Chapter 11
Rare Autoimmune Blistering Disorders

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Abstract The spectrum of autoimmune blistering disorders continues to evolve as previous associations become new entities, and these entities demonstrate distinct clinical, histologic, and immunohistochemical characteristics. The rare autoimmune blistering disorders present both diagnostic and therapeutic challenges to clinicians. Diagnostically, there can be overlapping features between the rare and more common autoimmune diseases. From a therapeutic standpoint, there is a general lack of studies that demonstrate treatment efficacy and outcomes in these entities leading to clinical practice gaps. This chapter will review the clinical and histological features of lichen planus pemphigoides (LPP), bullous lichen planus (BLP), bullous systemic lupus erythematosus (SLE), IgA pemphigus, and subcorneal pustular dermatosis (SPD), and provide an evidence-based review of the treatment options reported in the literature.

Keywords Autoimmune bullous • Lichen planus pemphigoides • Lichen planus • Bullous pemphigoid • IgA pemphigus • Bullous lupus • Subcorneal pustular dermosis • Sneddon-Wilkinson

Abbreviations

BP	Bullous pemphigoid
BMZ	Basement membrane zone
BP180	Bullous pemphigoid 180 antigen
BP230	Bullous pemphigoid 230 antigen
C3	Complement component 3
DIF	Direct immunofluorescence
DEJ	Dermoepidermal junction
Dsc1	Desmocollin-1

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N. Sami (ed.), *Autoimmune Bullous Diseases: Approach and Management*,
DOI 10.1007/978-3-319-26728-9_11

Dsg1	Desmoglein-1
Dsg3	Desmoglein-3
EBA	Epidermolysis bullosa acquisita
ELISA	Enzyme-linked immunosorbent assay
H&E	Hematoxylin and eosin
IgA	Immunoglobulin A
IEN	Intraepidermal neutrophilic
IgG	Immunoglobulin G
IIF	Indirect immunofluorescence
LP	Lichen planus
LPP	Lichen planus pemphigoides
NC	Non-collagenous
PUVA	Psoralen plus ultraviolet A
SLE	Systemic lupus erythematosus
SPD	Subcorneal pustular dermatosis
TNF	Tumor necrosis factor

Lichen Planus Pemphigoides

Clinical Features

Lichen planus pemphigoides (LPP) is a rare autoimmune bullous disorder, with less than 100 cases described in the English literature to date. It is characterized by the presence of lesions of lichen planus (LP) as well as vesicles and bullae arising in areas of LP and in uninvolved skin [1, 2]. The vesicles and bullae are subepidermal and demonstrate features of bullous pemphigoid (BP), including the presence of bullous pemphigoid 180 antigen (BP180) [2]. When LPP was first reported, there was controversy over whether it represented two coinciding conditions or a single disease with characteristics of both lichen planus and bullous pemphigoid. It is now understood to be a separate entity that consists of features of LP and BP, and is distinguishable from BP by the nature of the circulating autoantibodies. While BP180 is present in both LPP and BP, autoantibodies react to region 4 within the BP180 non-collagenous (NC)-16a domain in LPP, whereas autoantibodies in BP react to regions 2 and 3 [2]. Diagnostic criteria for LPP used by some authors include: lesions with the clinical appearance of vesicles or bullae arising on both lesions of LP and uninvolved skin, histopathology demonstrating both a subepidermal blister and features of LP, and direct immunofluorescence (DIF) of peri-lesional skin demonstrating linear deposition of complement component 3 (C3) and/or immunoglobulin G (IgG) along the dermoepidermal junction (DEJ) [3].

LPP usually presents in middle-aged adults, with a slight female preponderance and no particular racial predominance [1, 3]. In a review of 78 cases of LPP, the mean age at diagnosis was 54 years, with a peak in incidence among adults in their fifth and sixth decades of life [3]. LPP occurs rarely in children, with less than 20 cases of childhood LPP described to date [4]. In a review of 12 children with LPP,

the mean age at diagnosis was 12 years and there was a higher incidence in boys [5]. Clinically, LPP is characterized by the development of lesions typical of lichen planus followed by the development of tense vesicles and bullae, though rare cases have been reported with lichen planus and bullous lesions occurring concomitantly. The lesions of LP are erythematous or violaceous papules and plaques that are classically described as pruritic, polygonal, and planar (Fig. 11.1) [4]. In the following weeks to months, bullous lesions arise in areas of erythema, normal skin, the oral mucosa, or within lichenoid lesions (Fig. 11.2). Similar to the presentation of bullous pemphigoid, the blisters of LPP are tense, dome-shaped, and can be hemorrhagic or contain clear fluid. Bullae tend to develop on the extremities, although they have been reported as generalized eruptions in few patients [3]. Oral mucosal involvement in

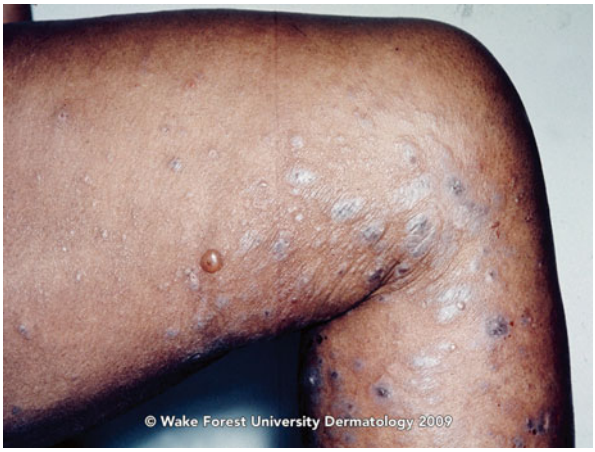

Fig. 11.1 Lichen planus pemphigoides. Violaceous, polygonal, flat-topped lesions of lichen planus on the lower extremity with a tense, dome-shaped blister

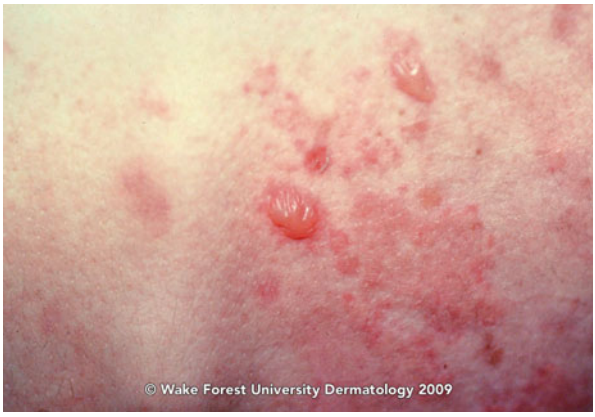

Fig. 11.2 Lichen planus pemphigoides. Clear fluid-filled tense bullae arising on erythematous skin

the form of erosions, white dots, and streaks are also seen in a minority of patients (36 %). On average, the average time elapsed between the development of LP lesions to the development of vesiculobullous lesions of LPP is 8.3 months, while simultaneous appearance of lesions has been observed in up to 6 % of cases [3].

Histologically, the lichenoid lesions of LPP demonstrate classic histopathological features of lichen planus and the bullae demonstrate features of bullous pemphigoid [1]. Biopsy specimens with hematoxylin and eosin (H&E) staining from cutaneous lichenoid lesions demonstrate hyperkeratosis, hypergranulosis, and acanthosis. Colloid bodies of Civatte are seen in some cases, with a band-like lymphocytic infiltrate in the upper papillary dermis. Vesicles and bullae demonstrate a subepidermal blister with associated edema and infiltration of eosinophils, and perivascular mixed inflammatory infiltrates consisting of eosinophils, histiocytes, and lymphocytes [3]. Direct immunofluorescence studies performed on peri-lesional skin biopsies show linear deposition of IgG, C3, and fibrinogen along the basement membrane zone (BMZ) [4]. Indirect immunofluorescence (IIF) studies demonstrate circulating IgG autoantibodies to keratinocyte cell surfaces. When performed, enzyme-linked immunosorbent assay (ELISA) tests often demonstrate positivity for IgG antibodies to desmoglein-1 (Dsg1), BP180, and BP230 [2–4].

The pathogenesis of LPP is not completely understood. Although most cases are idiopathic, there are few reports of LPP developing in association with drugs, phototherapy, and in one case, hepatitis B virus infection [6–9]. The most common culprit medications reported are angiotensin converting enzyme inhibitors such as ramipril and captopril [7–9]. One theory suggests that damage to basal cells in LP can expose sequestered antigens or produce new antigens that lead to autoantibody formation and subsequent bullous lesions. In a study examining circulating antibodies before and after the diagnosis of LPP, autoantibodies to the basement membrane zone were detectable after the development of bullae, but not before. Furthermore, once the bullae were controlled with therapy, anti-BP180 antibodies were no longer detectable [2]. The diagnosis of LPP can be confirmed based on histopathological findings of both LP and subepidermal bullae, and DIF findings of linear deposits of IgG and/or C3 in the BMZ [3].

Systemic Treatment

Systemic Corticosteroids

The use of systemic corticosteroids to treat LPP has been reported most widely in the literature. In greater than half of the cases, systemic corticosteroids alone have been used to successfully treat LPP. In most reports, the bullous eruption resolves within a few weeks of therapy and while there have been relapses reported in patients after several years of disease clearance, the recurrence rate of LPP appears lower than the rate seen in bullous pemphigoid. The recommended dosage is 0.5 mg/kg daily, or 40–60 mg daily for adults [10].

