

Case Report

Childhood Bullous Pemphigoid: A Case Report and Literature Review

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Abstract

Bullous pemphigoid is a very rare dermatologic disorder in children. We report a 1-year and 9-month-old boy, who was diagnosed childhood bullous pemphigoid on the basis of clinical findings and confirmed by skin biopsy showing subepidermal blisters with dermal layer infiltrated with neutrophils, a unique histological finding. The result mimicked the histological findings of linear immunoglobulin A bullous disease. Direct immunofluorescence showed linear deposits of IgG and C3 at dermal-epidermal junction, similar to epidermolysis bullosa acquisita and bullous systemic lupus erythematosus. We suggested the differential diagnosis of subepidermal blisters should include linear immunoglobulin A bullous disease of childhood, epidermolysis bullosa acquisita and bullous systemic lupus erythematosus.

Keywords: Bullous pemphigoid; Childhood; Subepidermal blisters; Linear immunoglobulin A bullous disease; Epidermolysis bullosa acquisita

Abbreviation: BP: Bullous Pemphigoid; DIF: Direct Immunofluorescence; IIF: Indirect Immunofluorescence; BMZ: Basement Membrane Zone; LABD: Linear Immunoglobulin A Bullous Disease; EBA: Epidermolysis Bullosa Acquisita; SLE: Systemic Lupus Erythematosus

Introduction

Bullous pemphigoid (BP) is an autoimmune subepidermal blistering disorder which is induced by autoantibodies against the dermoepidermal junction of skin and adjacent mucous membrane. The elderly is mostly affected, and childhood bullous pemphigoid is rare. Lesions of childhood BP are large, tense bullae that can be found in all areas of body, including inner sides of the thigh, forearms, axillae, lower part of the abdomen, groin, palms and soles. Some patients may complain of pruritus. In addition, mucosal involvement is common in the pediatric population. Diagnosis, similar to that of adult, is based on clinical, histological, and immunopathological features. Classic histology reveals subepidermal blisters with dermal infiltration of predominantly eosinophils. Direct immunofluorescence (DIF) of skin biopsy of unblistered, perilesional skin (normal-looking skin) reveals linear deposition of IgG and/or complement 3(C3) along the basement membrane zone (BMZ). Indirect immunofluorescence (IIF) shows presence of circulating IgG anti-basement membrane zone antibodies [1-4]. We report a case of childhood bullous pemphigoid whose skin biopsy showed subepidermal blisters with dermal layer infiltrated with neutrophils.

Case Report

A 1-year and 9-month-old boy, with history of atopic dermatitis, was referred to our service with complaint of multiple vesicles off and on over face, trunk, limbs and groin area for 2 months. According to his father's statement, these skin lesions appeared in groin area first and extended to back and neck. Itchy sensation was also noted but no fever. Some of the lesions subsided spontaneously and some appeared at other sites. Two days ago, multiple bullae and vesicles developed on hands and feet (Figure 1). There was no similar symptoms within family members. The child was not on any medication, and was vaccinated as recommended. There was no fever, nausea vomiting or diarrhea. Physical examinations on admission revealed maculopapular

lesions on head, trunk, and limbs with involvement of palms and soles. Multiple blisters were found on genital area, and oral mucosa was not affected. Routine laboratory tests were normal.

Under impression of herpes simplex virus-1 infection, acyclovir was used initially. Spontaneous resolution and reappearance of vesicles developed on limbs and shoulders along with intermittent fever. IV oxacillin was administered for possible superimposed bacterial infection. Blood culture yielded no organism. Acyclovir was used for 10 days, and discontinued due to poor response. Due to persistent symptoms, skin biopsy was performed. Differential diagnosis then included linear IgA dermatosis and dermatitis herpetiformis. Histologic examination showed subepidermal blister. Dense neutrophils and cells debris were noted with scanty eosinophils (Figure 2). DIF showed linear deposits of IgG and C3 at dermal-epidermal junction (Figure 3). DIF exam of IgA and IgM showed negative findings. IIF of IgG showed weak linear immunofluorescence at dermal-epidermal junction at the titer equal to or less 1:10. ANA was negative and C3/C4 was within normal range. Double immunofluorence staining of DIF was done and C3 immune complex deposition above type IV collagen was demonstrated (Figure 4). Under impression of childhood bullous pemphigoid, oral prednisone therapy was initiated at a dose of 0.5 mg/ kg per day. Rapid improvement with resolution of bullae was observed without any recurrence after prednisolone treatment.

Discussion

Bullous pemphigoid mostly affects the elderly. Childhood bullous pemphigoid occurs very rarely, and mucosa involvement is common in children. The lesions of childhood BP are large, tense bullae with diffuse distribution, affecting the inner side of the thigh, forearms, axillae, lower part of the abdomen, groin, palms and soles. Diagnosis is based on clinical, histological, immunopathological features [1-3].

