

CASE & REVIEW

Infantile bullous pemphigoid treated with intravenous immunoglobulin therapy

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A 3-month-old boy presented with a 2-week history of rapidly spreading skin rashes. Physical examination revealed generalized urticarial plaques with tense bullae and small vesicles. Histologic examination and immunofluorescence established the diagnosis of bullous pemphigoid. The disease was resistant to conventional therapies with the combination of corticosteroids, dapsone, and erythromycin. Finally, intravenous immunoglobulin therapy brought about a remarkable improvement. We suggest that intravenous immunoglobulin therapy is a valuable treatment option for intractable bullous pemphigoid in infants as well as in adults. (J Am Acad Dermatol 10.1016/j.jaad.2007.08.005.)

Bullous pemphigoid (BP) is an autoimmune blistering skin disorder associated with tissue-bound and circulating IgG autoantibodies directed against BP antigens 180 and 230.¹ BP usually develops in the elderly, and is quite rare in infants. We report a 3-month-old infant with BP, which was resistant to systemic administration of corticosteroid, but successfully treated with intravenous immunoglobulin (IVIG) therapy.

CASE REPORT

A previously healthy 3-month-old boy visited our hospital on January 10, 2004, with generalized erythema and blisters. He had had no vaccinations and his family history was unremarkable. His mother had noted erythematous skin lesions on his soles 2 weeks before. Erythema rapidly spread over his trunk and extremities with the formation of multiple blisters. Physical examination revealed urticarial plaques with tense bullae, small vesicles, and erosions on most of his body (Fig 1). On his back, urticarial annular erythematous lesions were noted. Mucous membranes were not affected.

The results of routine laboratory tests revealed a hemoglobin of 9.7 g/dL and white blood cell count of 8000/ μ L, with 12.1% neutrophils, 18.2% eosinophils, 13.1% monocytes, and 44.5% lymphocytes. C-reactive protein levels were slightly elevated at 1.1 mg/dL. The antinuclear antibody titer produced negative results and other laboratory values were within normal limits.

The biopsy specimen taken from a vesicle on the arm revealed subepidermal bulla with dense infiltration of eosinophils and mononuclear cells (Fig 2). Direct immunofluorescence showed a linear deposition of IgG and C₃ at the dermoepidermal junction. Indirect immunofluorescence demonstrated IgG class of ant basement membrane antibody at a titer of 1:80. In a 1M NaCl split skin test, IgG was bound to the epidermal side. On an immunoblotting assay, immunoblotting bands of 180 and 230 kd were detected. The value of anti-BP antigen 180 recombinant protein IgG antibody was elevated at 187.29 on an enzyme-linked immunosorbent assay (normal range: <15).

The initiation of oral prednisolone (10 mg/d [1.4 mg/kg/d]) resulted in no improvement. Therefore, the dose of prednisolone was increased to 20 mg/d, followed by the addition of erythromycin (21 mg/d) and dapsone (12.5 mg/d). However, erythema and new blisters continued to develop. Then, prednisolone was changed to dexamethasone (3 mg/d) on day 17 of hospitalization. Although new blister formation stopped, erythema remained. Five weeks later, when the dose of dexamethasone was gradually tapered to 0.75 mg/d, new blisters recurred rapidly. Pulse therapy with methylprednisolone sodium succinate (80 mg/d [10 mg/kg/d]) was started on day 57 of hospitalization. Neutrophil count, however, decreased to 119/ μ L. Pulse therapy was

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Fig 1. Tense bullae and vesicles on arm. Some blisters are ruptured and eroded.