Although systemic corticosteroid therapy is an effective first-line therapy that has demonstrated good clinical response, there are undesirable side effects, particularly in children. In rare reports of LPP in children, different systemic agents were required after difficulty tapering systemic steroid treatment. In one case of LPP in a 2-year-old child, the disease was controlled with systemic corticosteroids at a dose of 2 mg/kg daily. However, attempts to taper the dose below 1 mg/kg daily resulted in recurrent flares of severe bullous disease. The patient was begun on low dose methotrexate and was able to be successfully tapered off systemic steroids [11]. In another case of LPP in a 6-year-old child, topical corticosteroid therapy resulted in no response, and oral prednisolone at 1 mg/kg/day resulted in the cessation of bullae formation within 4 days. However, tapering resulted in flares at 5 and 10 weeks, and again when steroids were stopped. During 2 years of follow-up, the patient had recurrence of LP lesions but not bullous lesions [5].

Dapsone

Dapsone (4,4′-diaminodiphenyl sulphone), traditionally used as an anti-infectious agent, has demonstrated many uses for noninfectious inflammatory dermatologic diseases. There are several cases in adults and children that have documented the successful treatment of LPP with dapsone, either as a single agent or in combination with other systemic agents. In two reports of adults with LPP, dapsone was used in conjunction with oral methylprednisolone and resulted in disease control. After 12 weeks on oral steroids and 16 weeks of dapsone, one patient had no recurrence of any skin lesions after 1 year [12]. In another patient who was previously treated with erythromycin and nicotinamide with little response, dapsone 50 mg daily was used with topical corticosteroids. Within 1 week, bullous lesions began to regress and dapsone was continued for 4 months until complete clearance was achieved. Over 18 months of follow-up there were no recurrences of bullous lesions, although lesions of LP recurred and were managed with topical corticosteroids [13]. There are also reports of poor response to dapsone. In a patient treated with dapsone 100 mg/day, no response was seen after 2 weeks. Once therapy was switched to oral methylprednisolone, there was expedient resolution of skin lesions and steroid therapy was discontinued after only 2 months [12].

In a report of two cases of childhood LPP, both patients were treated successfully with a combination of topical corticosteroids, oral prednisolone, and dapsone. In one patient, clinical remission was achieved within 10 months, and BP180 ELISA remained borderline positive. In another patient, systemic treatment lasted for 19 months, and the patient had mild recurring LP plaques 2 years later that responded to topical steroids, while the BP180 ELISA remained borderline positive [4].

Antibiotics and Nicotinamide

The combined use of antibiotics and nicotinamide (or niacinamide) has been reported in autoimmune bullous diseases. This combination of drugs acts to inhibit

neutrophil or eosinophil chemotaxis, inhibit antigen-induced histamine release, suppress antigen responses, and suppress lymphocyte transformation [14]. In the treatment of LPP, therapy with erythromycin and nicotinamide has been reported in children, whereas tetracycline antibiotics have been used in adults, with varying success. In a child diagnosed with LPP, the patient was to begin therapy with dapsone 50 mg daily and topical steroids, but while awaiting the results of glucose-6-phosphatase testing, began treatment with oral erythromycin 30 mg/kg daily in four divided doses and nicotinamide 150 mg three times a day. After 1 week, this was then replaced by dapsone 50 mg daily and topical steroids. The patient had cessation of new bullae within 1 week, and had complete clearance by 4 months. After an 18-month period of follow-up, the patient had no recurrence of bullae, and lesions of LP were treated with topical corticosteroid therapy [13].

In an adult with LPP, initial treatment with oral prednisone induced remission of the disease, but in the presentation of a new flare 3 years later, the patient was treated with tetracycline 500 mg four times daily and nicotinamide 500 mg three times daily. This regimen led to rapid clearance of skin lesions, however, tetracycline was replaced with doxycycline 100 mg twice daily due to the development of renal insufficiency. Bullous eruptions recurred at each attempt to discontinue doxycycline and nicotinamide, and would respond to reinstitution of both drugs [14].

Other Immunosuppressive Agents

Methotrexate has been used as an adjuvant immunosuppressive agent with prednisolone. In one report, a young child with LPP demonstrated response to prednisolone 2 mg/kg daily, but attempts to taper below 1 mg/kg daily resulted in a severe flare of the bullous component of the disease. Methotrexate 0.5 mg/kg daily was initiated and led to disease clearance after 4 weeks of treatment, and prednisolone was tapered over 8 weeks. Follow-up testing of serum anti-BP180 autoantibodies demonstrated decreasing levels along with clinical improvement. After 11 months of treatment with methotrexate, serum level of anti-BP180 autoantibodies decreased from 173 to 42 U/mL and the patient had no recurrence of disease during follow-up [11].

There are sparse reports of azathioprine being used as an adjunctive treatment for LPP. Only one case has been reported in which a patient was treated with combination therapy with prednisolone 40 mg daily, azathioprine 100 mg daily, and topical steroids. Disease control was maintained with prednisolone 25 mg and azathioprine 100 mg daily, although there was no report of subsequent follow-up [10].

In a case of prednisolone-resistant LPP, a patient with extensive lesions involving the soles and oral mucosa was treated with low dose cyclosporine A in combination with prednisolone. After the patient had minimal response to prednisone at 0.4 mg/kg daily, low dose cyclosporine A at 2 mg/kg daily was added and led to improvement of vesicles and bullae. As the patient's clinical lesions improved and the anti-BP180 antibody titer index decreased, cyclosporine A and prednisone were tapered, and the patient remained in remission [15].

Current Opinions

Lichen planus pemphigoides has features of both bullous pemphigoid and lichen planus, which can make treatment with just one modality suboptimal. Based on the severity of the disease, which is defined by the extent of body surface area involvement and severity of symptoms such as pruritus, treatments range from topical therapy to systemic immunosuppressive agents. Topical corticosteroids are an effective and safe first-line treatment in patients with limited cutaneous involvement, as it is used to treat both localized lichen planus and bullous pemphigoid. In cases with extensive cutaneous and/or mucosal involvement requiring systemic treatment, the most studied therapeutic agent for LPP is oral prednisolone. Compared to bullous pemphigoid, LPP has a much younger age of onset and typically follows a less severe clinical course, which makes corticosteroids a reasonable first-line treatment option. However, in patients with contraindications to systemic steroid therapy or in young children, dapsone is the next most commonly reported agent. Dapsone has demonstrated favorable results particularly in younger patients in whom chronic therapy with systemic corticosteroids is undesirable. However, if there are contraindications to dapsone such as glucose-6-phosphatase deficiency or the development of hemolytic anemia, other immunosuppressants such as methotrexate, azathioprine, and cyclosporine can be considered, although the literature reporting on the efficacy of these agents is sparse and anecdotal (Table 11.1). The use of combination therapy with antibiotics and nicotinamide is less favorable due to reports of patients with indefinite treatment duration and disease flares associated with discontinuation.

Deciding whether or not to discontinue a therapy or add an additional therapy can be difficult and depends largely on the extent of clinical response. When treating with systemic corticosteroids, many clinicians use the cessation of new bullae formation within the first 7–14 days as a sign of good clinical response in the initial treatment period. Beyond the initial clinical response, the next challenges are achieving a full clinical response and maintaining disease clearance while tapering medication(s). In the rare cases of extensive disease involvement including the oral mucosa, additional therapeutic measures such as dapsone can be useful adjunct treatments. Once disease control is achieved, tapering must be performed with close monitoring, either with follow-up clinic visits or telephone follow-up at a minimum of weeks 2, 4, 8, and 12. There is wide variability in response to tapering medications, evident by the variable lengths of total treatment periods reported in the literature, ranging between 3 and 18 months, and in some cases, indefinite maintenance therapy. While some patients demonstrate disease stability with no recurrence, other patients demonstrate rapid disease recurrence with medication tapering.

Discussion/Areas of Future Interest

There is limited literature on the efficacy of treatment options for LPP. The lack of evidence for the use of non-steroidal systemic agents is likely reflective of the extent of the typical success of systemic steroids in treating the disease. Few studies report

Table 11.1 Summary of rare autoimmune bullous diseases and treatment algorithm

Disease	Clinical presentation	Histology	Immunofluorescence	1st line treatment	2nd line treatment	3rd line treatment (anecdotal evidence only)
Lichen planus pemphigoides	Lesions of lichen planus with tense vesicles and bullae in areas of LP and normal skin	Hyperkeratosis, hypergranulosis, and band-like lymphocytic infiltrate in the upper papillary dermis, with subepidermal blister with associated edema and eosinophils	**DIF**: Linear deposition of IgG, C3, fibrinogen along BMZ **IIF**: Circulating IgG to Dsg1, BP180, and/or BP230	Systemic steroids (0.5 mg/kg/day)	Dapsone (50–100 mg/day)	Methotrexate Azathioprine Cyclosporine
Bullous lichen planus	Lesions of lichen planus with vesicles and bullae formation over pre-existing papules and plaques	Hyperkeratosis, hypergranulosis, basal vacuolar cell degeneration, with subepidermal blister containing fibrin, eosinophils, and neutrophils	**DIF**: No linear deposition of IgG or C3. Coarse granular deposits of fibrinogen at DEJ only **IIF**: No circulating antibodies	Systemic steroids (0.5 mg/kg/day)	Dapsone (200 mg/day as single therapy) (25–50 mg/day if used as adjuvant therapy) Acitretin (30 mg/day)	Cyclosporine (1–5 mg/kg/day)
Bullous systemic lupus erythematosus	Vesicles and bullae coalescing to form elongated, arciform, or irregular shapes	Subepidermal blister with neutrophils, karyorrhectic debris with occasional lymphocytes, histiocytes, and eosinophils	**DIF**: Granular or linear deposition of IgG, IgA, IgM, and/or C3 in BMZ **IIF**: Circulating IgG to type VII collagen (NC1)	Dapsone (25–50 mg/day)	Methotrexate Mycophenolate mofetil	Rituximab Systemic steroids

IgA pemphigus	Vesicles and bullae that evolve into pustules that coalesce into annular or circinate lesions with central crust	Intraepidermal neutrophilic pustules or vesicles and neutrophilic infiltration in the epidermis	**DIF**: IgA deposition throughout entire epidermis (IEN) or upper epidermis only (SPD). **IIF**: Circulating IgA1 only	Systemic steroids (0.5–1.0 mg/kg/day)	Dapsone (25–125 mg/day) Acitretin	Colchicine (0.5–2 mg/day) Adalimumab
Subcorneal pustular dermatosis	Vesiculopustular lesions that coalesce to form annular or circinate lesions that evolve into crusted lesions with pustules at the periphery	Subcorneal separation with aggregates of keratin and neutrophils within the clef	**DIF**: Negative for IgA and IgM **IIF**: No circulating antibodies	Dapsone (50–200 mg/day)	Colchicine (0.5 mg twice daily) Etretinate/acitretin	Infliximab Etanercept PUVA Systemic steroids

DIF direct immunofluorescence, *IIF* indirect immunofluorescence, *BMZ* basement membrane zone, *Dsg* desmoglein, *BP* bullous pemphigoid, *mg* milligrams, *DEJ* dermoepidermal junction

on the level of autoantibody titers throughout the course of the disease, although it can be used as a guide for response to treatment. Further research is needed to evaluate the utility of monitoring autoantibody levels and the correlation between autoantibody titers and disease severity.

