Case Report

IgA Pemphigus: Subcorneal Pustular Dermatosis Type

- A case report with vesicle and pustular eruption for 13 years cured with dapsone in 3 weeks

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IgA pemphigus is a newly characterized group of autoimmune intraepidermal blistering diseases presenting as vesiculopustular eruptions with a predilection in axillary and groin areas. Immunopathologically, IgA deposition in the intercellular space of the epidermis is present in all cases of IgA pemphigus by direct immunofluorescence. However, unlike pemphigus vulgaris, IgA pemphigus carries a relatively benign course. Herein we reported a case of subcorneal pustular dermatosis type IgA pemphigus associated with monoclonal IgA gammopathy. The eruptions cleared with dapsone 50 mg daily for three weeks and no recurrence was found after 6-months follow-up. (Dermatol Sinica 26: 258-263, 2008)

Key words: IgA pemphigus, Subcorneal pustular dermatosis, Monoclonal IgA gammopathy

INTRODUCTION

IgA pemphigus is a rare bullous dermatosis caused by IgA autoantibodies.[1] Clinical manifestations include localized or generalized itching blisters and pustules. According to histopathology and direct immunofluorescence (DIF) features, IgA pemphigus can be divided into two subtypes: subcorneal pustular dermatosis type (SPD type) and intraepidermal neutrophilic dermatosis type (IEN type).[1, 2]

CASE REPORT

A 62-year-old man without underlying systemic diseases had experienced generalized itching tiny vesicles and pustules on the trunk and limbs with a predilection of the flexures for 13 years (Fig. 1). These vesicles and pustules (Fig. 2) ruptured in a few days with crusted macules and papules formation, and tended to coalesce to form desquamative plaques. The oral mucosa was not involved. A skin biopsy taken 3 years ago showed nonspecific dermatitis. Topical steroid was used with only partial improvement. Because of persistent skin eruption, a second skin biopsy was done and showed subcorneal neutrophilic pustules with dyskeratotic cells and few acantholytic cells (Fig. 3). Perivascular infiltrates of neutrophils, lymphocytes and eosinophils were present in upper dermis. DIF revealed intercellular deposition of IgA

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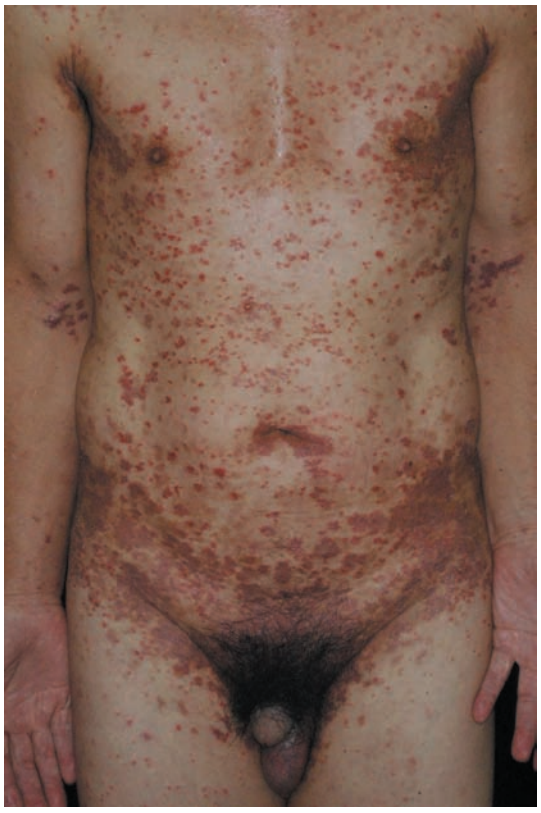

Fig. 1

Diffuse erythematous papules and plaques with mild desquamation over trunk and limbs, more prominent on axilla and groins.

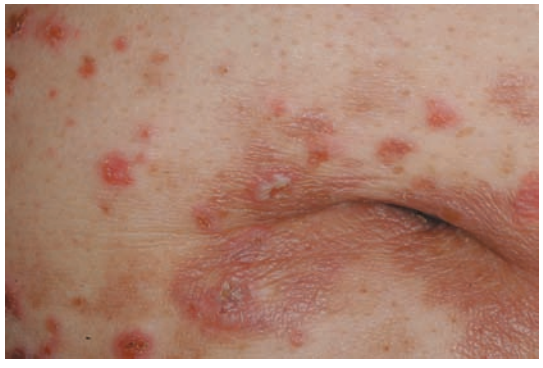

Fig. 2

Tiny pustules on erythematous plaques over the periumbilical area.