stopped for 2 days, and erythromycin and dapsone were discontinued under the suspected diagnosis of drug-induced leukopenia or viral infection. Soon after, the diagnosis of cytomegalovirus infection was established, based on the elevated titer of anti-cytomegalovirus IgM antibody at 1:672. After pulse therapy, oral dexamethasone (0.75 mg/d) was continued for 1 week, and new blister formation decreased. On day 65 of hospitalization, new bullae and urticarial erythema again spread over his whole body. Resumption of erythromycin and dapsone was not effective. A 5-day course of IVIG therapy (2.5 g/d [300 mg/kg/d]) was initiated. After 4 days of IVIG therapy no new skin lesions developed. One week later resolution of all lesions was obtained. The dose of dexamethasone was gradually tapered to 0.4 mg/d and erythromycin was discontinued. Recurrence of blistering occurred on day 105 of hospitalization. A second course of IVIG was given, which resulted in rapid improvement. Dapsone was discontinued, and 7 months later dexamethasone was tapered off. No relapse has been seen during a 16-month follow-up period.

DISCUSSION

Infantile BP is quite rare. To our knowledge, only 33 cases, 19 boys and 14 girls, have been reported (Table I).¹⁻³⁰ In 26 of 33 cases (78.8%) the disease started within 6 months after birth. This fact raised the possibility that IgG antibody transferred from the mother may be responsible for the development of BP. However, there are no reports of positive indirect immunofluorescence in any of the patients' mothers.* On the other hand, some cases suggest a correlation to vaccination²⁻¹⁰ similar to some adult cases with BP.³¹⁻³³ Our patient did not receive any vaccine before the development of BP.

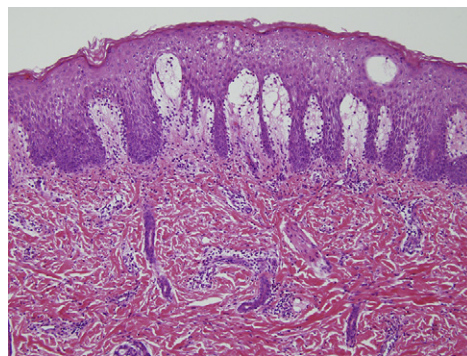


Fig 2. Histologic findings showed subepidermal bulla with eosinophils within cavity. Perivascular infiltration of lymphocytes and eosinophils were noted in papillary dermis. (Hematoxylin-eosin stain; original magnification: $\times 100$.)

Skin lesions first developed on the hands and feet in 15 cases, more specifically the palms and soles in 11 cases. Mucosal involvement was noted in 6 of 29 infantile cases (20.7%). In childhood cases, it was reported that mucous membrane could be affected in 72% and in adults, 10% to 40%.¹¹ Therefore, the frequency of mucous lesions in infant BP is the same as in adult BP.

In most cases of infantile BP, response to conventional treatments is good with excellent prognosis. Corticosteroid therapy was effective in 8 cases,^{2-4,11,13-16} 6 cases were successfully treated with a combination of corticosteroid and dapsone,¹⁷⁻²¹ and 4 cases with a combination of corticosteroid and sulfapyridine.^{1,12,22,23} Two cases were cured with sulfapyridine alone.^{24,25} Other drugs used in combination with systemic corticosteroids include erythromycin, nicotinamide, or mycophenolate mofetil.^{5,10} One patient showed no response to corticosteroids but was successfully treated with the addition of mycophenolate mofetil.¹⁰ We could find only one case treated with IVIG, in which the disease recurred after treatment.²⁶ In our case, conventional treatments failed to control the disease and methylprednisolone pulse therapy had to be stopped because of a cytomegalovirus infection. Finally, we initiated IVIG treatment with which we achieved a remarkable improvement.

