ORIGINAL REPORT

Clinical Features, Diagnosis and Treatment of Different Types of Paediatric Pemphigus

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Pemphigus is a rare and life-threatening autoimmune disease that is easily ignored in children. This study aimed to attract attention to pemphigus in the paediatric population for better understanding and recognition of the clinical characteristics and management in children's different subtypes of pemphigus. The case series involved a retrospective record review of 3 patients who were referred to a department of dermatology from January 2022 to January 2024. All patients experienced a delayed diagnosis, but were eventually definitively diagnosed with pemphigus vulgaris, pemphigus foliaceus, and pemphigus erythematosus, because they all have intraepidermal blisters and elevated serum antibodies against Dsg1/Dsg3. In all 3 cases, systemic corticosteroids were used in combination with or without steroid-sparing adjuvants. The patient with pemphigus vulgaris experienced a recurrence due to discontinuous treatment; the other 2 patients achieved mostly remission after treatment, with the length of follow-up ranging from 5 to 12 months. Pemphigus in children has its own clinical characteristics and similar literature concerning improved strategies for clinical assessment and treatments are reviewed and discussed.

Key words: pemphigus vulgaris; pemphigus foliaceus; pemphigus erythematosus; children; treatment.

Submitted Dec 20, 2024. Accepted after revision Feb 4, 2025

Published Mar 9, 2025. DOI: 10.2340/actadv.v105.42776

Acta Derm Venereol 2025; 105: adv42776.

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SIGNIFICANCE

We report 3 cases of different types of pemphigus that rarely occur in children and hope to attract attention to how to identify early and effectively manage pemphigus in the paediatric population.

Pemphigus is a group of chronic autoimmune blistering diseases characterized by flaccid blisters and erosions of the skin and/or mucosa, due to the presence of autoantibodies against the adhesion proteins (Dsg1 and/or Dsg3), which can hold keratinocytes in epithelia together. Pemphigus can lead to sociopsychological burden and is life-threatening if left untreated, due to it having a long and progressive course that is accompanied by a persistent loss of body fluids and proteins and secondary microbial infections (1).

Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are the 2 major types of pemphigus, which account for over 90% of pemphigus. PV is the most common type of pemphigus, encompassing approximately 70% of all cases (2, 3). Pemphigus mainly occurs in adults aged 40–60 years with a geographic and ethnic distribution (4). It is estimated to affect approximately 1–10 patients per 1,000,000 per year (5, 6), and the ratio of males to females is 1:1.1–5 (7). The incidence of pemphigus in the paediatric population has not been described in detail. It is estimated that 1.4–3.7% of PV cases occur in the paediatric population (8). However, another report suggests a prevalence of PV of 30.5/million children in Germany, with no sex preference (9). PF has regional variations and is quite common in local children, with incidences of 10–26% of cases occurring before the age of 14 years. However, the sporadic form of PF is very rare in children, and the mean age of onset is 7.7 years (10). Pemphigus erythematosus (PE), a benign form of PF with a female preference, has a reported age of onset ranging from 5–84 years and it seems a higher proportion of cases are in the age group 2.5–20 years (11, 12).

Due to its rarity and variability, there is often a delayed diagnosis and treatment in the paediatric group. The reported average time from first symptoms to a final correct diagnosis was 10 months (13,14). Reasons for this delay include lack of awareness in recognizing the clinical features and failure to make the correct diagnosis. Herein, we described 3 cases of PV, PF, and PE and review similar reports in child pemphigus. We aimed to attract attention to pemphigus in the paediatric population for better understanding and recognition of the clinical characteristics and management in this group.

MATERIALS AND METHODS

A total of 3 patients with a definite diagnosis of pemphigus who were hospitalized in the Department of Dermatology of the Children's Hospital of Chongqing Medical University were recruited from January 2022 to January 2024. Clinical data were obtained from electronic medical records. The skin biopsy spe-

cimens were collected after obtained informed consent by the parents. Haematoxylin-eosin (H&E) staining was done to check the intraepidermal blisters with acantholysis through histopathology; direct immunofluorescence (DIF) was done to check the intercellular deposits of IgG in the epidermis; and enzyme-linked immunosorbent assay (ELISA) was done to check the circulating IgG antibodies against Dsg3 and/or Dsg1.

The skin biopsy specimens and blood samples obtained from 3 patients with PV, PF, and PE. The clinical, histologic, serologic findings, and treatments are described as follows.

