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Chapter 3

Bullous Pemphigoid

Derya Yayla, Pelin Hizli and Yeşim Yayla

Additional information is available at the end of the chapter

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Abstract

Bullous pemphigoid (BP) is a chronic, acquired, autoimmune bullous disease characterized by subepidermal bullae. It is usually seen in the elderly but, rarely, may also be seen in children. Autoantibodies against hemidesmosomal proteins BP230 (BPAG1) and BP180 (BPAG2 or type XVII collagen) are blamed for the pathogenesis. Clinically, it is characterized by large, tense blisters. Blisters can occur on normal skin or erythematous base with a predilection of flexural aspects of the limbs, abdomen, groin and axillae. Mucous membrane involvement is seen in about 10–35% of the patients. For treatment, general maintenance of BP patients is the first step. Systemic steroids are the common treatment agents. But localized disease can be treated successfully with topical corticosteroids. The common immunosuppressive agents are azathioprine, mycophenolate mofetil, methotrexate, chlorambucil and less often cyclophosphamide. In a minority of resistant cases, intravenous immunoglobulins, plasma exchange, anti-CD20 immunotherapy (rituximab), leflunomide, chlorambucil and methotrexate may be effective.

Keywords: blistering diseases, tense bullae, BP230, BP180, gestational pemphigoid

1. Introduction

Bullous pemphigoid (BP) is a chronic, acquired, autoimmune bullous disease characterized by subepidermal bullae [1–4]. It is the most common bullous disease, and its incidence has been gradually increasing [2, 5]. It is usually seen in the elderly, but rarely may also be seen in children [2, 6, 7]. In general, the clinical manifestations are tense bullae, urticarial lesions and intense pruritus [3, 5, 7]. Although mucosal findings are not common, oral findings are observed in 10–25% of cases [4, 5]. Autoantibodies against hemidesmosomal proteins BP230 (BPAG1) and BP180 (BPAG2 or type XVII collagen) are blamed for the pathogenesis [2].

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2. History

In 1953, Walter Lever, M.D. was the first who described that BP was a distinct disease from pemphigus [8, 9]. In 1967, Jordon, Beutner et al. demonstrated the circulating autoantibodies against the epidermal basal membrane zone (BMZ) in patients with bullous pemphigoid using the immunofluorescence method [9].

3. Epidemiology

The annual incidence is approximately 6–7 new cases per million [8]. While the incidence in Europe ranges from 7 to 43 per million [10], this rate is 2.6 per million in Basra and 14 per million in the North East Scotland [2]. It is often seen in the elderly population (particularly in over 65 years of age) and more frequent in men [5, 11]; however, it has been cited in many studies that it is seen with equal frequency in both genders [4]. Patients older than 90 years have also a relative risk 300 times higher than those younger than 60 years [5]. Although it is rare in children, its incidence has been increasing [7]. In addition, there are no geographical or ethnic differences [4, 8].

4. Etiology

4.1. Genetic factors

No strong association was found with any of the HLA class I and II DR antigens [12]. Nevertheless, in some studies, HLA class II alleles were found to be more frequent in BP patients than in the general population [11]. A significant association with DQB1*0301 alleles was also found in Caucasians, while there was an association with DRB1*04, DRB1*1101 and DQB1*0302 alleles in Japanese patients [11]. In some studies, residual essential amino acids were detected in positions 71–77 of the DQB1 gene in patients with BP [5].

4.2. Environmental factors

It has been shown that furosemide, psoralen, ibuprofen, galantamine, hydrobromide, ACEi, spironolactone, penicillin, levofloxacin, metronidazole may lead to BP [13]. Adalimumab and etanercept (TNF-alpha blockers) associated BP cases have also been reported [5]. Another cause blamed in the etiology is vaccinations. BP may develop after 1 day–4 weeks of vaccination. In particular, most infantile BP cases have been described after the first dose [14]. In addition, trauma, radiotherapy and UVB exposure may cause bullous lesions by uncovering BP antigens [5]. In contrast to pemphigus vulgaris, no relationship between any dietary factor and BP has been found yet [5].