In adult BP, it has been reported that about 70% of patients showed a beneficial clinical response to IVIG therapy.³⁴⁻³⁶ Engineer and Ahmed³⁴ recommended more than 400 mg/kg/d for 5 days. More than one cycle was necessary to prevent recurrence. Headache, nausea, and vomiting may occasionally occur in some patients, but no significant adverse effects were observed.^{34,35} In our patient, BP recurred 3 weeks after the first cycle; however, the second cycle of IVIG was sufficient for the

*Ref. 2,4,6,8,11,13,15,20-22,24,29,30

Table I. Reported cases of bullous pemphigoid in infancy; clinical and immunopathologic features

Author	Y	Age, mo/sex	Clinical presentation		Immunofluorescence			Effective treatment	Course
			Initial lesions	Mucosal involvement	DIF	IIF on intact skin and split skin (titer)	Immunoblotting		
Gould et al ¹³	1977	3.5/M	Hands and feet	None	IgG	1:5	—	Prednisolone (20 mg/d)	Resolution No recurrence 10 mo later
Marsden et al ²⁴	1979	3/M	Hands and feet	None	IgG, C3	1:80	—	Sulfapyridine	Resolution
Tanno et al ²⁷	1979	11/M	Chest, leg	None	IgG	Positive	—	Betamethasone (1.5 mg/d), dapsone, tocopheryl acetate	Partial response Repeated recurrence
Marsden et al ²⁸	1980	8/F	—	—	IgG, C3	Positive	—	—	Death from hemolytic anemia (probably coincidental)
Takaiwa et al ¹⁷	1981	5/M	Face, soles	None	IgG, C3	1:64	—	Dexamethasone (1 mg/d), dapsone	Resolution
Marsden ²²	1983	4/F	Palms and soles	Present	IgG, C3	1:1280	—	Prednisolone (20 mg/d), sulfapyridine	Improved but still active 10 mo later
Yagi et al ¹⁴	1985	3/M	Soles	None	IgG, C3	Negative	—	Dexamethasone (0.5 mg/d)	Resolution No recurrence 7 mo later
Tamaki et al ²⁹	1988	4/F	Hands, feet, and forearms	—	IgG, C3	1:80	—	Topical steroids	Resolution
Tani et al ¹⁸	1988	4/F	—	Present	IgG, C3, IgA	Epidermal Positive	—	Betamethasone (1.4 mg/d), dapsone	Resolution No recurrence 1 y later
Suzuki et al ¹⁵	1989	2/F	Palms and soles	None	IgG, C3	Negative	—	Betamethasone (1 mg/d)	Resolution No recurrence 3 mo later
Nemeth et al ¹¹	1991	2.5/F	Palms and soles	Present	IgG, C3, IgA	Negative	—	Prednisolone (1 mg/kg/d)	Resolution No recurrence 3 y later
Oranje et al ³	1991	4/M	Face, hands, and feet	None	IgG, C3, weak IgA, IgM, fibrinogen, IgE	NA	NA	Prednisolone (2 mg/kg/d)	Resolution No recurrence 10 y later
Saurat et al ²⁵	1991	3/M	Feet	—	—	—	—	Sulfapyridine	Resolution No recurrence 3 y later
Sakamoto et al ¹⁹	1993	2/M	Hands and feet	None	IgG, C3	Positive	—	Betamethasone, dapsone	Resolution

(Continued)

