IgA/IgG Pemphigus: A New Atypical Subset of Pemphigus?

Cezary Kowalewski[1], Takashi Hashimoto[2], Masayuki Amagai[3], Stefania Jablonska[1], Wojciech Mackiewicz[1] and Katarzyna Wozniak[1]

Departments of Dermatology, [1]Medicine University of Warsaw, Koszykowa 82a, O2-008 Warszawa, Poland, [2]Kurume University School of Medicine, Kurume, and [3]Keio University School of Medicine, Tokyo, Japan. E-mail: sjablonska@pro.onet.pl

Accepted November 11, 2005.

Sir,

The classical types of pemphigus are well characterized clinically, histologically and immunologically. The target antigens were found to be desmoglein 1 (Dsg1) for pemphigus foliaceus and Dsg3 for pemphigus vulgaris (1). However, there are atypical cases which could not be classified into either of these types. At present two major atypical forms are recognized: pemphigus herpetiformis (PH) (2, 3) and IgA pemphigus with its subsets: subcorneal pustular dermatosis (SPD) (4–6) and intraepidermal neutrophilic IgA dermatosis (IEN) (7–9).

The clinical pattern of PH and IgA pemphigus may to varying degrees resemble dermatitis herpetiformis (erythematous, herpetiform eruption, often in annular arrangement). The histological pattern is not characteristic since subcorneal acantholysis may be slight or absent (10).

Since the clinical and histological differentiation of PH and IgA pemphigus might be difficult or even not possible, the diagnosis is based on immunological findings: IgG antibodies in PH (3) and IgA antibodies in IgA pemphigus (6, 8, 11). The most interesting problem is coexistence in some cases of both IgA and IgG antibodies, referred to as IgA/IgG pemphigus (12). Since this subset of pemphigus is still not known we present under this name a case with clinical and histological features of PH and immunological pattern of IgA pemphigus of IEN type and reactivity of both IgG and IgA antibodies exclusively to Dsg1.

CASE REPORT

A 33-year-old woman had a 2-year history of erythematous and vesiculo-bullous itchy eruptions on the trunk, neck and limbs. Some lesions were pustular, in places forming aggregates, some were covered with scales or superficial crusts (Fig. 1). The mucous membranes were not involved. The general condition of the patient was satisfactory. Six years ago she had had ovarian carcinoma which after the surgery was treated by chemotherapy (6 courses). There was no relapse in more than 5 years of follow-up. Four years after completion of the therapy a vesiculobullous eruption responsive to sulfones appeared. However, after withdrawal of sulfones she was admitted to hospital with widespread new lesions.

The histology showed superficial, partly subcorneal bullae filled with neutrophils.

Direct immunofluorescence analyses disclosed strong IgG and IgA intercellular staining throughout the whole epidermis, which was more pronounced in the upper parts (Fig. 2).

Both IgG and IgA circulating antibodies to keratinocyte cell surface were detected in different periods of the disease in the same titres: 80–640 (Fig. 3).

Immunoblot analysis using normal epidermal extracts did not show any specific protein bands for either IgG or IgA antibodies.

Specific enzyme-linked immunosorbent assay (ELISA) showed strong reactivity to Dsg1 of both IgG (index 242.96, by cut-off 20) and IgA (OD 1.702, positive > 0.15) antibodies, and no reactivity of IgG and IgA antibodies to Dsg3. Antibodies to Desmocollins (Dsc) 1–3 were not disclosed using Dsc cDNA transfected COS-7 cells.

The response to sulfones was dramatic. However, a prolonged therapy with dapsone 50–150 mg/day proved to be insufficient and had to be supplemented with 40 mg/day of prednisone, which produced clearing.

DISCUSSION

The case of IgA/IgG pemphigus presented here has the clinical features of PH with vesiculo-pustular itchy

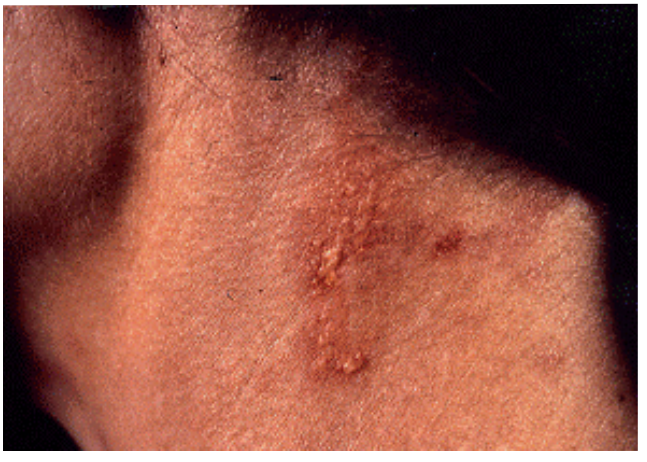

Fig. 1. Erythematous and brownish plaques with bullae and pustules. Aggregates of pustules and blisters, partially in circinate arrangement.