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5. Accompanying diseases

The incidence of malignancy is increased in BP cases (stomach cancer, lung cancer, etc.) [8, 15, 16]. There is also an increase in the incidence of psoriasis [8]. Although the immunogenetic and immunopathological mechanisms are not clear, it is considered that treatments for psoriasis (such as UVA-UVB) may play a trigger role for BP [8]. Another association is autoimmune diseases. BP is accompanied by some diseases such as rheumatoid arthritis, Hashimoto's thyroiditis, dermatomyositis and autoimmune thrombocytopenia [8]. In addition, multiple sclerosis, dementia, stroke, epilepsy, Parkinson's disease, Shy-Drager syndrome and ALS are the most common neurological diseases in BP patients [10]. Although the mechanism is not clearly understood, BP1 and BP2 antigens are considered to play a role as autoreactive antigens in brain and skin [10].

6. Pathogenesis

BP is a subepidermal bullous disease with autoantibodies against hemidesmosomal proteins, BP 180 and 230 [17]. Hemidesmosomes are cellular adhesion proteins that bind basal keratinocytes to the extracellular matrix of the epidermis [5]. BP180 is a type 2 transmembrane protein kinase, also known as collagen XVII, while BP230 is a cytoplasmic protein [5]. The main target in BP is the noncollagenous region of BP180 (NC16A). Both IgG- and IgE-type autoantibodies against this structure are developed [3].

The role of BP230 is not clearly known in pathogenesis [18]. Many studies support that anti-BP230 antibodies play an important role in the onset of clinical symptoms and in the bulla formation [19]. Only anti-BP230 antibodies are detected in the serum of a few patients, while both anti-BP180 and anti-BP230 antibodies are present in all BP patients [18].

Anti-BP180 autoantibody titers were found to correlate with disease activity, itch intensity, peripheral blood eosinophil count and disease duration [17, 18, 20]. This correlation could not be obtained with anti-BP230 autoantibody titers [18].

In addition, a significant increase in total serum IgE levels was observed in 75–77% of patients with BP [3, 20]. IgE autoantibodies are against the NC16A region of BP180, as in IgG [3]. These autoantibodies were injected into mice, and urticarial lesions were detected [3, 21].

In patients with BP, an autoreactive T-cell response against BP180 and BP230 develops, which stimulates B cells to produce pathogenic autoantibodies [11]. These T lymphocytes are in the CD4+ phenotype and produce both Th1 (e.g., INF-gamma) and Th2 cytokines (such as IL-4, IL-5 and IL-13), and their major epitopes are located on NC16 domain [11]. Th2 cytokines are especially important in the pathogenesis of the disease and with their release, IgG4-type autoantibodies against BP180 are developed [11].

Unlike the pemphigus group of diseases, the autoantibodies deposited in the BMZ are not sufficient to cause disease emergence [22]. After antigen–antibody reaction, complement deposition

and activation of both classical and alternative pathways are necessary for subepidermal bulla development [23]. IgG and IgE autoantibodies against BP180 activate the complement system, which triggers the onset of inflammatory events [1, 5]. Therefore, mast cell degranulation and the release of TNF alpha, PAF and other cytokines, matrix metalloproteinase 9 and leukotrienes occur [1, 5, 11]. Proteolytic enzymes released from eosinophils and neutrophil elastase break-down various extracellular matrix proteins and BP180 [9, 11]. Proinflammatory mediators such as protease, IL-5 and eotaxin are released from infiltrating eosinophils, contributing to tissue damage [11]. In conclusion, BP180 autoantibodies directly stimulate keratinocytes to express various cytokines (such as IL-6, IL-8) and enhance inflammatory response [11].

A variant of BP, namely pemphigoid gestationis (PG) is one of the rare, pregnancy-specific bullous dermatoses, also known as herpes gestationis [24, 25]. Usually occurring in the second or third trimester of pregnancy, it is characterized by vesiculobullous rashes [24]. The disease can be seen in any trimester of the pregnancy as well as postpartum [26]. The incidence ranges from 1/50.000 to 1/1700 [24, 27]. The triggering factors are not known [27]. Graves' disease is the most commonly detected secondary autoimmune disease [24]. Rarely, it may also be associated with hydatidiform mole and chorionic epithelioma [24].

John Laws Milton first described the disease in 1872, as herpes gestationis [24]. Although the pathophysiology of PG has not been clearly explained, it is considered that MHCII antigens present in the placenta lead to an immunological response with a cross-reaction to the maternal skin [24]. HLA DR3 and HLA DR4 antigens were more frequently detected in these patients [25, 26].