Bullous Lichen Planus

Clinical Features

Bullous lichen planus is a variant of lichen planus that presents with typical lesions of LP and vesicles and bullae over pre-existing papules and plaques. Unlike LPP, the bullae are often less extensive, and bullae tend to form only in areas of involved skin with lesions of LP, with few bullae rarely occurring in the adjoining skin (Fig. 11.3) [16]. In contrast, the bullous lesions of LPP form on both lesions of LP and normal skin. The bullous component of bullous LP is most prominent during an LP flare and has a similar distribution to lichen planus, with a predilection for the trunk and extremities. Pruritus is a common presenting symptom, which can precede the development of erythematous or violaceous papules and plaques with bullae forming at the periphery. The bullae are tense, non-hemorrhagic, and can form as a group of numerous vesicles [17, 18]. Oral involvement is uncommon but can occur in this entity. It usually presents as fluid-filled vesicles with surrounding reticular white streaks, often on the buccal mucosa and less commonly on the gingiva and inner aspect of the lips [19–21].

Histologically, bullous LP demonstrates features of lichen planus such as hyperkeratosis, focal hypergranulosis, prominent basal vacuolar cell degeneration, and

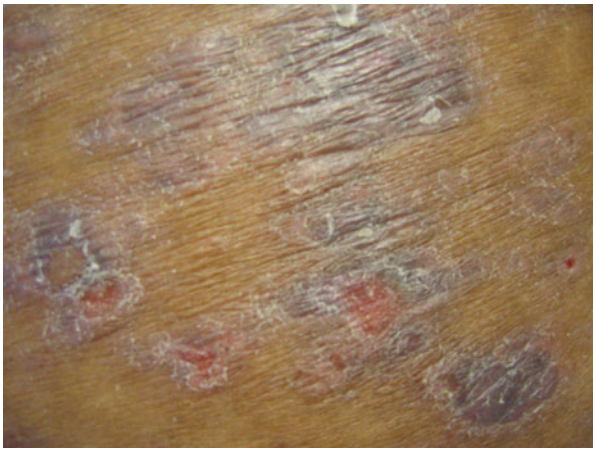

Fig. 11.3 Bullous lichen planus. Erosions where bullae occurred within lesions of lichen planus

band-like lymphohistiocytic cell infiltrates in the upper dermis with few eosinophils that hug the epidermis, leading to the creation of a subepidermal cleft [16]. The subepidermal bullae contain fibrin strands, eosinophils, neutrophils, and occasional histiocytes. Inflammatory cells are also found along the BMZ at the edge of the blister, and perivascular lymphohistiocytic infiltrates can be seen in the papillary and reticular dermis. Although bullous LP can be clinically resemble bullous pemphigoid and LPP, DIF will characteristically lack the linear deposits of immunoglobulins and C3 at the BMZ, and show only reticular and coarse granular deposits of fibrinogen at the dermoepidermal junction. Indirect immunofluorescence will demonstrate immunoglobulins in the stratum granulosum with no circulating antibodies [18, 20].

The pathogenesis of bullae in this entity is thought to be due to upper dermal inflammation, extensive liquefactive degeneration and vacuolation of the basal layer [5]. Few cases have reported bullous LP occurring in response to certain drugs such as intravenous contrast, labetolol, and hepatitis B virus vaccines [22–24]. Theories behind this association suggest that drug-induced lichen planus can be initiated by a cell-mediated immune response to an induced antigenic change in the skin or mucosa. From a diagnostic perspective, bullous LP can clinically be mistaken for bullous pemphigoid or LPP; however, the indirect and direct immunofluorescence assays are distinct in bullous LP and will guide the diagnosis.

Treatment

Systemic Corticosteroids

Corticosteroids are considered the first-line and the most widely used therapeutic agent to treat lichen planus and its variants [25]. Systemic steroids are used in cases of LP that are refractory to topical therapy, extensive in body surface area involvement, or in exanthematous or ulcerative forms. Lichen planus is generally responsive to corticosteroids, and bullous LP appears to have a similar response profile. In case reports that describe the treatment of bullous LP with systemic steroids, the most common doses reported are prednisolone 0.5–1.0 mg/kg daily. In one report of an adult patient, oral prednisolone 40 mg daily was used to treat bullous LP, and was tapered in 6 weeks leading to regression of all skin lesions and with no disease flare or relapse throughout a 6-month follow-up period [16]. Systemic steroids were also reported in a case of a child with bullous LP, at a treatment dose of 20 mg daily. After treatment for approximately 6 weeks, the patient had good response to therapy with no adverse effects. Oral mini-pulse therapy has also been reported in patients, using 5 mg betamethasone orally as a single daily dose on two consecutive days each week, in conjunction with topical betamethasone dipropionate twice daily. This was tapered to 0.5 mg each week, and stopped after 10 weeks. In pulse therapy, potential side effects are decreased and the authors reported adequate disease control with no recurrence after 12 months [26].

Acitretin

Although there are no specific studies or reports that discuss the use of acitretin in patients with bullous LP, it is one of the only treatments for lichen planus that has been studied in a double-blind placebo-controlled trial. In this study, patients with LP were treated with 30 mg acitretin daily for 8 weeks. In 64 % of all patients, there was remission or improvement of symptoms, including pruritus, papulosis, and erythema. Side effects were minimal, with cheilitis and dry mouth being the most commonly reported adverse reactions [25].

Cyclosporine

Cyclosporine has only been studied for the treatment of lichen planus in small uncontrolled case series or case reports. This agent is a systemic treatment that can be used for lichen planus after patients have demonstrated resistance or lack of response to acitretin and/or corticosteroids. Doses used in the literature have been reported between 1 and 5 mg/kg daily, as low doses appear to be sufficient to control the disease [25].

Dapsone

Dapsone has been reported in the treatment of lichen planus and its variants, used alone or more often as an adjunctive agent with corticosteroids. In a review of the use of dapsone as a single agent for lichen planus, 92 patients with any clinical variant of LP were treated with dapsone 200 mg daily for 16 weeks. Complete response was seen in 65 % of patients while 19 % achieved partial response to treatment [25]. In other cases, dapsone was used in combination with prednisone, either if prednisone alone did not achieve complete clearance of disease or as an additional agent during the tapering of steroids. In case reports of patients with LP involving the oral mucosa, dapsone appeared to have increased efficacy in improving oral lesions and in tapering prednisone. Patients were initially treated with 40 mg of prednisone daily, and as prednisone was decreased to 20 mg daily, dapsone at 25 mg daily was added to prevent disease flare. However, in another report, low dose dapsone (25 mg daily) and systemic steroids were sufficient to induce remission in a patient, but tapering to low doses of either dapsone or prednisone resulted in disease flares, which were treated with higher doses of dapsone (50 mg for the first flare, and 100 mg for the second flare) [18].

Current Opinions

There are no reports in the literature beyond anecdotal case reports that specifically evaluate or review the efficacy of different treatment methods for bullous LP. This is likely due to the fact that bullous LP is rare, underreported, and often treated by

clinicians under the same guidelines used for treating lichen planus, as this clinical variant does not require a markedly different treatment course. By and large, the main difference between bullous LP and classic lichen planus is the presence of bullae, which can be more concerning to the patient, and rupture and lead to the exposure of more cutaneous sources of entry for infection. Although there are few reports suggesting that bullous LP can be more resistant to treatment than classic LP, this generalization is solely based on anecdotal observations and individual experiences, as the incidence of bullous LP within the population of patients with lichen planus is still not well defined. Corticosteroids and acitretin either alone or in combination are the systemic therapies for lichen planus that have been most extensively used and reported. Adjunctive treatment options include cyclosporine and dapsone, with varying reports of success (Table 11.1) [17]. The approach to the treatment of bullous lichen planus is similar to that of lichen planus, although clinicians should be aware of a possibly higher rate of treatment resistance to the typical first or second-line treatments.

Areas of Future Interest

Further studies on the epidemiology and disease course of bullous LP are warranted. There is limited literature evaluating bullous LP separately from other clinical variants of LP, likely due to the rarity of the disease. Although some authors believe that the clinical course of bullous LP is more recalcitrant to standard therapies for lichen planus, there is scant data to support this notion. Areas of future interest include characterization of the epidemiology of bullous LP, features of the clinical course, and the potential role of other therapeutic options that are used for lichen planus, such as phototherapy.