Table I. Cont'd

Author	Y	Age, mo/sex	Clinical presentation		Immunofluorescence			Immunoblotting	Effective treatment	Course
			Initial lesions	Mucosal Involvement	DIF	IIF on intact skin and split skin (titer)				
Ostlere et al ¹²	1993	12/M	Hands and feet	None	IgG, C3	1:100 Epidermal	190-kd Epidermal (Unknown antigen)	Prednisolone (1 mg/kg/d), sulfapyridine	Resolution Recurrence with tapering steroids	
Nagano et al ²⁰	1994	3/M	Hands and feet	None	IgG, C3	— Epidermal (1:512)	BP180	Prednisolone (18 mg/d), dapsone	Resolution No recurrence 9 mo later	
Kirtschig et al ²³	1994	6/F	—	None	IgG, C3	Positive Epidermal	220-kd Epidermal	Prednisolone, sulfapyridine	—	
Cambazard et al ⁴	1994	4/M	Hands, forearms	None	IgG, C3	1:100 —	BP230	Prednisolone (2 mg/kg/d)	Resolution No recurrence 7 y later	
Nakamura et al ¹⁶	1997	2/M	Face	—	IgG, C3	1:160 Epidermal	BP180	Betamethasone (0.2 mg/kg/d)	Resolution No recurrence 6 mo later	
Amos et al ⁶	1998	3/F	Feet	None	IgG, C3	Negative	NA	Topical steroids	Resolution No recurrence 1 y later	
Cunha et al ⁵	1998	2.5/M	Trunk	None	C3	1:40 Epidermal	BP180, BP230	Prednisolone (2 mg/kg/d), dapsone, erythromycin, nicotinamide	Resolution No recurrence 10 mo later	
Trüeb et al ²⁶	1999	8/M	Hands and feet	Present	IgG, C3	NA Epidermal (1:10)	120-kd Dermal BP180 recombinant	Dexamethasone (3 mg/d), IVIG Pulse glucocorticoid therapy, prednisolone (15 mg/d), dapsone	Resolution but recurrence 2 wk later Resolution after pulse therapy	
Santis et al ⁷	1999	7/F	Palms and soles	None	IgG, C3	Negative	—	Hydroxyzine pamoate	Resolution No recurrence 3 mo later	
Sawada et al ⁸	1999	4/F	Soles	None	IgG, C3	1:320 Epidermal	—	Topical steroids	Resolution	
Chimanovitch et al ²¹	2000	4/F	Face, hands, and feet	None	IgG, C3	— Epidermal	Weak BP180	Methylprednisolone (0.5 mg/kg/d), dapsone	Resolution	
		5/M	Hands and feet	None	C3, weak IgG, faint IgA, IgM	— Epidermal	Weak BP180	Prednisolone (0.5 mg/kg/d), dapsone	Resolution No recurrence 14 mo later	

Baykal et al ²	2001	3.5/M	Hands and feet	None	IgG, C3	1:10 Epidermal	BP180	Methylprednisolone (1 mg/kg/d)	Resolution
Fisler et al ¹⁰	2003	5/M	Hands and feet	None	IgG, C3, weak IgA	NA	NA	Topical steroids	No recurrence 5 mo later
		8/F	Palms and soles	Present	IgG, C3	NA	NA	Prednisolone (2 mg/kg/d), mycophenolate mofetil (20 mg/kg/d)	Resolution but recurrence after discontinuation of steroids Resolution with readministration Partial response Exacerbation with tapering steroids
Kinbara et al ³⁰	2003	2.5/M	Face	None	IgG, C3	1:80 Epidermal (1:80)	BP180	Betamethasone (0.4 mg/kg/d), clarithromycin	Resolution No recurrence 5 mo later
Katsuura et al ⁹	2003	4/F	Palms and soles	None	IgG, C3, weak IgA, IgM	—	—	White petrolatum, antihistamine	Resolution No recurrence 6 mo later
Kuenzli et al ¹	2004	9/F	Palms and soles	Present	IgG, C3	— Epidermal	Negative	Prednisolone (1 mg/kg/d), sulfapyridine	Resolution No recurrence 1 y later
Current case	2007	3/M	Soles	None	IgG, C3	1:80 Epidermal	BP180, BP230	Dexamethasone (3 mg/d), dapsone, erythromycin IVIG	Partial response Recurrence with tapering steroids Resolution after 2 cycles IVIG therapy

BP180, Bullous pemphigoid antigen 180; BP230, bullous pemphigoid antigen 230; DIF, direct immunofluorescence; F, female; IIF, indirect immunofluorescence; IVIG, intravenous immunoglobulin; M, male; NA, not assessed; —, unknown.

improvement of the skin lesions. No adverse effects were observed in either cycle.

In conclusion, IVIG should be considered as the treatment of choice for infantile patients with BP who are resistant to conventional therapies or in whom significant adverse side effects develop.

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