The pathogenesis is similar to BP, and there are autoantibodies against the NC16A domain of BP2 antigen [25, 26]. In 10% of patients, autoantibodies against BP1 antigen are present [26]. Following this antigen-antibody interaction, complement activation takes place, and eosinophil chemotaxis occurs in the BMZ, where the antigen-antibody complex is present [25]. Eosinophil degranulation also leads to damage in the dermoepidermal region and bulla formation [25].

7. Clinical features

BP shows a clinical polymorphism [28]. Clinically, it is characterized by large, tense blisters. Blisters can occur on normal skin or erythematous base with a predilection of flexural aspects of the limbs, abdomen, groin and axillae [29]. The most common initial clinical presentations are pruritic eczema or urticarial-like erythema without blisters and it is called nonbullous phase [30, 31]. Itching of various degrees may be seen in the course of the disease. However, significant pruritus is more frequent, and therefore, it may be the only manifestation of the disease, especially in older patients [30, 32].

BP commonly starts with pruritus and nonspecific skin lesions. Pruritus may persist for many months before the eruption [30, 33]. Therefore, physicians should consider BP in differential

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diagnosis of elderly patients with long-term persisting pruritus and nonspecific eczema-like or urticarial lesions [31]. Blisters frequently occur after 1–3 weeks of nonbullous phase. Nonbullous urticarial lesions may stay several months before the blisters occur [33].

In bullous stage, vesicles and bullae appear on normal or erythematous skin together with urticarial and infiltrated papules with an annular or figurate pattern [34]. Blisters are tense, filled with serous fluid, sometimes hemorrhagic, and Nikolsky sign is negative (**Figure 1**) [29, 34, 35].

Blisters usually appear in symmetric distribution. A central resolution commonly occurs, and postinflammatory hyperpigmentation and milia may be seen. Additionally, persistent erythema may occur and remain for many weeks at the site of the prior blisters [29, 33, 36].

Mucous membrane involvement is seen in about 10–35% of the patients. Most affected mucous membrane is buccal mucosa [29]. In buccal mucosa, mucosal erosions are common, while intact blisters are rare [37]. Involvement of other mucosal sites like nose, esophagus, pharynx or anogenital system is relatively rare [34].

Unusual clinical variants of BP previously described depending on different clinical presentations are as follows: dyshidrosiform BP, intertrigo-like BP, prurigo-nodularis-like BP, vesicular BP, papular BP, eczematous BP, erythrodermic BP, lymphomatoid papulosis-like BP, lichen planus pemphigoides and BP with TEN-like lesions.

Several different localized forms are pretibial BP, peristomal BP, umbilical BP, vulvar BP, stump pemphigoid (distal end of amputated limbs), BP on paralyzed limbs, BP on body sites of radiotherapy [34, 35, 38]. The most common localized form is pretibial BP. Another localized form is vulvar BP and is seen in young girls presenting with vulvar erosions, blisters and ulcers. Localized forms either may not progress for years or generalization may occur [29, 37].

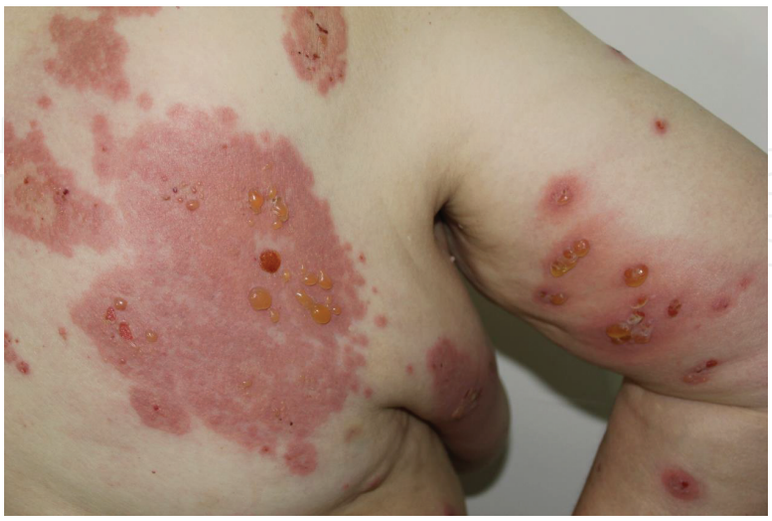

Figure 1. Nikolsky negative blisters and erythematous plaques on upper extremity and shoulders.