Bullous Systemic Lupus Erythematosus

Clinical Features

Systemic lupus erythematosus (SLE) is a multi-organ system autoimmune disease that classically presents with cutaneous manifestations such as a malar rash, oral ulcers, discoid lesions, and photosensitivity, seen in up to 76 % of patients during the disease course. Bullous systemic lupus erythematosus is a rare autoantibody-mediated bullous dermatosis that is seen in 1–5 % of patients with SLE [27–29]. In an epidemiologic study in France, the incidence of bullous SLE was reported to be 0.2 cases per million people, and in a series of 67 patients with subepidermal immunobullous disorders, 3 % had bullous SLE [30]. Patients with SLE can also present with a wide range of antibodies that lead to autoimmune bullous dermatoses such as bullous pemphigoid, dermatitis herpetiformis, pemphigus vulgaris, pemphigus

foliaceus, linear IgA disease, and epidermolysis bullosa acquisita (EBA). Bullous SLE is a separate autoimmune bullous dermatosis that has been described more recently. It is characterized by a widespread vesiculobullous eruption, with clinical and histological findings resembling bullous pemphigoid or dermatitis herpetiformis. There are at least three different types of bullous SLE based upon the location of the autoantibody in the basement membrane. The most common type of bullous SLE demonstrates antibodies against components of type VII collagen, which can resemble EBA [28].

Clinically, bullous SLE is seen predominantly in African American women in the second and third decades of life. It has only been reported in rare cases in children and adolescents. In relation to SLE, the bullous eruption can occur before the onset of SLE or at any point throughout the disease course; however, patients with bullous SLE tend not to develop other cutaneous manifestations of lupus. Although the onset of bullous SLE eruptions does not necessarily parallel systemic disease activity, there are few reports of bullous flares coinciding with an exacerbation of SLE [31]. The primary lesions are tense vesicles and larger bullae that can be filled with either clear or hemorrhagic fluid and arise in erythematous or normal skin. Multiple vesicles or bullae can form in a cluster, which expand and coalesce to form elongated, arciform, or irregular shapes [30]. Several reports have described erythematous plaques with annular or targetoid erythema multiforme-like configurations. Patients can develop lesions on both sun-exposed and non-sun-exposed skin, but demonstrate a predilection for the flexural and extensor surfaces. Facial and intraoral involvement is relatively common, with common sites including the perioral skin, lip vermillion, oral mucosa, and tongue [32]. Less commonly, the upper trunk and supraclavicular regions are involved [1, 29]. Lesions can be asymptomatic or associated with pruritus or burning sensations. Intraoral lesions initially appear as tense bullae that evolve into painful erosions [33].

On histological examination, the blisters of bullous SLE are subepidermal and contain large numbers of neutrophils and karyorrhectic debris, with occasional lymphocytes, histiocytes, and eosinophils (Fig. 11.4). These findings can appear identical to the histology of dermatitis herpetiformis, which is characterized by subepidermal vesicles and papillary-tip neutrophil microabscesses. In biopsies of nonbullous skin, there are neutrophilic microabscesses in the subepidermis, and marked dermal edema with mixed inflammatory cell infiltrates consisting of neutrophils, eosinophils, lymphocytes, and histiocytes in the upper dermis. On DIF of lesional and perilesional skin, all major classes of immunoglobulins and C3 are often seen in the epidermal basement membrane zone and perivascularly in either granular (60 %) or linear (40 %) patterns [29, 30]. The granular pattern can be differentiated from the pattern seen in dermatitis herpetiformis as the pattern of deposition is not confined to the tips of the dermal papillae as they are in dermatitis herpetiformis. In terms of immunoglobulin deposition, IgG is nearly uni-

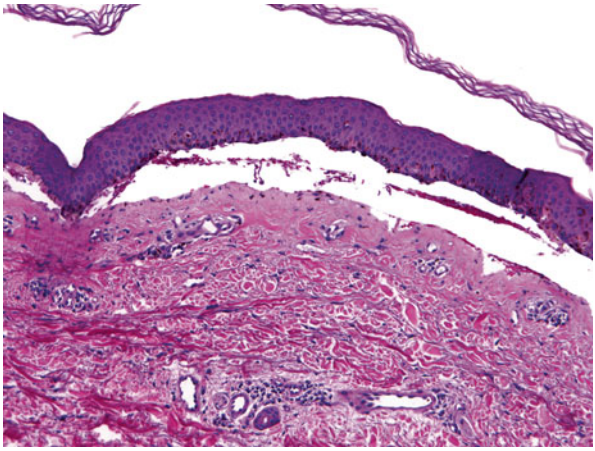

Fig. 11.4 Bullous systemic lupus erythematosus. Subepidermal bulla with neutrophils and karyorrhectic debris. H&E, 10×

versally present, observed in up to 100 % of patients, followed by IgA in 67 % and IgM in 50 %, and complement seen in 77 % of cases [1, 28]. Indirect immunofluorescence is negative for anti-BMZ antibodies [34]. Circulating antibodies are also found in bullous SLE, most commonly to type VII collagen in the NC1 domain.

The major antigenic epitope in bullous SLE is the fibronectin region of the NC1 domain of type VII collagen, which is also seen in patients with EBA. This region plays an important role in mediating the interaction between anchoring fibrils and other matrix proteins. By anchoring fibrils that cross-link the lamina densa and dermal matrix, this region helps to maintain adhesion at the DEJ. In bullous SLE, the presence of circulating antibodies against this epitope prevents interactions between the collagen and extracellular matrix, which leads to the formation of blisters and complement-mediated damage [29].

The diagnosis of bullous SLE can be challenging, as lesions can mimic those of bullous pemphigoid, linear IgA, and the inflammatory variant of EBA. The diagnosis can be made based on criteria that was originally proposed by Camisa and Sharma in 1983, which includes a diagnosis of SLE (according to criteria of the American College of Rheumatology), vesicles and bullae that arise on but are not limited to sun-exposed skin, histopathology compatible with dermatitis herpetiformis, negative IIF for circulating anti-BMZ antibodies, and DIF positive for IgG or IgM, and often IgA at the BMZ [34, 35]. Laboratory testing may reveal positive antinuclear antibody, positive anti-double-stranded DNA antibody, positive anti-Smith antibody, positive antiribonucleoprotein antibody, and/or hypocomplementemia [34].

Treatment

Dapsone

Dapsone is considered the mainstay of the treatment for bullous SLE. The striking response and clearance of lesions in response to dapsone can also be used to confirm the diagnosis, especially in cases where the clinical presentation is difficult to distinguish from EBA. Anecdotally, improvement with initiation of low doses (25–50 mg daily) of dapsone is usually dramatic, with cessation of new blister formation within 24–48 hours and clearance within 1 week. Although there are few studies that evaluate the efficacy of dapsone, in an analysis of 19 patients with bullous SLE, 17 showed improvement within days to weeks of initiation of 50–100 mg daily of dapsone therapy [36]. In one case of a young boy with bullous SLE resistant to systemic corticosteroids and mycophenolate mofetil (MFA), the addition of dapsone at a dose of 200 mg daily for 3 days led to significant regression of disease. The patient was continued on dapsone at decreased doses and tapered over 5 months [34]. Relapse of the disease can be seen with tapering and withdrawal of medication, although flares are rapidly responsive to reinstitution of therapy. Maintenance doses of dapsone between 25 and 50 mg/day are used during the taper process, and in most cases, dapsone can be discontinued with maintained disease control within 12 months [19, 30, 37].

Systemic Corticosteroids

Bullous SLE has demonstrated higher resistance to systemic corticosteroid therapy and other immunomodulators than other manifestations of SLE. High-dose corticosteroids are often used for the treatment of systemic symptoms of SLE, but are relatively ineffective in treating the cutaneous component [30]. However, in eruptions of bullous SLE that occur in the setting of SLE disease flares, treatment with both corticosteroids and other immunosuppressants is prudent [28].

Rituximab

Rituximab is a CD20 chimeric monoclonal antibody that has approved uses for non-Hodgkin lymphomas and rheumatoid arthritis. It has been used off-label in many autoimmune diseases, including SLE. In a report of one case, rituximab was used successfully in a patient with bullous SLE refractory to prednisone and immunosuppressives, including azathioprine and mycophenolate mofetil. After failure with these therapies, the patient was on prednisone and treated with two intravenous infusions of rituximab 1000 mg separated by 2 weeks. Cutaneous bullous lesions improved within 10 days of the first dose of rituximab, and cleared by 2 weeks after the second dose. The patient was subsequently able to be tapered down to 10 mg daily of prednisone [38].

Other Immunosuppressive Agents

Methotrexate has been reported in individual cases in the literature as an effective treatment in the treatment of bullous SLE. In one case report, a patient developed a severe bullous eruption concurrently with a flare of lupus serologies, which had previously been controlled. The patient also had an extensive history of intolerance to numerous drugs in the past, and was thus begun on therapy with oral methotrexate 10 mg weekly. This resulted in rapid and complete clearance of cutaneous lesions, with successful taper and discontinuation of methotrexate [39].

Mycophenolate mofetil is a 2-morpholinoethyl ester of mycophenolic acid that inhibits DNA synthesis by selective inhibition of inosine monophosphate dehydrogenase. It acts as an immunosuppressive agent by targeting T- and B-lymphocytes predominantly, inhibiting T- and B-cell proliferation, inducing apoptosis of T-cells, and inhibiting antibody production by B-cells. In one study of bullous SLE in childhood, MFA and erythromycin were used in combination to treat an eruption of bullous SLE. This combination was found to be an effective therapeutic regimen, with erythromycin acting as an anti-inflammatory agent [40, 41].