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Specific criteria of childhood BP have been suggested to help early diagnosis:

- 1. Patients aged 18 years and younger with the clinical appearance of tense blisters on erythematous or normal skin with or without mucous membrane involvement and having subepidermal blisters with eosinophils, and
- 2. Linear deposits of IgG or C3 at the epidermal basement membrane zone on DIF, or circulating IgG anti-basement membrane zone autoantibodies on IIF[2].

The etiology of childhood BP is not clear, and possible causes reported include nonspecific maternal antibodies[5], primary autoimmune disease in infancy[6] and foreign antigen (e.g. infectious agents, drugs, and vaccines)[7]. Treatments include anti-inflammatory agents and immunosuppressants. Antibiotics will be used when secondary bacterial infection is found. Childhood BP usually has favorable prognosis [8].

The histopathology of BP shows subepidermal blister formation with eosinophils infiltration. DIF reveals the presence of linear deposition of IgG and/or C3 at dermoepidermal junction. Collagen XVII (BP180) and BP 230, the targed antigen, are found in the hemidesmosome on the epidermal side above the type IV collage (which is part of the basement membrane component within lamina densa) [9-12]. In our case, the histological examination revealed subepidermal blister with dense neutrophils and cells debris. DIF examination showed linear deposits of IgG and C3 at dermoepidermal junction. The result mimicked the histological findings of linear immunoglobulin A bullous disease (LABD) of childhood and was similar to the DIF of epidermolysis bullosa acquisita (EBA) and bullous systemic lupus erythematosus (bullous SLE).

LABD of childhood, one of the most common autoimmune bullous diseases in children, is a chronic bullous disease of IgA disease. The disease affects children before 5 years old of age. The



Figure 1: Tense bullae and vesicles at groin area first; marked involvement of lower extremities, face, trunk, palms and soles.



Figure 2: Skin specimens with hematoxylin and eosin stain, presenting (a) a subepidermal blister (black arrow) (40X), (b) with predominant neutrophils infiltration (red arrow) (400X).



Figure 3: DIF showed linear deposition of C3 (a,b) and IgG (c,d).



Figure 4: Double immunofluorescence staining of DIF (100X) revealed C3 (yellow-green) deposited above type IV collagen (orange) at the dermal-epidermal junction (white arrows).

lesions of this disease are clear, and/or hemorrhagic vesicles or bullae on skin. Histological examinations showed subepidermal blisters with neutrophils infiltration, though mononuclear cells and eosinophils may also be seen. DIF confirms the diagnosis. DIF of skin biopsy from perilesional skin showed linear deposition of IgA along dermoepidermal junction [2]. EBA is a chronic autoimmune subepidermal blistering disease, and is found rarely in childhood. The disease is characterized by circulating autoantibodies IgG against type VII collagen, a component of anchoring fibrils which bind the basement membrane to the underlying dermis. Concurrent disease has been reported in patient with EBA. The clinical presentation of EBA is skin fragility, blisters and dystrophic change. The treatment of EBA is usually not satisfactory. Some options such as azathioprine, dapsone, colchicine, corticosteroids, mycophenolate mofetil, and intravenous immunoglobulins (IVIG) have been reported [2,13]. Bullous SLE is an autoimmune disease with underlying diagnosis of SLE. The target antigen is also type VII collagen[14]. Skin biopsy is characterized by subepidermal blisters with predominantly neutrophils. DIF showed IgG deposition along the BMZ [2].