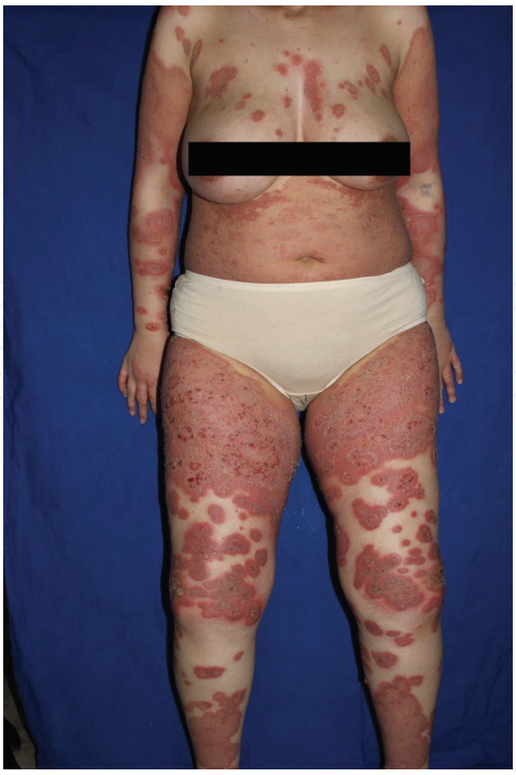

Figure 2. Targetoid lesions and erythematous eruptions involving upper and lower extremities.

Pemphigoid nodularis is a rare clinical type of BP commonly seen in elderly women. It may present with prurigo-nodularis-like intensely itchy nodules, papules and BP-like blisters together [39, 40].

In childhood BP, there are some clinical differences. Commonly, the disease first appears acrally in infants and then may generalize. The face, palms and soles are frequently affected. Genital involvement is seen in older children [41]. In most children, the disease lasts less than 1 year [37].

PG is a special clinical variant of BP seen especially during late pregnancy, but it may occur at any time of pregnancy or immediately after delivery. In general, it starts from the abdomen, especially from periumbilical region as urticarial erythema. Then, herpetiform vesicles may occur at the periphery of the erythema. Tense bullae on erythematous base may also be present [35, 42]. Rapidly, it may progress to a pemphigoid-like eruption involving entire body (**Figure 2**). Generally, face, scalp and oral mucosa are not affected.

After delivery, flare of the disease is seen in 75% of patients, and in some patients, explosive onset of blistering occurs within hours. Usually, PG disappears spontaneously within 3 months after delivery [34, 37]. Recurrences may be associated with menstruation and oral contraceptive usage. In subsequent pregnancies, recurrence with early onset and a more severe disease are common [37].

Ten percent of newborns develop skin lesions due to the maternal antibodies [34]. But the eruption is self-limited and does not need treatment [29].

8. Histology

The most valuable diagnostic biopsy for BP is that taken from early small blisters [29]. The histopathologic findings of BP under light microscopy are subepidermal bullae without acantholysis and eosinophil-rich superficial dermal infiltrate.

The amount of superficial dermal infiltrate varies, as does the cellular content. Hence, the biopsies may be categorized as granulocyte-rich and granulocyte-poor, depending on whether the biopsy was taken form inflamed or noninflamed region. Eosinophils are usually the predominant inflammatory cells of the infiltrate, whereas some biopsies may show neutrophil predominance [37, 43].

In urticarial lesions at the prodromal stage, the histopathologic findings may not be specific. There may be only a superficial dermal infiltrate of lymphocytes, histiocytes and abundant eosinophils with papillary dermal edema and eosinophilic spongiosis occasionally [44].

9. Special tests

In 23% of BP patients, biopsies were not used in the diagnosis of BP; at that point, direct immunofluorescence (DIF), indirect immunofluorescence (IIF) and ELISA are critical for correct diagnosis [37].

In almost all patients, direct IF of perilesional healthy skin shows thin, linear (tubular or toothpaste pattern) and continuous deposition of IgG and/or C3 along the BMZ [45–49]. Predominantly, the deposition of IgG1 and IgG4 has been shown; also, all IgG subclasses and IgE have been reported. False-negative results are more common on lower extremities. Close analysis of the pattern of immune deposition may be helpful for us to differentiate autoimmune blistering diseases. For example, there is an n-serrated pattern in BP and linear IgA bullous dermatosis and u-serrated pattern in epidermolysis bullosa acquisita EBA [50].