Current Opinions

Bullous SLE is a rare bullous cutaneous manifestation of SLE that is typically resistant to treatment with corticosteroids. Due to the rarity of disease, there is only anecdotal evidence upon which therapeutic measures can be guided. Dapsone at low-to-intermediate doses is often enough to induce remission of bullous lesions, as doses higher than 1.5 mg/kg daily tend to increase the risk of hemolytic anemia while not demonstrating any additional treatment efficacy. In cases that are more complex, either due to concurrent systemic and/or visceral symptoms of SLE or resistance to initial treatment, combination treatment with other immunosuppressives such as methotrexate and mycophenolate mofetil appear to have additional effectiveness. Corticosteroid therapy, which is noted to be relatively ineffective in treating bullous SLE as an isolated treatment, may be part of the treatment of bullous SLE when it occurs in the setting of a flare of SLE. Rituximab has only limited anecdotal evidence for its use in bullous SLE, and should be reserved in cases of treatment failure with other agents first (Table 11.1).

Areas of Future Interest

Further studies on the comparative efficacies of second-line immunosuppressive agents such as methotrexate and mycophenolate mofetil, among others, are needed. Currently, individual experiences are the driving force behind which second-line treatments are chosen by clinicians, and it is unclear which may be more effective

when bullous SLE occurs in isolation of systemic disease, compared to bullous SLE occurring in the setting of a SLE flare. The ability to distinguish optimal treatment measures in these two settings will likely have a significant impact on the clinical course of patients with this disease.

IgA Pemphigus

Clinical Features

IgA pemphigus is a rare autoimmune intraepidermal bullous entity, with only 70 cases reported in the literature up to 2010 [42]. Although the frequency and racial distribution are unknown due to the rarity of the disease, a review of case reports reveal a slight female predominance, and average age of presentation in the 5th decade of life [43]. There are various other terms that are synonymous to this entity, including intraepidermal neutrophilic IgA dermatosis, intercellular IgA dermatosis, intraepidermal IgA pustulosis, IgA pemphigus foliaceus, and IgA herpetiform pemphigus.

There are two types of IgA pemphigus identified, which include the subcorneal pustular dermatosis (SPD) type and the intraepidermal neutrophilic (IEN) type. Both types have a similar clinical appearance, but can be distinguished by antigen expression. The SPD type demonstrates reactivity against desmocollin-1 (Dsc-1), which is expressed most strongly in the upper epidermis. In the IEN subtype, the autoantigen has been identified as desmoglein-1 and/or desmoglein-3 (Dsg 3) [42]. Clinically, IgA pemphigus presents as a vesiculopustular eruption that can develop on normal or erythematous skin. While other types of pemphigus diseases will be positive for IgG autoantibodies, IgA pemphigus is characterized by the presence of tissue-bound and circulating IgA antibodies that target desmosomal or non-desmosomal cell surface components in the epidermis. The onset of lesions is typically subacute, and they initially present as tense bullae that evolve into flaccid fluid-filled blisters. As neutrophils accumulate, the lesions transform into pustules (Fig. 11.5) [43]. Multiple pustules often form in a group and coalesce into an annular, circinate or serpiginous pattern with a central crust. The areas most commonly involved are the axilla, groin, trunk and proximal extremities. Less commonly, there can be scalp, postauricular, and intertriginous involvement. Mucous membrane involvement is rare in this entity, with only one report of oral mucosal and perianal involvement [44]. Pruritus is reported in approximately 50 % of patients.

On histological examination, the hallmark finding of IgA pemphigus is the presence of intraepidermal neutrophilic pustules or vesicles and neutrophilic infiltration in the epidermis. Acantholysis may be seen, and is often mild when it is present. The extent of acantholysis seen in IgA pemphigus is less than that seen in classic pemphigus. In the subcorneal type, the pustules are located in the upper epidermis, whereas they are suprabasilar and involve the lower or entire epidermis in the intraepidermal type [42]. On DIF of perilesional skin, IgA deposition is seen on the cell surfaces of epidermal keratinocytes (Fig. 11.6). In the SPD type, IgA antibodies are only found in the upper

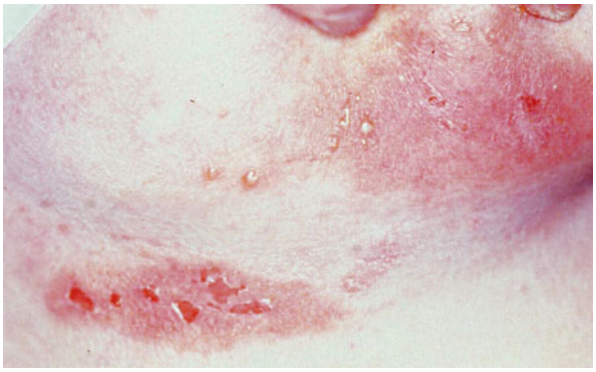

Fig. 11.5 IgA pemphigus. Vesicles and pustules seen in the inframammary region of a woman

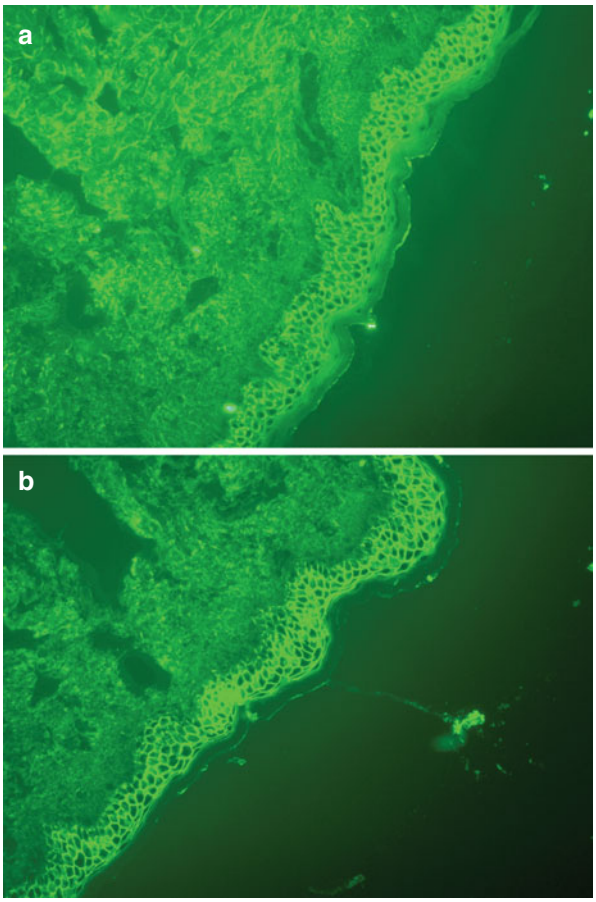

Fig. 11.6 IgA pemphigus. (**a**) DIF showing IgA deposition throughout the entire epidermis. (**b**) IgG deposition, demonstrating weaker staining than IgA

epidermis, whereas they are seen throughout the entire epidermis in the IEN type. Deposition of IgG or C3 may also be seen but will demonstrate weaker staining than IgA [42]. On indirect immunofluorescence, circulating IgA autoantibodies exclusively within the subclass of IgA_1 are seen. In contrast to classic pemphigus, the titers for autoantibodies are lower in IgA pemphigus, and the sensitivity of indirect immunofluorescence is approximately 50 % [43].

The pathogenesis of IgA pemphigus is thought to occur through the reaction of IgA to keratinocyte cell surfaces. The autoimmune targets of the IgA autoantibodies include Dsc1, Dsg1 and Dsg3. Desmocollin and desmoglein glycoproteins are members of the cadherin superfamily, which are calcium-dependent cell adhesion molecules. IgA antibodies bind to keratinocyte cell surface antigens, which leads to the accumulation of neutrophils in the epidermis and leads to intraepidermal blistering [45]. Thus, the gold standard for the diagnosis of pemphigus is demonstration of IgA autoantibodies directed against the cell surface of keratinocytes.

IgA pemphigus has been reported in association with malignancies, including IgA gammopathy, multiple myeloma, and chronic lymphocytic leukemia [42, 46, 47]. However, there are no reports of patients with IgA pemphigus with mortality linked directly as a result of IgA pemphigus, and thus is considered to be less life-threatening than other types of pemphigus [43].

Treatment

Systemic Corticosteroids

Systemic corticosteroids are considered to be the mainstay of treatment of IgA pemphigus, in combination with topical corticosteroids. The suggested dose when initiating steroid therapy is 0.5–1 mg/kg daily. However, few studies have demonstrated the efficacy of systemic steroids in IgA pemphigus in particular. In fact, in a case series of 9 patients with IgA pemphigus, 4 patients were treated with prednisone 0.5–1.5 mg/kg daily, and 3 had no response, while 1 patient had partial remission while on therapy [48].

Dapsone

The main effect of dapsone in the treatment of IgA pemphigus is thought to be through the suppression of neutrophil infiltration. Dapsone as a first-line treatment for IgA pemphigus was studied in a small case series of 6 patients. Patients received doses ranging from 25–125 mg daily. In 1 patient with IEN type disease, complete response was observed. In 2 patients with SPD type, only partial response was achieved. In the 3 remaining patients, dapsone was discontinued due to side effects of methemoglobinemia and hemolysis [48].

Colchicine

Colchicine has been studied in small subsets of patients with IgA pemphigus. The rationale behind colchicine as a potential therapeutic agent is its successes in treating other neutrophilic dermatoses. However, patients with IgA pemphigus have demonstrated limited response to colchicine. In a series of 5 patients treated with colchicine (0.5–2 mg per day), 4 patients did not respond to therapy, and the remaining patient was lost to follow-up [48]. In a report of 2 patients with SPD type IgA pemphigus treated with colchicine, clinical response was achieved within 2–3 weeks of therapy with colchicine 0.5 mg three times daily. However, despite initial responsiveness to therapy, relapses with severe disease exacerbations were noted each time colchicine was discontinued [49].