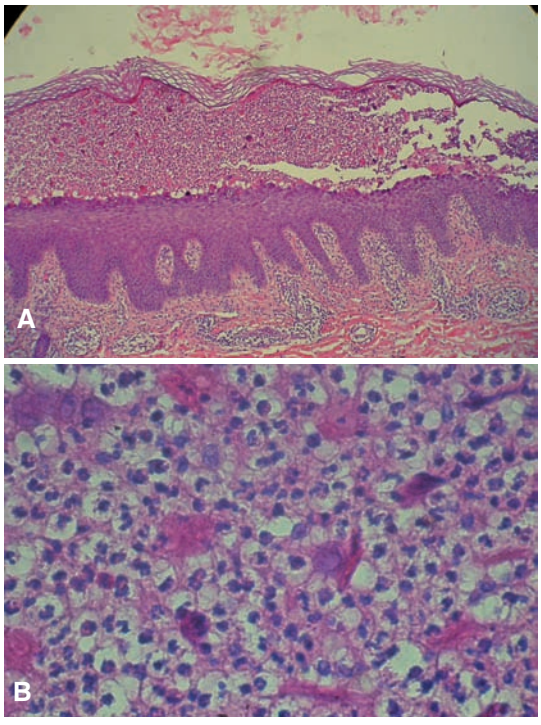

Fig. 3

(A) Biopsy from a pustular lesion showed subcorneal pustule, psoriasiform hyperplasia of epidermis, and superficial perivascular infiltration of inflammatory cells. (H&E, original magnification x100).

(B) Numerous neutrophils and dyskeratotic keratinocytes were found in the subcorneal pustule. (H&E, original magnification x400).

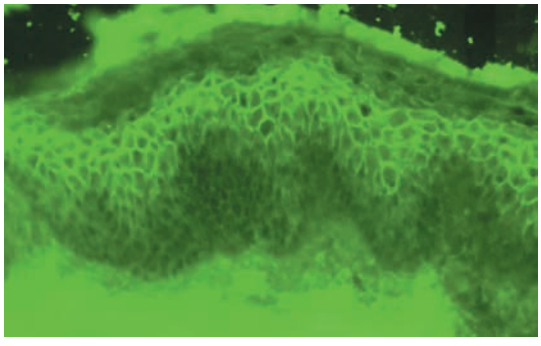

Fig. 4

Direct immunofluorescence revealed intercellular IgA deposition in the upper epidermis.

in the upper epidermis (Fig. 4). Indirect immunofluorescence (IIF) was negative. Laboratory data showed elevated serum IgA 555mg/dL (reference range: 82-453), and IgE 1366 KU/L (reference range: 80-120). Monoclonal IgA kappa chain gammopathy was found by serum immunoelectrophoresis. No hematological malignancy was detected

Table. 1 Comparison Between SPD Type and IEN Type of IgA Pemphigus

	SPD type	IEN type
Clinical manifestation	Flaccid vesicles or pustules on face, trunk and limbs. Pustules tend to coalesce to form annular or circinate pattern with crusts formation. Rare mucosa involvement.	Similar as SPD type
Histopathology	Subcorneal pustules filled with numerous neutrophils, no or few acantholytic cells	Intraepidermal pustules contains neutrophils, no or few acantholytic cells
DIF	Intercellular IgA deposition over upper epidermis	Intercellular IgA deposition over whole epidermis
Autoantigen	Desmocollin 1	Unknown
Associated disease	Monoclonal IgA gammopathy, Sjögren syndrome, rheumatoid arthritis	HIV infection, ulcerative colitis, Crohn's disease
Treatment	Dapsone, systemic steroids, topical steroids, colchicine, azathioprine, sulphapyridine, PUVA, sulphamethoxazole, clarithromycin	Dapsone, systemic steroids, topical steroids, colchicine, sulphapyridine, cyclophosphamide, plasmapheresis

by serological and imaging examinations. The final diagnosis of this patient was SPD type IgA pemphigus associated with monoclonal IgA gammopathy. Oral dapsone 50 mg daily was administered and the skin eruption resolved after 3 weeks of treatment with post-inflammatory hyperpigmentation. No recurrence was found after 6-months follow-up.