There are circulating anti-basement membrane zone IgG and IgE autoantibodies in 60–80% (approximately 70%) of the BP patients [47–49, 51–56]. These autoantibodies typically bind to epidermal side of 1 M NaCl-split human skin substrate or less often binds to both dermal and epidermal sides. Even if not routinely used, computer-aided fluorescence overlay antigen mapping (FOAM) shows the exact localization of the immune deposition [56]. For IIF, 1 M NaCl-split human skin is rather preferred than intact human skin or monkey esophagus. By incubating the human skin with 1 M NaCl, the epidermis will be separated from the dermis at lamina lucida. Using 1 M NaCl-split skin substrate has another advantage, and it can be used

to differentiate BP from EBA. EBA autoantibodies bind to the base or the floor of the split skin (i.e., dermal side), but BP autoantibodies bind to the roof of it (i.e., epidermal side).

This is not the only histological difference between EBA and BP. C3 deposition is sometimes absent in EBA but is nearly always present in BP, and type-4 collagen stains the roof of the blister in EBA, whereas it stains the base in BP. In more than 70% of patients, there are circulating anti-BMZ autoantibodies [57, 58]. Unlike pemphigus, in BP, circulating IIF autoantibody levels do not show the disease activity or the extent of the disease [59].

ELISA has been found to be fairly specific (90%), especially ELISA that is using recombinant proteins, which bind to specific regions of the BP antigens like the NC16A part of BP180 and the C-terminus of BP180 or BP230 [60, 61]. ELISA has also proven to be sensitive for detecting the circulating antigen-specific IgG and IgE autoantibodies, so for that reason, ELISA is useful in both research and clinical settings. ELISA tests are commercially available with sensitivity of 89% and specificity of 98% [62].

Almost three out of four patients have antigen-specific IgE detectable by IF and ELISA [20, 54, 63–67]. Patients with antigen-specific IgE antibody may develop more severe form of disease. IgE plays a role in attracting eosinophils to skin lesions, so patients with antigen-specific IgE antibody may develop instant urticarial-like lesions [21, 65, 66].

Sometimes, elderly patients with pruritic cutaneous eruptions or healthy subjects have low titer false-positive results. Approximately 7% of the normal population has anti-BP180 antibodies detectable by ELISA but shows no clinical or histological features of the disease; therefore, ELISA must be used in appropriate conditions not as a screening method [68].

Similar to BP, the main diagnostic marker of PG is the linear deposition of C3 along BMZ of perilesional healthy skin. The linear deposition of C3 is observed in 100%, but linear IgG deposition is only seen in 30% of PG patients. On conventional IIF testing, nearly 30% of PG patients have a circulating IgG anti-basement zone antibody. But when complement-enhanced IIF testing is used, nearly 75% of patients show PG factor (a complement-fixing anti-BMZ IgG1 autoantibody) [34].

10. Treatment

General maintenance of the patient is the first step in the treatment of BP patients. It is important to drain the large blisters because the serous fluid inside the blisters makes an essential environment for infections. If there is any local pain, infection possibility should be kept in mind and after taking wound culture, a proper antibiotic has to be started.

Treatment of BP depends on the extent of disease and mostly on clinical experience rather than controlled clinical trials [69–79].

Systemic steroids are the common treatment agents. But localized disease can be treated successfully with topical corticosteroids [48, 49, 80]. In recent studies, clobetasol propionate

cream 0.5% was applied twice daily to the entire surface of the body so the patients received a daily dose of 40 g [72]. This amount of high-potency topical corticosteroid may result in high systemic absorption and can cause local and systemic side effects [81]. This kind of topical treatment is very difficult and expensive to apply, and these controlled studies did not emphasize the patients' ability to reach complete disease-free period as with systemic corticosteroids. Nevertheless, potent topical corticosteroids can control even generalized BP and may be safer than oral corticosteroids [77–79, 81]. Topical tacrolimus can also be a useful agent in some cases of localized pemphigoid [80, 82–85].

Patients with generalized disease are usually treated with oral prednisone [80, 86, 87]. For more extensive disease, a regimen of oral prednisone at a dose of 0.5–1 mg/kg/day can control the disease within 1–2 weeks. Afterwards, the dose can be tapered over a period of 6–9 months. On some occasions, pulse methyl prednisolone therapy may be required for rapid controlling of active blister formation [88]. Systemic corticosteroids are always associated with serious side effects (like osteoporosis, diabetes and immunosuppression) and in elderly patients, these side effects may be even more severe [89].