Case 1

A 5-year-old boy presented to us with a 6-month history of recurrent painful erosions in the mouth and glans. No familial history of auto-immune bullous disease was mentioned. He had been treated as a case of drug eruption for several days because he had suffered an upper respiratory tract infection and took some oral antibiotics before the outbreak of a rash a few days earlier. Physical examination showed diffuse encrustations and plaques on the scalp, irregular ulcerations in the mouth, flaccid blisters of different size on the extremities and trunk, partially ruptured into erosions with black-brown scabs and the fingernails were slightly affected (**Fig. 1**A–G). Nikolsky's sign was positive.

Laboratory tests were done to exclude paraneoplastic pemphigus (PNP) and bullous pemphigoid (BP). Blood chemistry, autoimmunity tests (e.g., ANA, ANCA, C3, C4, BP180, BP230), plus chest and abdominal enhanced CT were normal except for a positive microbiological detection from the skin lesions with *Pseudomonas aureus aerogenes* and *Enterobacter aeruginosa*. Skin biopsy found supra-basal blistering with acantholysis (Fig. 1H). DIF revealed intercellular IgG deposition (Fig. 1I) and ELISA was positive for both Dsg1 and Dsg3; a diagnosis of PV was made. During hospitalization, IV methylprednisolone (MPS) (2–4 mg/kg/day) was administered along with topical mometasone furoate and fusidic acid. A few days later, the skin and mucosal lesions began to improve. However, with the MPS tapered, mucosal ulcers and skin lesions reappeared in previously affected areas. Cyclosporine A (CsA) 5mg/kg/day was then added to MPS 1.6 mg/kg/day to obtain a steroid-sparing effect and finally help reduce the MPS. The skin lesions gradually improved and the patient was successfully discharged. However, the rashes relapsed again after 2 months of follow-up due to intermittent medication. MPS and CsA were being continued and the patient is currently being followed up.

Case 2

A 10-year-old girl presented to us with a history of painful and itching skin lesions for 1 month. She had been treated as a case of impetigo for several days with no significant improvement. Before the rash began, she had influenza A and improved after treatment with antipyretics, cephalosporins, and oseltamivir. Physical examination showed diffuse greasy scales on the scalp, and infiltrating erythema with yellowish and smelly scales on the upper chest and back, merged into clusters. Dried erosions were scattered along the extremities (**Fig. 2**A–D). Nikolsky's sign was positive. There was no nail or mucosal involvement and a lack of typical blisters. Laboratory tests including blood chemistry, serology for viruses,