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	Age/Sex	lassa kasawa a t		A				_
Reference		invoivement		Associated disorders or		Immunofluorescence		
		Skin on presentation	Oral mucosa	possible trigger factors	Histology	DIF*	180kDa **	Treatment
Rita E. Fisler, 2003[9]	5m/M	Palms, soles	None	DT [#] vaccine	eosinophils	lgG,C3, weaker IgA	NA	Topical steroids
	8m/M	Palms, soles	Present	None	Mixed neutrophils, eosinophils	lgG,C3	NA	Prednisolone(2mg/kg/day), dapsone, mycophenolate mofetil
	7 y/M	Vulval area	vagina	None	Cell-free	lgG,C3	NA	Topical steroids
Stéphane Kuenzli, 2004[16]	9m/F	Wide spread, palms, soles	vagina	None	eosinophils	lgG,C3	present	Prednisolone(1mg/kg/day), sulfapyridine
Ting XIAO, 2007[3]	3.5m/M	face, trunk, hands and feet	None	DTP [#] vaccine	neutrophils	C3	present	high-dose i.v. immunoglobulin
Gino Tripodi, 2007[17]	42m/F	Not described	present	IBD	Not described	Not described	NA	Plasma exchange
Maria Isabel Martinez- De Pablo, 2007[18]	5m/M	trunk, face, lower limbs	present	None	eosinophils	lgG,C3,IgA(faint)	NA	Prednisolone(2mg/kg/day)
	5m/M	hands, feet, and trunk	None	None	eosinophils	lgG,C3,IgA(faint)	NA	Prednisolone(1mg/kg/day)
	12m/M	scalp, trunk, limbs, palms, soles	None	None	Not described	lgG,C3	NA	Dapsone(1mg/kg/day), Prednisolone(1mg/kg/day)
	4m/M	abdomen, limbs, scalp, palms, soles	None	None	eosinophils	lgG,C3	NA	Prednisolone(1mg/kg/day)
Ana María Sáenz, 2007[19]	15m/M	trunk, neck, limbs, face, palm, soles	Present	None	lymphocytes,eosinophils	lgG,C3	present	Prednisolone(1mg/kg/day)
V. Majmudar, 2008[20]	10w/F	scalp, trunk, inner thighs	None	DTaP#/IPV#/Hib# vaccine	eosinophils	lgG,C3	present	Prednisolone(2mg/kg/day)
Zulal Erbagci, 2008[6]	6m/M	palms, soles, lower extremities, scalp and ear lobes	present	Hyper-IgE syndrome	eosinophils	lgG,C3	NA	Prednisolone(1mg/kg/day), oral antibiotics
Moben Mirza, 2008[21]	7y/M	glans penis	None	None	lymphocytes, plasma cells and rare eosinophils	lgG,C3	NA	corticosteroids
Karen A. Marcus, 2009[22]	3y/F	Trunk, extremities	None	VZV [#] vaccine	eosinophils	C3,weaker lgG, lgM	present	Prednisolone(2mg/kg/day), Dapsone(1mg/kg/day)
Tomoko TOYAMA, 2009[23]	5m/F	trunk, extremities, hands and feet	None	DTP [#] vaccine	lymphocytes,eosinophil	lgG,lgM,C3	present	Topical steroids
	5m/F	face, fingers, trunk, extremities, palm, soles	None	BCG vaccine	Lymphocytes, eosinophils	lgG	present	Topical steroids
Fox JC, 2010[8]	16y/F	>70% of her total body surface area	None	atopy	eosinophils	NA	NA	Prednisolone(1mg/kg/day), mycophenolate mofetil (MM), topical agent
The present case, 2012	21m/M	face, trunk, limbs, groin area, palm, soles	None	None	Neutrophils	lgG,C3	NA	Prednisolone (0.5 mg/kg/day)

NA: non available

*DIF: direct immunofluorescence

**180kDa: BP 180, type XVII collagen, components of junctional adhesion complexes called hemidesmosomes

*DT: diphtheria and tetanus vaccine; DTP: diphtheria, tetanus and pertussis vaccine; DTaP: Diphtheria and tetanus toxoid with acellular pertussis vaccine; IPV: inactivated polio vaccine; Hib: haemophilus influenzae type b vaccine; VZV: varicella vaccine

Table 1: Summary of Childhood bullous pemphigoid case reports since 2003.

In our case, the DIF of perilesional skin showed linear deposits of IgG and C3 at dermoepidermal junction which is the gold standard diagnosis of bullous pemphigoid. Double immunofluorescence staining of DIF revealed C3 immune complex deposition above type IV collagen. The characteristic histochemical findings in the skin biopsy of our patient suggested a diagnosis of childhood BP.

past ten years (Table 1). The age of all patients was all less than 18 years old. The involvement of lesions was generalized. The lesions in palms and soles were more common in childhood than adult and some cases had mucosa involvement. The associated disorders or possible trigger factors were varied. Six cases accepted vaccinations before disease developed. There was one case with history of inflammatory bowel disease, another with hyperimmunoglobulin E syndrome and the other with atopy. Histological findings found predominantly eosinophils,

We reviewed case reports of childhood bullous pemphigoid over the

although two cases were neutrophils predominant. DIF of all cases showed linear deposition of IgG and/or C3 at the dermoepidermal junction, except two cases with IgM deposition. The treatments almost were anti-inflammatory agents and immunosuppressants with or without topical agent. Only two cases were treated with high dose IVIG and plasma exchange.

Predominant neutrophils of subepidermal blisters in bullous pemphigoid are very rare histological findings. Lara Andrachuk[15] reported a case of a 59-year-old woman with bullous eruption, and the histologic examinations of her skin lesions showed subepidermal blisters with linear arrangement of neutrophils. He suggested that bullous pemphigoid should be considered in the differential diagnosis of neutrophil-rich subepidermal bullous disease with dermatitis herpetiform and LABD.

Conclusion

Childhood bullous pemphigoid is a rare disease. The diagnosis depends on the combinations of clinical history, histological findings, and immunofluorescence. Prognosis of childhood BP is good and the duration is often limited to one year when correct treatment is prescribed. The differential diagnosis of subepidermal blisters should include linear immunoglobulin A bullous disease of childhood, epidermolysis bullosa acquisita, bullous systemic lupus erythematosus and bullous pemphigoid. Appropriate treatment can only be based on correct and rapid diagnosis.

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