DISCUSSION

IgA pemphigus is an autoimmune bullous dermatosis recognized in recent decades. In 1982, Walach described a case of subcorneal pustules with intercellular IgA deposition in ther upper layer of epidermis, under the name of "subcorneal pustular dermatosis and monoclonal IgA".[3, 4] Since then, similar cases had been published and known as either intraepidermal neutrophilic IgA dermatosis, intercellular IgA dermatosis, IgA pemphigus foliaceus, IgA herpetiform pemphigus, intraepidermal IgA pustulosis, or intercellular IgA vesiculopustular dermatosis.[5-7] "IgA pemphigus" was first proposed by Hodak *et al.* in 1990 and has became the most common entity.[3] It occurs most commonly in the middle age and elders, although several pediatric cases are also reported.[7, 8] Based on pathology and DIF findings, IgA pemphigus can be further divided into two subtypes, namely, SPD type and IEN type.[1, 2] SPD type

is more common than IEN type. The comparision between two subtypes is listed on Table 1. The pathogenesis of IgA pemphigus is analogous to pemphigus vulgaris.

Circulating IgA autoantibodies target specific components of desmosomes between keratinocytes and result in intraepidermal blisters formation.[1] Desmocollin 1 (Dsc1) is confirmed to be the autoantigen of SPD type IgA pemphigus.[9-11] Desmocollin (Dsc) is an important transmembrane glycoprotein of desmosome and belongs to cadherin supergene family.[9] Similar to desmoglein, there are also three isoforms of Dsc named Dsc1, Dsc2 and Dsc3.[12] The autoantigen of IEN type is still to be determined, although desmoglein 1 and desmoglein 3 have been demonstrated in a few reports.[9, 12] The result of immunoelectron microscopic study revealed that the antigen of IEN type may not be a desmosomal component.[12]

Initial manifestations of IgA pemphigus are flaccid vesicles and pustules on erythematous bases. Blisters and pustules ruptured quickly to form crusted papuloplaques with confluent tendency. Nikosky sign is negative.[7] The whole body can be involved with a predilection of flexures, such as axilla, groin and submammary area.[1, 3] Mucosa is usually free of lesions.[1, 4, 7] SPD type and IEN type can not always be distinguished by clinical presensations. Other differential diagnoses include subcorneal pustular dermatosis, pemphigus foliaceus, dermatitis herptiformis, linear IgA dermatosis and bullous impetigo.[4] Pathologically, subcorneal neutrophilic pustules and perivascular mixed infiltrates can be found. Intercellular IgA deposition in the epidermis is the main characteristic of DIF finding in IgA pemphigus.[12] IIF using human skin as substrate detects circulating IgA antibodies in about a half of patients. The titers are usually low and may decrease after successful treatment. However, antibody titer does not has good correlation to disease activity.[7]

IgA pemphigus has been reported to be associated with monoclonal IgA gammopathy.[7] Other associated diseases include rheumatoid arthritis, Sjögren syndrome, ulcerative colitis, Crohn's disease, and HIV infection.[3, 7] Monoclonal IgA gammopathy is found in about 20% of IgA pemphigus patient which may precede or follow IgA pemphigus but is usually detected at the same time.[13, 14] Besides, all of them are SPD type. Because of the rarity, the relationship is not clear.[14] However, some authors think that a complete survey for hematological disorders is necessary in all patients with IgA pemphigus.[15]

As for treatment, dapsone is the first-line drug of choice for IgA pemphigus.[1, 3, 4, 6, 7] The initial dosage is 50-100 mg daily.[7] Systemic steroid and retinoid acid (acitretin or isotretinoin) are alternatives when dapsone can not be used.[6, 16] There are also a few successful reports using colchicine, azathioprine, sulphapyridine, azithromycin, cyclophosphamide, plasmaphoresis, PUVA, and topical steroids.[6, 17-19] In conclusion, IgA pemphigus usually runs a benign course and can be under well control if appropriate therapy is given.[1, 15] Physicians should keep IgA pemphigus in mind while approaching patients with bullous eruption.