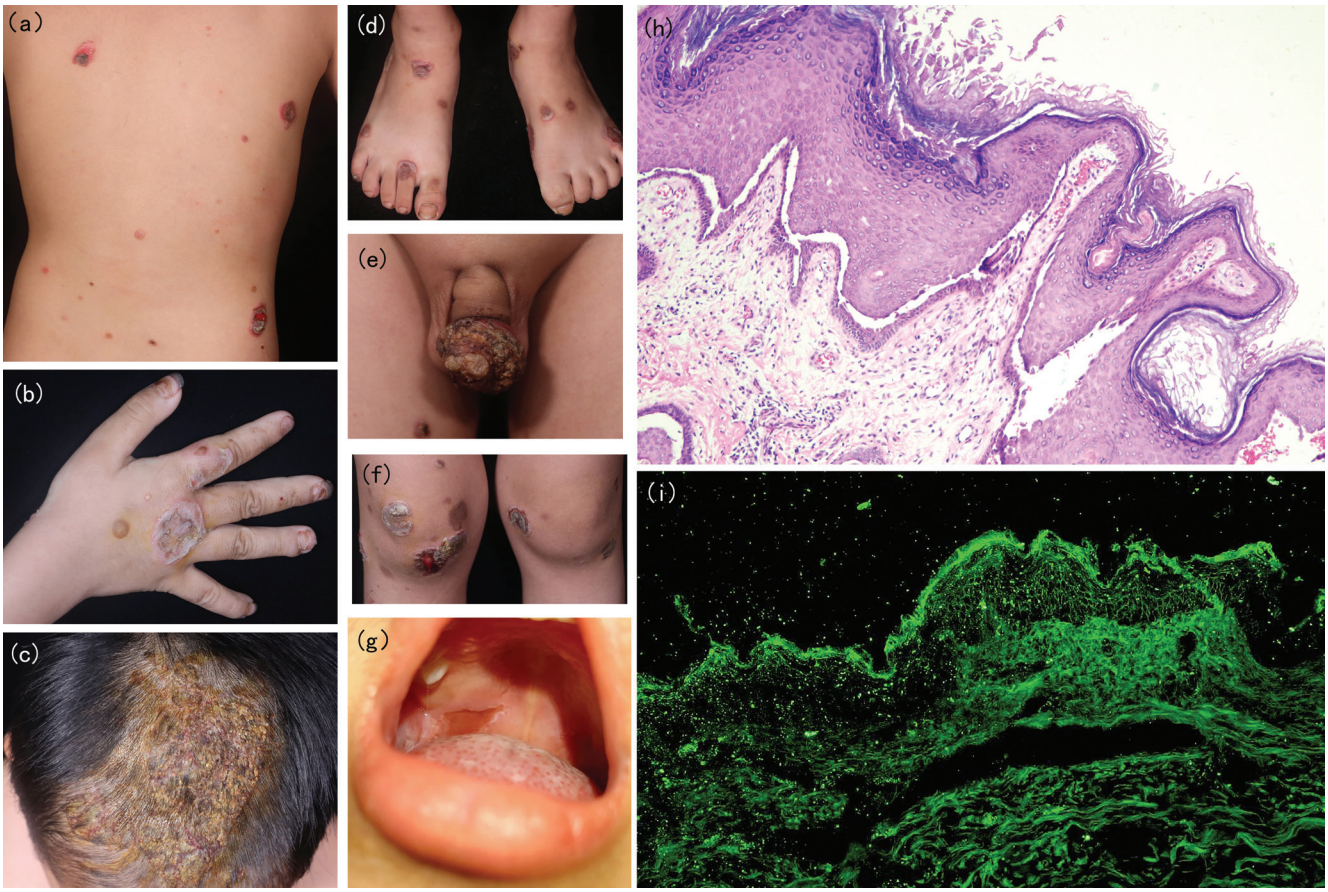

Fig. 1. Clinical features and laboratory tests of a patient with pemphigus vulgaris (PV). (a–g) Clinical manifestation; (h) histology of PV showing intraepidermal suprabasal blistering with acantholysis (haematoxylin-eosin staining, 20x); (i) fluorescent deposits of IgG between intercellular spaces of spinous layer (green) in direct immunofluorescence (DIF).