Retinoids

There are a few case reports that have described the use of retinoids such as isotretinoin and acitretin for the treatment of IgA pemphigus. In one study, isotretinoin, which is a first generation retinoid, was used to treat a patient with subcorneal pustular dermatosis type IgA pemphigus who was not effectively controlled with conventional therapeutic regimens. The patient demonstrated a rapid response to treatment with isotretinoin 20 mg daily, and had complete clearance of skin lesions within 3 weeks [50].

Acitretin, which is a metabolite of etretinate, a second-generation retinoid, has been reported as another second-line treatment option for patients with severe and/or treatment resistant IgA pemphigus. In one report, a patient with severe IgA pemphigus requiring frequent hospitalizations was treated with acitretin, and was only able to achieve partial remission on therapy [48]. In another case report, good response to acitretin in SPD type IgA pemphigus was seen in a patient with a new flare of disease. The patient was treated with 50 mg/day for 3 months with disease control, and then reduced to a maintenance dose of 25 mg every 2 days [51].

Adalimumab

Adalimumab is a recombinant human immunoglobulin antibody that targets tumor necrosis factor (TNF)-α. The mechanism for its effect in IgA pemphigus is thought to be due to the inhibition of TNF-α, which leads to the inhibition of neutrophil infiltration in the epidermis. In one case, adalimumab was used in conjunction with mycophenolate mofetil in a patient who had failed therapy, due to a lack of response to treatment or due to complications associated with alefacept, cyclosporine, acitretin, broadband ultraviolet B therapy, dapsone, methotrexate, and topical and oral corticosteroids [52].

Current Opinions

Similar to the classic autoimmune bullous dermatoses, corticosteroid therapy appears to be the most accepted first-line treatment for IgA pemphigus. As a disease within the pemphigus group, many clinicians may approach the treatment of IgA pemphigus similarly to the treatment approach to pemphigus vulgaris. Although systemic corticosteroid treatment seems to be anecdotally well accepted as first-line, the literature supporting the use of systemic corticosteroids is scant and controversial. Dapsone and colchicine, which demonstrate anti-inflammatory and anti-neutrophil effects, can also be used relatively safely and are treatment options to consider, especially if there are any relative or absolute contraindications to prolonged corticosteroid therapy. Retinoids are a second-line treatment option. However, disease flares are seen once therapy with retinoids is stopped, and long-term maintenance dosing appears to be necessary to maintain disease control. The use of biologics such as adalimumb is still being explored in IgA pemphigus, and should be considered third-line or in cases that have demonstrated resistance or treatment failure to numerous other therapies first (Table 11.1).

Areas of Future Interest

Despite the general acceptance of corticosteroids as first-line therapy, there is little evidence that demonstrates its efficacy in the treatment of IgA pemphigus. Studies that compare the efficacy of corticosteroids to other first-line treatment options such as colchicine and dapsone would be helpful in shedding light on the management of this disease. In treatments such as retinoids where anecdotal evidence is either sparse or mixed, further studies are indicated.

Subcorneal Pustular Dermatosis

Clinical Features

Subcorneal pustular dermatosis (SPD), also known as Sneddon-Wilkinson disease, is a rare chronic pustular dermatosis initially described by Sneddon and Wilkinson in 1956 [53]. It is seen in higher rates among middle-aged or elderly women, and is rarely seen in children or adolescents. It is characterized by a sterile pustular eruption that is often asymptomatic and follows a cyclic and relapsing course [54]. Classically, the pustules are described as half-pustular and half-clear fluid-filled blisters that coalesce to form annular or circinate lesions on normal or erythematous skin, which evolve into crusted lesions within days. The lesions heal centrally while new pustules may appear at the periphery (Fig. 11.7). The distribution of SPD is symmetric, with a predilection for flexural areas such as the axillae, groin,

abdominal folds, and inframammary areas. Involvement of the face, palms, soles, and mucous membranes is uncommon [55, 56].

Histological examination of a representative lesion demonstrates subcorneal separation with focal aggregates of keratin and neutrophils in the cleft. In the epidermis, mild spongiosis with focal exocytosis of neutrophils without acantholysis can be seen. In the upper dermis, there are patchy infiltrates composed of lymphocytes, histiocytes, and neutrophils. There can also be perivascular infiltration of neutrophils, and rarely eosinophils and mononuclear cells in the dermis that accompany the pustule formation (Fig. 11.8) [55]. In contrast to the subcorneal type of IgA pemphigus, direct immunofluorescence is negative for IgA and IgM in classic SPD, whereas IgA pemphigus will demonstrate positive immunofluorescence with intercellular IgA deposits against desmocollin-1 [56]. An important component of the diagnosis of SPD is demonstrating sterility of the subcorneal pustule filled with neutrophils, an absence of acantholysis, and negative immunofluorescence. Thus, staining for infectious etiologies are often obtained. Gram stains will be negative for bacteria and periodic acid-Schiff stain negative for fungal organisms.

Although the etiology of SPD is not clear, theories include infectious or autoimmune causes. There are known associations between SPD and other autoimmune-related disorders including pyoderma gangrenosum, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, hyperthyroidism, and multiple

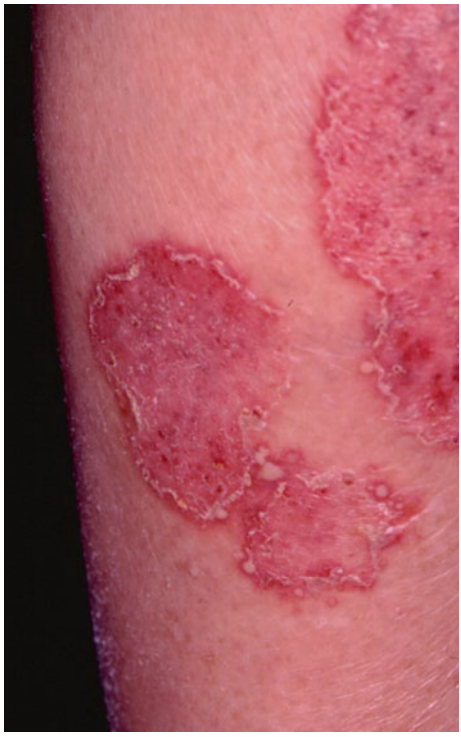

Fig. 11.7 Subcorneal pustular dermatosis. Annular, erythematous lesions with crust and pustules at the periphery

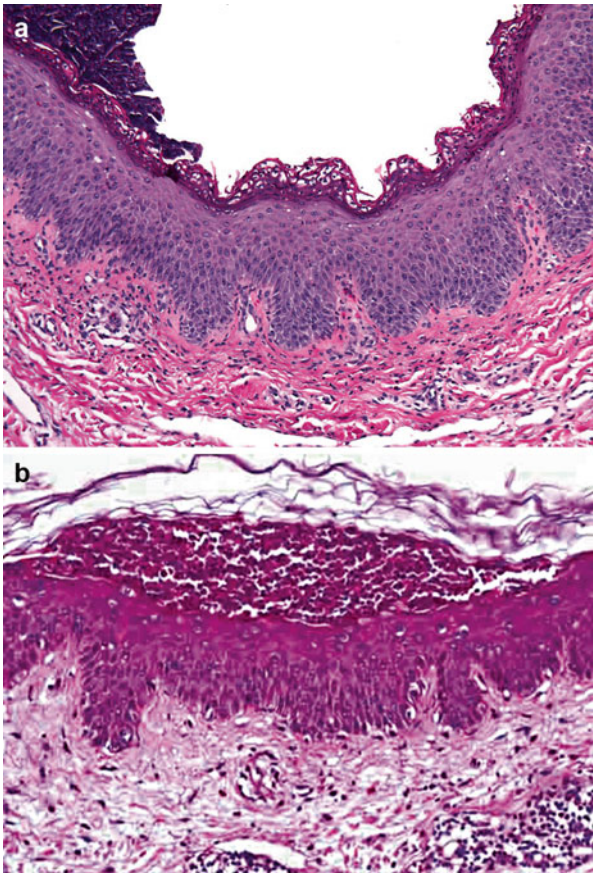

Fig. 11.8 Subcorneal pustular dermatosis. (**a**) Patchy infiltrates of lymphocytes, histiocytes, and neutrophils in the upper dermis. H&E, 10×. (**b**) Subcorneal separation with aggregates of keratin and neutrophils within the clef. H&E, 20×

myeloma, as well as anecdotal associations with mycoplasma pneumonia, Sjogren's syndrome, multiple sclerosis, and malignancies such as IgA myeloma. Some authors recommend basic screening in patients with this disorder for other common autoimmune diseases such as rheumatoid arthritis and monoclonal gammopathy and screening for underlying myeloma by evaluating for urine and serum paraproteinemia [56].

Treatment

Dapsone

Dapsone is considered a first-line agent for the treatment of SPD. Its mechanism of action is through the inhibition of the cytotoxic effects of peripheral neutrophils [58]. Most cases report a dramatic response to dapsone within 4 weeks of

treatment, and it is used in doses between 50 and 200 mg/day. In a case report of a child with SPD, dapsone 30 mg daily resulted in nearly complete healing of cutaneous lesions within 2 weeks of therapy. After 4 weeks, treatment was continued on alternate days for another month and then stopped with no recurrence or flare [54]. However, there are cases of refractory SPD or intolerance to dapsone due to methemoglobinemia or hemolytic anemia which can be limiting factors. In one report of resistant SPD, oral dapsone 50 mg daily was used in a patient for 3 months, and then in combination with colchicine for 3 months with no response. The patient had significant side effects of diarrhea and 20-pound weight loss and therapy was discontinued [56]. Furthermore, patients may require a maintenance dose to prevent disease flare [57].