REFERENCES

1. Robinson ND, Hashimoto T, Amagai M, *et al.*: The new pemphigus variants. J Am Acad Dermatol 40: 649-671, 1999.
2. Hashimoto T, Yasumoto S, Nagata Y, *et al.*: Clinical, histopathological and immunological distinction in two cases of IgA pemphigus. Clin Exp Dermatol 27: 636-640, 2002.
3. De Oliveira JP, Gabbi TV, Hashimoto T, *et al.*: Two Brazilian cases of IgA pemphigus. J Dermatol 30: 886-891, 2003.
4. Nishikawa T, Hashimoto T: Dermatoses with intraepidermal IgA deposits. Clin Dermatol 18: 315-318, 2000.
5. Niimi Y, Kawana S, Kusunoki T: IgA pemphigus: A case report and its characteristic clinical features compared with subcorneal pustular

dermatosis. J Am Acad Dermatol 43: 546-549, 2000.
6. Yasuda H, Kobayashi H, Hashimoto T, *et al.*: Subcorneal pustular dermatosis type of IgA pemphigus: demonstration of autoantibodies to desmocollin-1 and clinical review. Br J Dermatol 143: 144-148, 2000.
7. Ongenae KC, Temmerman LJ, Vermander F, *et al.*: Intercellular IgA dermatosis. Eur J Dermatol 9: 85-94, 1999.
8. Bruckner AL, Fitzpatrick JE, Hashimoto T, *et al.*: Atypical IgA/IgG pemphigus involving the skin, oral mucosa, and colon in a child: a novel variant of IgA pemphigus? Pediatr Dermatol 22: 321-327, 2005.
9. Hashimoto T: Recent advances in the study of the pathophysiology of pemphigus. Arch Dermatol Res 295: S2-S11, 2003.
10. Hashimoto T, Kiyokawa C, Mori O, *et al.*: Human desmocollin 1 (Dscl) is an autoantigen for the subcorneal pustular dermatosis type of IgA pemphigus. J Invest Dermatol 109: 127-131, 1997.
11. Hashimoto T, Ebihara T, Dmochowski M, *et al.*: IgA antikeratinocyte surface autoantibodies from two types of intercellular IgA vesiculopustular dermatosis recognize distinct isoforms of desmocollin. Arch Dermatol Res 288: 447-452, 1996.
12. Hashimoto T: Immunopathology of IgA pemphigus. Clin Dermatol 19: 683-689, 2001.
13. Aste N, Fumo G, Pinna AL, *et al.*: IgA pemphigus of the subcorneal pustular dermatosis type associated with monoclonal IgA gammopathy. J Eur Acad Dermatol Venereol 17: 725-727, 2003.
14. Harman KE, Holmes G, Bhogal BS, *et al.*: Intercellular IgA dermatosis (IgA pemphigus)--two cases illustrating the clinical heterogeneity of this disorder. Clin Exp Dermatol 24: 464-466, 1999.
15. Gniadecki R, Bygum A, Clemmensen O, *et al.*: IgA pemphigus: the first two Scandinavian cases. Acta Derm Venereol 82: 441-445, 2002.
16. Ruiz-Genao DP, Hernandez-Nunez A, Hashimoto T, *et al.*: A case of IgA pemphigus successfully treated with acitretin. Br J Dermatol 147: 1040-1042, 2002.
17. Hodak E, Lapidoth M, David M: Effect of colchicine in the subcorneal pustular dermatosis type of IgA pemphigus. J Am Acad Dermatol 40: 91-94, 1999.
18. Sibley Hash K, Rencic A, Hernandez MI, *et al.*: Aggressive immunosuppressive therapy for a refractory case of IgA pemphigus. Arch Dermatol 138: 744-746, 2002.
19. Bliziotis I, Rafailidis P, Vergidis P, *et al.*: Regression of subcorneal pustular dermatosis type of IgA pemphigus lesions with azithromycin. J Infect 5: E31-E34, 2005.

角質層下膿疱性皮膚病亞型免疫球蛋白A天疱瘡
- 一例13年皮疹以 Dapsone 3 週治癒之病例報告

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免疫球蛋白A(IgA)天疱瘡是一種新歸類的自體免疫皮膚水疱性疾病。其臨床表現為搔癢的水疱性與膿疱性皮疹，好發位置為身體對摩的部位 (如腋下與腹股溝)。此類病人取皮膚病灶作直接免疫螢光染色可發現IgA在表皮細胞間沈積。然而，與尋常性天疱瘡相異的是，IgA天疱瘡的病程是比較輕微而且預後較好。我們提出一位角質層下膿疱性皮膚病亞型 IgA天疱瘡合併單株IgA免疫球蛋白症的案例。此病人接受每日口服 dapsone 50 mg治療三星期後，皮疹獲得顯著的改善，停藥後半年亦無復發現象。（中華皮誌：26: 258-263, 2008）