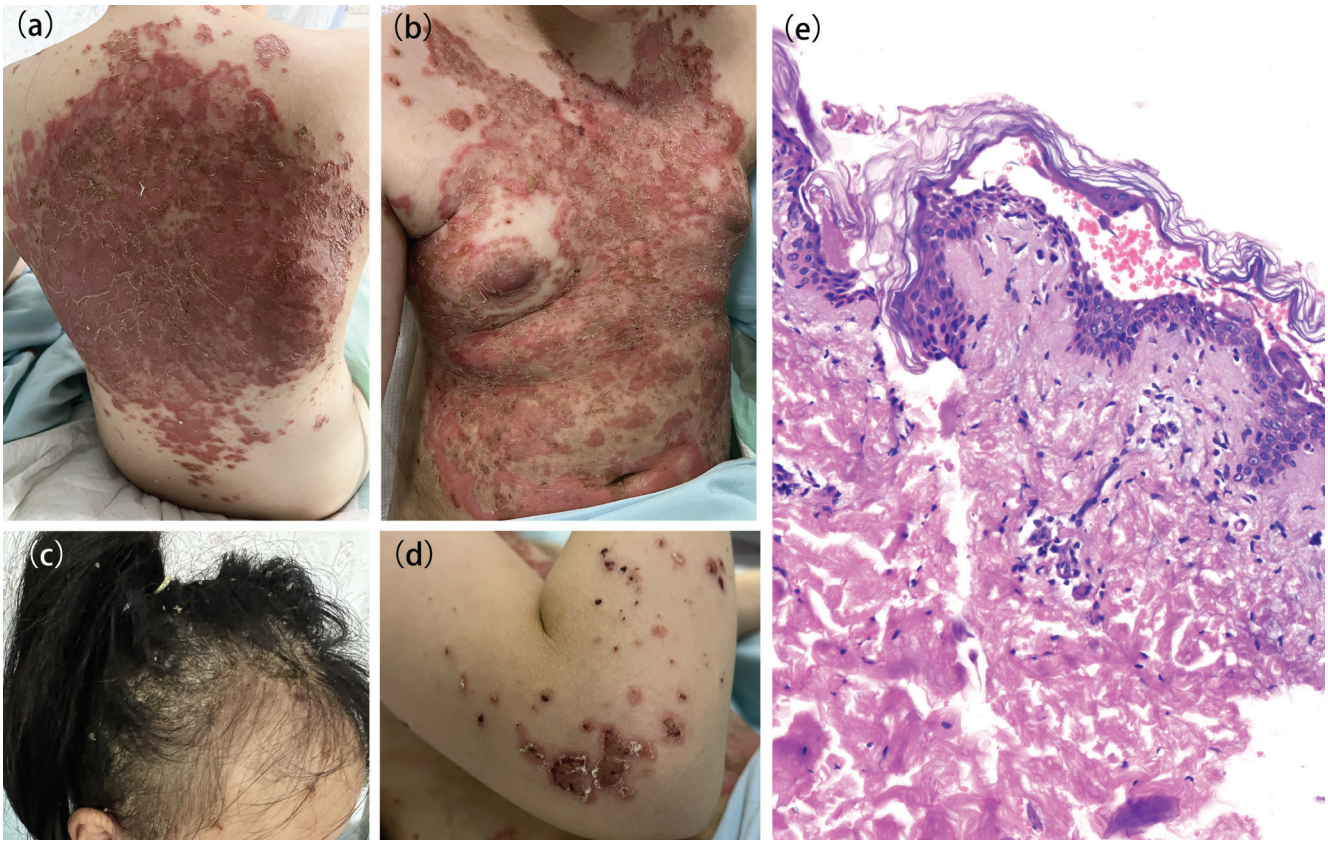

Fig. 2. Clinical features and laboratory tests of a patient with pemphigus foliaceus (PF). (a–d) Clinical manifestation; (e) histology of PF showing intraepidermal sub-corneal blister with acantholysis (haematoxylin-eosin staining, 20x).

and autoimmunity tests were normal except for elevated serum IgE level. The histology examination found sub-corneal blisters with acantholysis (Fig. 2E), ELISA was positive for Dsg1 and negative for Dsg3, so the diagnosis of PF was made.

The treatment we gave this patient initially was MPS (0.8 mg/kg/day) and then tapered every 2 weeks, along with topical mometasone furoate and mupirocin ointment. The patient had a good response to treatment. During treatment, the patient developed Cushing's syndrome and hyperlipidaemia due to excessive egg supplementation. Therefore, when MPS was reduced to 0.4 mg/kg/day, methotrexate (MTX) was added at the same time to obtain a steroid-sparing effect and help reduce the MPS. During the 12 months of follow-up, there was no recurrence of the rash.

Case 3

A 13-year-old boy presented to us with recurrent erythematous scaly plaques and crusted erosions over his body for 7 months. He had been treated as a case of seborrheic dermatitis for several months with no significant improvement. He reported pain and itching and was sensitive to sunlight exposure. Physical examination showed squamous erythema on his scalp and face, over the nose and cheeks in a butterfly distribution. Flaccid blisters, erosions, and crusted lesions were scattered on his upper chest, back, abdomen, and limbs (**Fig. 3**A–C). Nikolsky's sign was positive. The visible mucosae were disease-free. Laboratory tests including blood chemistry and autoimmune tests (e.g., ANA, ANCA, C3, C4, RF) were normal. A skin biopsy taken from a blister showed an intraepidermal blister with acantholysis of the granular layer (Fig. 3D). ELISA was positive for Dsg1 and negative for Dsg3, and a diagnosis of PE was made. The treatment we gave the patient initially was MPS (0.6 mg/kg/day) and then tapered every 2 weeks, along with topical application of mometasone furoate; the rash gradually improved after 1 week of treatment. MPS was tapered over the next 5 months and there was almost no recurrence of the rash during follow-up.