Colchicine

Colchicine has a known inhibitory effect on polymorphonuclear leukocytes, and has known efficacy in the treatment of other dermatologic diseases characterized by leukocyte chemotaxis and neutrophilic infiltration such as Behcet's disease and Sweet's syndrome. In one report of colchicine use for SPD, colchicine was used as an alternative treatment in a patient who developed an allergic reaction to dapsone. The patient was started on oral colchicine 0.5 mg twice daily and the pustular lesions subsided within 1 week, after which the dose was reduced to 0.5 mg daily. The drug was well tolerated and there was no recurrence with discontinuation [59].

Retinoids

In a review of 12 cases of SPD treated with etretinate, almost all cases were initially resistant to dapsone and few had undergone trial with colchicine with no response. In all but two cases, complete response was seen after treatment with etretinate, ranging in dose from 20 to 100 mg daily. In the remaining cases, one patient showed partial response and one patient showed no response and was considered a treatment failure. However, almost all patients who responded to etretinate required continuous maintenance treatment after 15 months of treatment [60].

In another patient who failed treatment with dapsone, acitretin 0.5 mg/kg daily (25 mg/day) was used. The resolution of the pustular eruption was seen within 2 weeks, and the dose of acitretin was decreased to 10 mg daily. After 4 months of disease clearance, acitretin was discontinued, and no relapses were noted up to 30 months after discontinuation [61]. In a case of juvenile SPD, a 10-year old girl was treated with acitretin 0.5 mg/kg daily (10 mg/day). Within 4 weeks, the patient was noted to have almost complete clearance of cutaneous lesions, with the exception of few erythematous plaques on the hands. Treatment was continued with 10 mg acitretin every other day for 1 month, and there were no relapses or significant adverse events reported [55].

Biologics

There are few reports of patients with SPD treated with TNF-α inhibitors. In one case, infliximab was used in a patient with a 7-year history of SPD that was resistant to multiple therapeutic regimens including colchicine, retinoids, systemic glucocorticosteroids, UV phototherapy, azathioprine, and intolerant to dapsone. At one point, the patient initially had good response to acitretin 0.6 mg/kg daily and methylprednisolone 1.3 mg/kg daily used in conjunction, but eventually the clinical response to this regimen was no longer sufficient, and the patient was begun on infliximab. Infliximab was given as a single intravenous dose of 5 mg/kg, infused over 2 hours. Within 24 hours of receiving the first dose, the pustules disappeared within 2 days. Around 12 days after the infusion, pustules began to form again, and another infusion of infliximab was administered at 2 weeks, after which there was another mild relapse of papules without pustules. This minor flare was treated with oral methylprednisolone, and the patient's disease was maintained over 3 months with this treatment and with additional acitretin. The patient remained in remission on maintenance therapy with low dose acitretin [62].

In three cases reported in the literature, patients with recalcitrant SPD were treated with etanercept and achieved excellent disease clearance within 1 year. Two patients had previously failed treatment with dapsone, colchicine, acitretin, methotrexate, mycophenolate mofetil, psoralen plus ultraviolet A (PUVA), and narrowband ultraviolet B phototherapy. Both patients were treated with etanercept 50 mg twice weekly as monotherapy, and had significant improvement within 3–4 months. One patient demonstrated a flare of disease after 8 months, and adjunctive treatment with acitretin 25 mg every other day was sufficient in achieving disease clearance. At 13 months follow-up, patients were clear of disease, while continuing to take etanercept 50 mg twice weekly [63, 64].

Psoralen Plus Ultraviolet A

Psoralen plus ultraviolet A therapy has been used in SPD resistant to treatment with dapsone alone or in combination with colchicine. PUVA was initiated twice weekly for 6 weeks, followed by once weekly for 4 weeks, then once every other week for 2 months, and once a month thereafter. Mild flares of disease were seen with discontinuation of therapy, and maintenance PUVA therapy was required every 3 weeks [56]. There are also instances in which dapsone is initially effective, but after a flare and increase in dapsone dosing, patients continue to have inadequate control of disease. In one such case, the patient was additionally treated with PUVA for three sessions weekly on top of a lower dose of dapsone. Initial dosing was 1.5 J/cm^2. After 10 sessions, there was marked improvement, and after 15 sessions, the patient had almost complete clearance. After 5 weeks, the frequency of exposure was decreased to 2 sessions per week for 2 weeks, then 1 session per week. Six months after the initiation of PUVA, the patient required maintenance

with 1 session per week and 50 mg dapsone daily. In other reports, maintenance treatment is required, usually involving 1 session of PUVA per week, and dapsone 50 mg/day [65].

Systemic Corticosteroids

Systemic corticosteroids in conjunction with cyclosporine has achieved disease control in some cases after failure with first-line agents. In one case, treatment with dapsone, sulfapyridine, and acitretin were inadequate in controlling the disease, and upon presentation with a severe flare, the patient was treated with cyclosporine 3 mg/kg/day and prednisolone 1 mg/kg/day. Over 2 weeks the lesions resolved and healed with desquamation after 6 weeks. The patient was stopped on both drugs after 16 weeks, and had no flare, recurrence or complications over 12 months of follow-up [58]. In another case of severe SPD with diffuse cutaneous involvement and systemic symptoms of fever and leukocytosis, the patient was treated with cyclosporine 400 mg/day after developing an adverse reaction to dapsone. After 2 days of treatment, leukocytosis improved. Within 3 weeks, cyclosporine was discontinued as the pustular eruption showed marked improvement, and was clear within 4 weeks. The patient maintained therapy with prednisolone and was tapered over a course of 2 months [66].

Current Opinions

Dapsone is considered to be the first-line treatment for SPD due to its known efficacy in this entity. Despite differences in severity, a trial with dapsone should still be considered as first-line. Another agent to consider for SPD is colchicine, which has a well-established safety profile and efficacy in its use in patients with other neutrophilic dermatoses. Systemic retinoids, which have demonstrated uses in certain pustular dermatoses such as pustular psoriasis and pustulosis palmaris et plantaris, are not typically used in neutrophilic dermatoses, except in SPD. Retinoids show rapid effectiveness, and are usually better tolerated than dapsone, but often require maintenance therapy to avoid relapse of disease [55]. PUVA has demonstrated utility in the treatment of this disease, but requires patient compliance with regular visits and appears to require chronic maintenance therapy for disease control. Prolonged use of PUVA also carries risks of malignancies, which should be kept in mind in patients requiring chronic maintenance therapy. In cases where numerous other treatment agents have been exhausted, including systemic steroid therapy and other immunosuppressive medications TNF-α inhibitors have been used in a few reports with mixed success (Table 11.1). Appropriate laboratory work-up to rule-out occult infection should be performed prior to initiating treatment with anti-TNF-α agents.

Areas of Future Interest

There is a wide range of agents that have demonstrated some evidence of efficacy in the treatment of SPD; however it is difficult for clinicians to choose which agents to use once first-line therapy has failed. Further studies that can report on the efficacy of second-line therapies such as retinoids, PUVA, and steroids would assist in guiding treatment.

References

1. Calonje E, Brenn T, Lazaar A. Inherited and autoimmune bullous diseases. In: Calonje E, Brenn T, Lazar A, Mckee PH, editors. McKee's pathology of the skin. 4th ed. Saint Louis: Elsevier/Saunders; 2012.
2. Sekiya A, Kodera M, Yamaoka T, et al. A case of lichen planus pemphigoides with autoantibodies to the NC16a and C-terminal domains of BP180 and to desmoglein-1. Br J Dermatol. 2014;171(5):1230–5.
3. Zaraa I, Mahfoudh A, Sellami MK, et al. Lichen planus pemphigoides: four new cases and a review of the literature. Int J Dermatol. 2013;52(4):406–12.
4. Goldscheider I, Herzinger T, Varga R, et al. Childhood lichen planus pemphigoides: report of two cases treated successfully with systemic glucocorticoids and dapsone. Pediatr Dermatol. 2013;31(6):751–3.
5. Cohen DM, Ben-Amitai D, Feinmesser M, Zvulunov A. Childhood lichen planus pemphigoides: a case report and review of the literature. Pediatr Dermatol. 2009;26(5):569–74.
6. Maoz KB, Brenner S. Lichen planus pemphigoides triggered by narrowband UVB, paracetamol, and ibuprofen, with autoantibodies to 130 kDa antigen. Skinmed. 2008; 7(1):33–6.
7. Ben Salem C, Chenguel L, Ghariani N, et al. Captopril-induced lichen planus pemphigoides. Pharmacoepidemiol Drug Saf. 2008;17(7):722–4.
8. Zhu YI, Fitzpatrick JE, Kornfeld BW. Lichen planus pemphigoides associated with Ramipril. Int J Dermatol. 2006;45(12):1453–5.
9. Ogg GS, Bhogal BS, Hashimoto T, et al. Ramipril-associated lichen planus pemphigoides. Br J Dermatol. 1997;136(3):412–4.
10. Swale VJ, Black MM, Bhogal BS. Lichen planus pemphigoides: two case reports. Clin Exp Dermatol. 1998;23(3):132–5.
11. Duong B, Marks S, Sami N, Theos A. Lichen planus pemphigoides in a 2-year-old girl: response to treatment with methotrexate. J Am Acad Dermatol. 2012;67(4):e154–6.
12. Demirçay Z, Baykal C, Demirkesen C. Lichen planus pemphigoides: report of two cases. Int J Dermatol. 2001;40(12):757–9.
13. Harjai B, Mendiratta V, Kakkar S, Koranne RV. Childhood lichen planus pemphigoides – a rare entity. J Eur Acad Dermatol Venereol. 2006;20(1):117–8.
14. Fivenson DP, Kimbrough TL. Lichen planus pemphigoides: combination therapy with tetracycline and nicotinamide. J Am Acad Dermatol. 1997;36(4):638–40.
15. Washio K, Nakamura A, Fukuda S, Hashimoto T, Horikawa T. A case of lichen planus pemphigoides successfully treated with a combination of cyclosporine a and prednisolone. Case Rep Dermatol. 2013;5(1):84–7.
16. Verma R, Vasudevan B, Kinra P, et al. Bullous lichen planus. Indian J Dermatol Venereol Leprol. 2014;80(3):279.
17. Wagner G, Rose C, Sachse MM. Clinical variants of lichen planus. J Dtsch Dermatol Ges. 2013;11(4):309–19.

