid may involve biologic therapies when there is no response to topical corticosteroids, systemic corticosteroids, or corticosteroid-sparing agents. Rituximab is a commonly reported option, although there is insufficient data to determine its effectiveness. It is a humanized chimeric monoclonal antibody that destroys CD20+ B and pre-B cells. Rituximab has been observed to be effective in refractory cases, with complete responses in 85% of patients. Dupilumab, a human anti-interleukin (IL) receptor-alpha monoclonal antibody, has also shown improvement in patients with bullous pemphigoid in case studies. Omalizumab, an anti-immunoglobulin E (IgE) monoclonal antibody, has been associated with improvement in refractory cases in case reports (13,14).

Intravenous immune globulin (IVIG) is occasionally used to treat bullous pemphigoid and has been associated with clinical improvement in the majority of patients. However, further studies are needed to determine the optimal regimen and indications for IVIG. Other therapies such as oral Janus kinase (JAK) inhibitors and other medications have shown benefit in individual cases, but more research is needed to confirm their efficacy and safety (14).

Bullous pemphigoid has a variable clinical course, with a tendency to be chronic and relapsing. Long-term remission can occur after months to years, but the risk of relapse is high. Mortality in patients with bullous pemphigoid can be significant, with one-year mortality rates ranging from 11 to 48%. Complications secondary to treatments are a major cause of death in these patients (15).

In conclusion, bullous pemphigoid presents significant epidemiological variation and clinical complexity, necessitating a multidimensional approach to diagnosis and management. While therapeutic strategies have evolved, challenges persist in mitigating disease burden and improving patient outcomes, particularly in vulnerable populations. Continued research and clinical vigilance are crucial in advancing understanding and treatment of this debilitating autoimmune disorder.

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