DISCUSSION

In this study, we provide 3 cases of different types of pemphigus in children who were hospitalized over the past 2 years. Though most paediatric patients have clinical manifestations similar to adults, there are still slight differences between them. In the paediatric population, patients with PV have greater involvement of non-oral sites (genital and ocular mucosa) than adults. Patients with PF have a unique and specific pattern of skin lesions, which has been reported in cases of childhood PF described as "arcuate", "circinate", or "polycyclic" lesions (9, 15), similar to our case 2. In addition, eyelid involvement (16), hair loss (17), exfoliative (18), and erythrodermic (19) presentation have also been reported in childhood PF. In addition, patients in this age group have a benign course of relatively short duration, and lower mortality than adults. Thus, the relatively mild skin lesions and the rarity of the disease more easily lead to misdiagnosis in the paediatric population.

The clinical presentation varies among PV, PF, and PE due to the different distribution of Dsg antigens, which

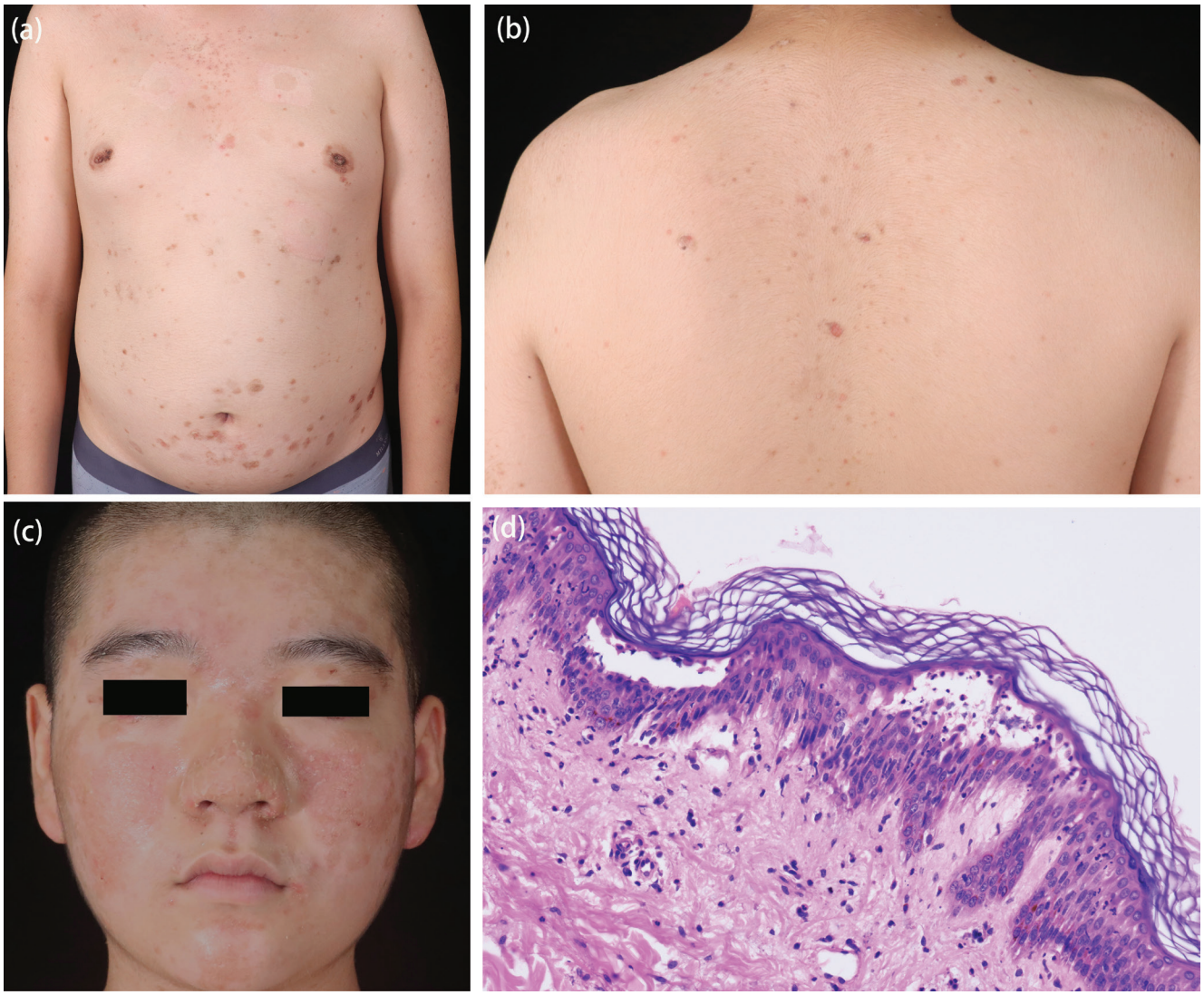

Fig. 3. Clinical features and laboratory test of a patient with pemphigus erythematosus (PE). (a–c) Clinical manifestation; (d) histology of PE showing sub-corneal blister with acantholysis in the epidermis (haematoxylin-eosin staining, 20x).