18. Camisa C, Olsen RG, Yohn JJ. Differentiating bullous lichen planus and lichen planus pemphigoides. J Am Acad Dermatol. 1984;11(6):1164–6.
19. Patil A, Prasad S, Ashok L, Sujatha GP. Oral bullous lichen planus: case report and review of management. Contemp Clin Dent. 2012;3(3):344–8.
20. Jindal R, De D, Kanwar AJ. Bullous oral lichen planus: an unusual variant. Indian Dermatol Online J. 2011;2(1):39–40.
21. Unsal B, Gültekin SE, Bal E, Tokman B. Bullous oral lichen planus: report of two cases. Chin Med J (Engl). 2003;116(10):1594–5.
22. Grunwald MH, Halevy S, Livni E, Feuerman EJ. Bullous lichen planus after intravenous pyelography. J Am Acad Dermatol. 1985;13(3):512–3.
23. Gange RW, Jones EW. Bullous lichen planus caused by labetalol. Br Med J. 1978; 1(6116):816–7.
24. Miteva L. Bullous lichen planus with nail involvement induced by hepatitis B vaccine in a child. Int J Dermatol. 2005;44(2):142–4.
25. Cribier B, Frances C, Chosidow O. Treatment of lichen planus: an evidence-based medicine analysis of efficacy. Arch Dermatol. 1998;134:1521–30.
26. Joshi A, Khaitan BK, Verma KK, Singh MK. Generalised and bullous lichen planus treated successfully with oral mini-pulse therapy. Indian J Dermatol Venereol Leprol. 1999;65(6):303–4.
27. dos Santos CE, Velho PH, Marques FM, Werner B, Aragão SC, Rachid Filho A. Bullous systemic lupus erythematosus in a pregnant woman: a case report. Rev Bras Reumatol. 2013;53(5):438–40.
28. Sebaratnam DF, Murrell DF. Bullous systemic lupus erythematosus. Dermatol Clin. 2011;29(4):649–53.
29. Grover C, Khurana A, Sharma S, Singal A. Bullous systemic lupus erythematosus. Indian J Dermatol. 2013;58(6):492.
30. Vassileva S. Bullous systemic lupus erythematosus. Clin Dermatol. 2004;22(2):129–38.
31. Poojary S, Rais S. Bullous systemic lupus erythematosus with lupus nephritis: a rare case of a subepidermal bullous disorder in a child. Cutis. 2012;89(1):17–21.
32. Nico MM, Lourenço SV. Multiple blisters along the lip vermilion are a clue to bullous lupus erythematosus. Acta Derm Venereol. 2012;92(4):404–5.
33. Anyanwu CO, Ang CC, Werth VP. Oral mucosal involvement in bullous lupus. Arthritis Rheum. 2013;65(10):2622.
34. Liu KL, Shen JL, Yang CS, Chen YJ. Bullous systemic lupus erythematosus in a child responding to dapsone. Pediatr Dermatol. 2014;31(4):e104–6.
35. Camisa C, Sharma HM. Vesiculobullous systemic lupus erythematosus. Report of two cases and a review of the literature. J Am Acad Dermatol. 1983;9:924–33.
36. Piette EW, Werth VP. Dapsone in the management of autoimmune bullous diseases. Dermatol Clin. 2011;29(4):561–4.
37. Sirka CS, Padhi T, Mohanty P, et al. Bullous systemic lupus erythematosus: response to dapsone in two patients. Indian J Dermatol Venereol Leprol. 2005;71(1):54–6.
38. Alsanafi S, Kovarik C, Mermelstein AL, Werth VP. Rituximab in the treatment of bullous systemic lupus erythematosus. J Clin Rheumatol. 2011;17(3):142–4.
39. Malcangi G, Brandozzi G, Giangiacomi M, et al. Bullous SLE: response to methotrexate and relationship with disease activity. Lupus. 2003;12(1):63–6.
40. Pehr K. Mycophenolate mofetil and erythromycin for bullous lupus erythematosus of childhood. J Cutan Med Surg. 2012;16(1):50–3.
41. Hamminga EA, Vermeer MH. Bullous systemic lupus erythematosus responding to mycophenolate mofetil. Eur J Dermatol. 2010;20(6):844–5.
42. Porro AM, Caetano Lde V, Maehara Lde S, Enokihara MM. Non-classical forms of pemphigus: pemphigus herpetiformis, IgA pemphigus, paraneoplastic pemphigus and IgG/IgA pemphigus. An Bras Dermatol. 2014;89(1):96–106.
43. Tsuruta D, Ishii N, Hamada T, et al. IgA pemphigus. Clin Dermatol. 2011;29(4):437–42.
44. Erdag G, Qureshi HS, Greer KE, Patterson JW. Immunoglobulin A pemphigus involving the perianal skin and oral mucosa: an unusual presentation. Cutis. 2007;80(3):218–20.

45. Geller S, Gat A, Zeeli T, et al. The expanding spectrum of IgA pemphigus: a case report and a review of the literature. Br J Dermatol. 2014;171(3):650–6.
46. Taintor AR, Leiferman KM, Hashimoto T, et al. A novel case of IgA paraneoplastic pemphigus associated with chronic lymphocytic leukemia. J Am Acad Dermatol. 2007;56:S73–6.
47. Aste N, Fumo G, Pinna AL, Biggio P. IgA pemphigus of the subcorneal pustular dermatosis type associated with monoclonal IgA gammopathy. J Eur Acad Dermatol Venereol. 2003;17(6):725–7.
48. Moreno AC, Santi CG, Gabbi TV, et al. IgA pemphigus: case series with emphasis on therapeutic response. J Am Acad Dermatol. 2014;70(1):200–1.
49. Hodak E, Lapidoth M, David M. Effect of colchicine in the subcorneal pustular dermatosis type of IgA pemphigus. J Am Acad Dermatol. 1999;40(1):91–4.
50. Gruss C, Zillikens D, Hashimoto T, et al. Rapid response of IgA pemphigus of subcorneal pustular dermatosis type to treatment with isotretinoin. J Am Acad Dermatol. 2000; 43(5):923–6.
51. Ruiz-Genao DP, Hernández-Núñez A, Hashimoto T, et al. A case of IgA pemphigus successfully treated with acitretin. Br J Dermatol. 2002;147(5):1040–2.
52. Howell SM, Bessinger GT, Altman CE, Belnap CM. Rapid response of IgA pemphigus of the subcorneal pustular dermatosis subtype to treatment with adalimumab and mycophenolate mofetil. J Am Acad Dermatol. 2005;53(3):541–3.
53. Sneddon IB, Wilkinson DS. Subcorneal pustular dermatosis. Br J Dermatol. 1956; 68(12):385–94.
54. Scalvenzi M, Palmisano F, Annunziata MC, et al. Subcorneal pustular dermatosis in childhood: a case report and review of the literature. Case Rep Dermatol Med. 2013;2013:424797.
55. Yayli S, Bahadir S, Alpay K, et al. A case of juvenile subcorneal pustular dermatosis successfully treated with acitretin. Int J Dermatol. 2006;45(9):1131–3.
56. Khachemoune A, Blyumin ML. Sneddon-Wilkinson disease resistant to dapsone and colchicine successfully controlled with PUVA. Dermatol Online J. 2003;9(5):24.
57. Cheng S, Edmonds E, Ben-Gashir M, Yu RC. Subcorneal pustular dermatosis: 50 years on. Clin Exp Dermatol. 2008;33(3):229–33.
58. Karadoğan SK, Aydoğan K, Başkan EB, Tunali S. A case of subcorneal pustular dermatosis treated successfully with a combination of cyclosporin and prednisolone. J Eur Acad Dermatol Venereol. 2007;21(4):536–7.
59. Pavithran K. Colchicine in the treatment of subcorneal pustular dermatosis. Indian J Dermatol Venereol Leprol. 1995;61(1):56–7.
60. Marlière V, Beylot-Barry M, Beylot C, Doutre M. Successful treatment of subcorneal pustular dermatosis (Sneddon-wilkinson disease) by acitretin: report of a case. Dermatology. 1999;199(2):153–5.
61. Canpolat F, Akpinar H, Cemil BC, et al. A case of subcorneal pustular dermatosis in association with monoclonal IgA gammopathy successfully treated with acitretin. J Dermatolog Treat. 2010;21(2):114–6.
62. Voigtländer C, Lüftl M, Schuler G, Hertl M. Infliximab (anti-tumor necrosis factor alpha antibody): a novel, highly effective treatment of recalcitrant subcorneal pustular dermatosis (Sneddon-Wilkinson disease). Arch Dermatol. 2001;137(12):1571–4.
63. Berk DR, Hurt MA, Mann C, Sheinbein D. Sneddon-Wilkinson disease treated with etanercept: report of two cases. Clin Exp Dermatol. 2009;34(3):347–51.
64. Bedi MK. Successful treatment of long-standing, recalcitrant subcorneal pustular dermatosis with etanercept. Skinmed. 2007;6(5):245–7.
65. Bauwens M, De Coninck A, Roseeuw D. Subcorneal pustular dermatosis treated with PUVA therapy. A case report and review of the literature. Dermatology. 1999;198(2):203–5.
66. Zachariae CO, Rossen K, Weismann K. An unusual severe case of subcorneal pustular dermatosis treated with cyclosporine and prednisolone. Acta Derm Venereol. 2000;80(5):386–7.