In order to minimize the side effects of oral glucocorticosteroids, immunosuppressive drugs can be used in conjunction with prednisone [80, 87, 90–96]. However, there are very few controlled trials for this common approach. The use of immunosuppressive drugs is controversial. They can also be used as second-line therapy if corticosteroids are contraindicated or fail to control the disease. The common immunosuppressive agents are azathioprine, mycophenolate mofetil (1.5–3 g/day), methotrexate, chlorambucil (0.1 mg/kg/day, frequently 4–6 mg/day), and less often cyclophosphamide (1–3 mg/kg/day). The dosage of azathioprine (0.5–2.5 mg/kg/day) is adjusted by thiopurine methyltransferase level, with this adjustment, the efficacy of azathioprine will increase and side effects will be decreased. Choosing an immunosuppressive agent primarily depends on side effect profile, patients' general status and doctors' experience.

When corticosteroids are contraindicated, few reports have described successful treatment of some patients with the combination of nicotinamide (500–2000 mg/day) and minocycline or tetracycline or erythromycin; or tetracycline alone [97, 98]. Sulfones can be used to treat some patients. If there is no glucose-6-phosphate dehydrogenase deficiency, dapsone and sulfapyridine have been reported to control the disease activity in 15–44% of BP patients [87, 99–101]. In a minority of resistant cases, intravenous immunoglobulins (IVIg) [102–104], plasma exchange [73], anti-CD20 immunotherapy (rituximab) [105–107], leflunomide [108], chlorambucil [109] and methotrexate [92, 94, 110] may be effective.

Even if the duration of treatment has not been clear yet, BP patients generally need to be treated for about 12–18 months. This period of time includes both active disease treatment and also a maintenance phase after cessation of active disease. This maintenance phase lasts for about 3–6 months, and during this phase, low-dose oral prednisone (<10 mg/day) or topical clobetasol propionate (10 g/week) is used [111]. As previously mentioned, initial doses of prednisone of 0.5–1.0 mg/kg/day or even less can control the disease. After new blister formation has stopped and erythema has disappeared—this usually has happened within 1–2 weeks—progressive tapering of prednisone over a 6–9-month period or rarely longer is recommended. Lowering the dose of 5 mg for every week until reaching 30 mg is commonly used. The patients' clinical

response should be monitored carefully, and lowering of the prednisone dose should be done according to this response. Because of the side effects of glucocorticoids, it is important to minimize the total dose and duration of the treatment. It is important to eliminate the complications of glucocorticoids by using osteoporosis prophylaxis and gastric protection, monitoring the cardiovascular function and infection risk [35].

BULLOUS PEMPHIGOID TREATMENT STEPS
General maintenance
Drainage of blisters
Prevention of local infections
Localized disease
Super potent topical corticosteroids (e.g., clobetasol propionate)
Topical immunomodulators (e.g., tacrolimus)
Nicotinamide in association with minocycline, doxycycline or tetracycline
Erythromycin
Dapsone, sulfonamides
Extensive or refractory disease
Oral corticosteroids
Azathioprine
Mycophenolate mofetil
Methotrexate
Chlorambucil
Cyclophosphamide
IVIg
Plasma exchange
Rituximab

The treatment of PG is similar to that of BP. But teratogenic side effects of some therapeutical agents for BP limit their usage during pregnancy. Mild cases of PG can be successfully treated with topical corticosteroids. But halogenated corticosteroids can cross the placenta, so class 6 and 7 corticosteroids are the safest (e.g., mometasone furoate, prednicarbate, methylprednisolone aceponate). For systemic treatment, prednisolone is the main choice because it is largely inactivated in the placenta (mother:fetus = 10:1). During the first trimester, especially between 8 and 11 weeks, there is a slightly increased risk of cleft lip/cleft palate. Nevertheless, if dosages are <10–15 mg/day, it appears to be safe. But for long-term use, risk of adrenal insufficiency in the newborn should be kept in mind, and fetal growth should also be monitored [112]. A few refractory cases may be treated with dapsone, doxycycline or minocycline ± nicotinamide, pyridoxine, cyclosporine, methotrexate, cyclophosphamide, gold and IVIg. But all these agents

with the exception of cyclosporine and IVIg should be avoided during pregnancy period. Plasmapheresis may be a rather safe treatment option during pregnancy if corticosteroid is contraindicated or fails to control the disease [34].

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