can be explained by the Dsg compensation theory (20). Patients with PV like case 1 have antibodies against Dsg1 and Dsg3, which results in epithelial acantholysis and mucosal erosions. Clinically, PV always begins with painful oral mucosal ulceration; it usually takes weeks or months for skin lesions to develop. But it should be mentioned that a small set of patients with PV may present with minimal or no mucosal involvement, and these patients may have relatively low titre of Dsg3 and high titre of Dsg1 antibodies (14). Patients with PF or PE have antibodies against Dsg1, which results in cutaneous involvement only. Blisters in PF/PE form in the sub-cornea of the epidermis and are more superficial and fragile than those in PV. Thus, scales and greasy crusts with erythematous bases rather than blisters are more common in PF. Seborrhoeic areas are easily affected, with the scalp and face most commonly involved, followed by the trunk or upper extremities (21). PE appears to be the mildest form of pemphigus (11). Patients may feel pruritus and facial lesions may be in a butterfly distribution and easily be confused with lupus erythematosus and seborrhoeic dermatitis. Thus, clinicians should be aware of the possibility of pemphigus if a child patient presents with a long course of painful blisters, erosions, or crusted erythema on the skin and/or mucous membranes, and conventional treatment has proved ineffective clinically.

Despite the aetiopathogenesis of pemphigus remaining largely unknown, trigger factors have been reported. Drugs, viral infections, vaccines, sun exposure, traumas, and emotional stress may worsen the disease (22). As in the cases we reported, both children had a history of respiratory tract infection before the onset of disease, which suggests that infection may be specific to this age group. Sometimes the infection and drugs taken happen at the same time; thus pemphigus onset was thought to be the probable consequence of both virus and drug effects on the immune response (23). In newborns, pemphigus has also been reported and is thought to be the result

of transplacental transmission of maternal antibodies. Almost all mothers had maternal disease, but there is no clear correlation between maternal antibody titre and neonatal pemphigus activity. Mucosal involvement in neonatal pemphigus was 27.6% and the most commonly involved site weas the trunk. Most newborns had a good prognosis and self-limited course (24–26).

The diagnosis of pemphigus is based on clinical presentation, histopathology of intraepidermal blistering and acantholysis, DIF of IgG/C3 deposition between acanthocytes on the intact perilesional skin or mucosa, indirect immunofluorescence (IIF) of positive serologic IgG, and/or ELISA of serum Dsg1 or Dsg3. Cutaneous lesions of pemphigus are more closely located or diffuse crusted erosions and not free of scars; palmoplantar sites are usually spared. Nikolsky's sign can help distinguish pemphigus from other subepidermal blister dermatoses, such as bullous pemphigoid or benign mucosal pemphigoid. Meanwhile, pemphigus has a relatively simple morphology and a relatively long course, which can be helpful in distinguishing pemphigus from other vesiculobullous dermatoses, such as erythema multiforme, skin infection, or paraneoplastic pemphigus (27). In fact, although DIF is the gold standard for the diagnosis, sometimes skin tissue samples are not easily taken in children, or technical issues may lead to false-negative DIF results (28). It should be noted that in a small set of patients with PF, histopathology may not find any typical intraepidermal blisters because they are too superficial. If the thin blister roof has detached, the remaining epidermis looks relatively normal. In that case, a very useful clue may be the presence of a peripheral rim of scale, or epidermal peeling may indicate that there has been a split (10, 18, 29). Furthermore, detection of serological autoantibodies also enables an accurate diagnosis in most patients. Thus, it is recommended to make the diagnosis of pemphigus on the following findings: typical clinical manifestations plus positive DIF examination; if DIF is negative, positive histopathology plus IIF or positive histopathology plus serum antibodies are needed (14,30). As our 3 cases, not everyone had a positive DIF, but all had compatible clinical features and intraepidermal blisters in the histopathology with positive serum antibodies against Dsg1 and/or Dsg3, so the diagnoses were made on that basis.

It is reported that the mortality of pemphigus in paediatric patients is 2.4-fold higher compared with the general population (31). Though the mortality is lower nowadays thanks to advanced treatments, paediatricians are increasingly concerned. Different countries and regions have issued guidelines on pemphigus, and the treatments vary with subtypes and severity (**Tables I** and **II**). In general, systemic corticosteroids (SCS) are the first-line treatment for all types of pemphigus; steroid-sparing adjuvants, such as mycophenolate mofetil, azathioprine, cyclophosphamide, MTX, and CsA, are always combined with SCS to reduce the course and side effects of SCS. However, due to the susceptibility of the paediatric population

Table I. PV treatment recommendations for induction therapy from different guidelines

Treatment recommendation	Guidelines (year)					
	DBC (2020)	EADV(2020)	ASMSG (2019)	BSD (2019)	FSD (2019)	BAD (2017)
First line	j PDN 0.5–1.5 mg/kg/day k combined with adjuvants: MMF 2g/day MTX 10–20 mg/week l PDN 0.5–1.0 mg/kg/day + RTX 2*I g fusion, 2 weeks apart	j RTX 2*1 g fusion, 2 weeks apart k PDN 0.5–1.5 mg/kg/day l PDN 0.5–1.0 mg/kg/day + RTX m PDN 0.5–1.5 mg/kg/day + adjuvants: AZA 1–2.5 mg/kg/day MMF 2g/day MPA 1440 mg/day	j PSL 1.0–1.5 mg/kg/day + adjuvants: AZA 2–2.5 mg/kg/day MMF 2 g/day MPA 1440 mg/day k PSL l.0 mg/kg/day + RTX l Pulsed IV MPS	j PDN 0.5–1.0 mg/kg/day k PDN 1.0–1.5 mg/kg/day + adjuvants: AZA l–3 mg/kg/day MMF l–3 g/day l pulsed IV MPS + adjuvants	j TCS k RTX 2*l g fusion, 2 weeks apart l RTX+PSL 0.5–l.0 mg/kg/day m PSL 1.0–1.5 mg/kg/day n PSL 1.0–1.5 mg/kg/day + adjuvants: AZA l–3 mg/kg/d MMF 2 g/d MTX 15–25 mg/week	j PSL 0.5–1.0 mg/kg/day k combined with adjuvants: AZA 2–3 mg/kg/day MMF 2–3 g/day RTX 2*I g fusion, 2 weeks apart
Second line	j pulsed IV MPS 0.5–lg/d*3day k PSL 0.5–1.5 mg/kg/day + adjuvants: AZA 0.5–1.5 mg/kg/day CsA 3–5 mg/kg/day CTX 2 mg/kg/day PO or 500 mg IV	j Pulsed IV MPS k RTX+PSL 1.5 mg/kg/day at most l PSL l.5 mg/kg/day + adjuvants: CTX 50 mg/d PO or 500–750 mg/month IV	PSL up to 2.0 mg/kg/day	j PDN 0.5–1.0 mg/kg/day + adjuvants: CsA 3–5 mg/kg/day MTX 10–20 mg/week CTX l–3 mg/kg/day PO or 500 mg IV k PDN + adjuvants+ RTX l RTX m RTX+IVIG n IVIG	j pulsed IV MPS k PSL l.0–l.5 mg/kg/day + adjuvants: CTX 50 mg/day PO or 500–750 mg/month IV l IA	PSL 0.5–1.0 mg/kg/day + alternate adjuvants (including RTX)
Third line	IVIG, PE, IA, SCT		IVIG, IA			IVIG, PE,IA, MTX,CTX

DBC: Dermatology Branch of China International Exchange and Promotion Association for Medical and Healthcare; EADV: European Academy of Dermatology and Venereology; ASMSG: Association of the Scientific Medical Societies in Germany; BSD Brazilian Society of Dermatology; FSD: French Society of Dermatology; BAD: British Association of Dermatologists; TCS: topical corticosteroids; MPS: methylprednisolone; RTX: rituximab; PDN: prednisone; PSL: prednisolone; IVIG: intravenous immunoglobulin; IA: immunoadsorption; MMF: mycophenolate mofetil; MPA: mycophenolic acid; CTX: cyclophosphamide; PE: plasma exchange; SCT: stem cell transplantation; CsA: cyclosporine A; MTX: methotrexate; AZA: azathioprine.

Table II. PF treatment recommendations for induction therapy from different guidelines

Treatment recommendation	Guidelines (year)					
	DBC (2020)	EADV(2020)	ASMSG (2019)	BSD (2019)	FSD (2019)	BAD (2017)
First line	Not discussed	j dapsone + TCS k TCS l RTX 2*1 g fusion, 2 weeks apart m PDN 0.5–1.5 mg/kg/day n PDN 0.5–1.0 mg/kg/day + RTX o PDN 0.5–1.5 mg/kg/day + adjuvants: AZA 1–2.5 mg/kg/day MMF 2 g/day MPA 1440 mg/day	j PSL 1.0–1.5 mg/kg/day + adjuvants: AZA 2–2.5 mg/kg/day MMF 2 g/day MPA 1440 mg/day k PSL l.0 mg/kg/day + RTX l pulsed IV MPS	j dapsone + TCS k Dapsone 0.1–0.2 g/day l TCS m PSL 0.25–1.0 mg/kg/day n PSL l.0 mg/kg/day + adjuvants: AZA 1–3 mg/kg/day MMF 1–3 g/day	j dapsone + TCS k dapsone l RTX m RTX + TCS m PSL 0.5–1.0 mg/kg/day + RTX n PSL 1.0–1.5 mg/kg/day o PSL 1.0–1.5 mg/kg/day + adjuvants: AZA 1–3 mg/kg/day MMF 2g/day MTX 15–25 mg/week	Not discussed
Second line		j pulsed IV MPS k RTX + PSL 1.5 mg/kg/day at most l PSL 1.5 mg/kg/day + adjuvants: CTX 50 mg/day PO or 500–750 mg/month IV	PSL up to 2.0 mg/kg/day	j RTX k RTX+IVIG l IVIG m IA	j pulsed IV MPS k PSL 1.0–1.5 mg/kg/day + adjuvants: CTX 50 mg/day PO or 500–750 mg/month IV l IA	
Third line			IVIG, IA			

DBC: Dermatology Branch of China International Exchange and Promotion Association for Medical and Healthcare; EADV: European Academy of Dermatology and Venereology; ASMSG: Association of the Scientific Medical Societies in Germany, BSD Brazilian Society of Dermatology; FSD: French Society of Dermatology; BAD: British Association of Dermatologists; TCS: topical corticosteroids; MPS: methylprednisolone; RTX: rituximab; PDN: prednisone; PSL: prednisolone; IVIG: intravenous immunoglobulin; IA: immunoadsorption; MMF: mycophenolate mofetil; MPA: mycophenolic acid; CTX: cyclophosphamide; CsA: Cyclosporine A; MTX: methotrexate; AZA: azathioprine.

to the adverse effects of SCS and immunosuppressive agents, RTX, a CD20 monoclonal antibody, approved by the FDA in 2018, alone or combined with short-term SCS is also recommended as a first-line therapy for adults with PV in some guidelines (32–35). Increasing reports in the literature now suggest that RTX with or without adjuvants has similar effects to SCS with adjuvants in rates of clinical remission, partial remission and relapse, shorter time to remission, and longer duration of remission (35). Moreover, RTX has lower adverse events compared with SCS and adjuvants, and appears to be well tolerated in children with pemphigus. Despite the robust adult literature, supportive paediatric trials reporting treatment with RTX are limited. Additional consideration should be included as to how RTX affects children's growth and development, and interventions such as vaccination (36). Based on this, experts recommend administering vaccines 2–4 weeks prior to commencement of RTX, otherwise optimal vaccination is expected to occur at least 6 months after the last dose of RTX (37, 38). Surprisingly, infections were reported to be not as common in paediatric patients as they were in adults. Instead, mild infusion reactions were more common and no long-term adverse effects on growth and development were found in the paediatric population (39). However, the dosage, frequency, treatment cycle duration, and maintenance therapy duration of RTX in paediatrics still lack large samples and multi-centre clinical studies.

In conclusion, pemphigus in the paediatric population is rare but should be taken into consideration if a patient has painful skin lesions that last for a long time and do not respond to conventional treatment. It should be remembered that infection should always be initially considered and excluded. Treatment is challenging in the paediatric group and special consideration of medications is required. In addition, experienced paediatric dermatologists and nurses in infant and child care are also needed for management of the skin lesions. Overall, the majority of children with pemphigus usually have a better prognosis and response to treatment.

ACKNOWLEDGEMENTS

The authors would like thank the patients and their parents, who cooperated significantly with this study.

The authors have no conflicts of interest to declare.

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