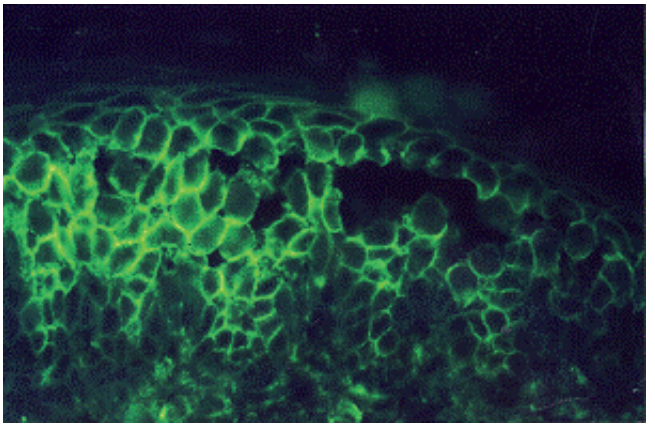

Fig. 2. Direct immunofluorescence: IgG intercellular deposits throughout the epidermis, more pronounced in the upper parts.

 ISSN 0001-5555
DOI: 10.2340/00015555-0060

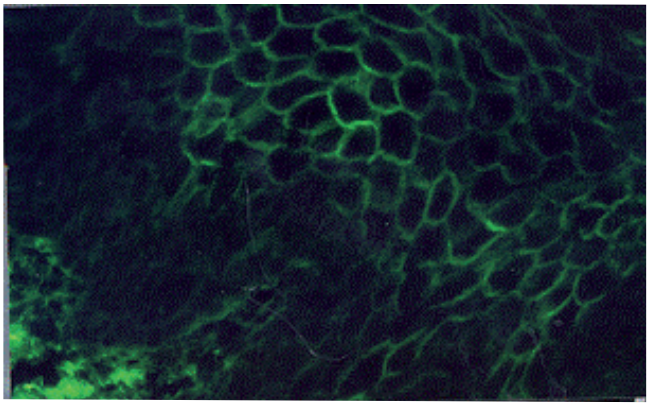

Fig. 3. Indirect immunofluorescence on monkey oesophagus: IgG keratinocyte cell surface antibodies (titre 1/320).

eruption, and histological features of both PH and subcorneal pustular dermatosis. It differs from PH by presence of IgA antibodies reactive, similarly as IgG antibodies, to Dsg1. From the SPD type of IgA pemphigus it differs by absence of reactivity to Dsc1, and from both SPD and IEN by presence not only of IgA, but also of IgG antibodies. A similar case with clinical and histological features of PH, and *in vivo* bound and circulating IgA as well as IgG antibodies, both reactive to Dsg1 in ELISA was reported by Oiso et al. (13).

Our previous case of this type with coexistent IgA and IgG antibodies to keratinocyte cell surface, also reactive exclusively to Dsg1, was reported as PH with IgG and IgA antibodies to Dsg1 (14). Specific IgG and IgA ELISA disclosed high titres of IgA and IgG anti-Dsg1 antibodies, and no reactivity to Dsg3. In contrast to SPD type of IgA pemphigus, there was also no reactivity to Dsc1, as shown on COS-7 cells transfected with cDNA of human Dsc. Thus, also this case due to high titres IgA antibodies could not be classified either as SPD type of IgA pemphigus, nor as PH.

Coexistent IgG and IgA autoantibodies in atypical cases of pemphigus are probably present more often than hitherto recognized. We have previously described another such case as unusual acantholytic bullous dermatosis with antibodies reactive exclusively to Dsc1 (15). In spite of reactivity of antibodies to Dsc, such cases can neither be diagnosed as IgA pemphigus of SPD or IEN, nor PH type because of presence of IgG and IgA antibodies, and the most suitable name appears to be IgA/IgG pemphigus (12). It is not clear whether IgA/IgG pemphigus should be regarded as a separate atypical form of pemphigus or as an overlap of PH and IgA pemphigus. It is conceivable that a shift between PH and IgA pemphigus may occur, in analogy with documented shifts between pemphigus vulgaris and pemphigus foliaceus. It is not known whether the coexistence of anti-IgG and anti-IgA Dsg antibodies is stable, how it relates to the clinical presentation in various periods of the disease and how it affects response to therapy. The answers to these questions will have to await studies of more cases with follow-up times long enough to make the detection of shifts in clinical presentation and autoantibody patterns possible.

REFERENCES

1. Amagai M. Pemphigus: autoimmunity to epidermal cell adhesion molecules. Adv Dermatol 1996; 11: 319–352.
2. Jablonska S, Chorzelski TP, Beutner EH, Jarzabek-Chorzelska M. Herpetiform pemphigus, a variable pattern of pemphigus. Int J Dermatol 1975; 14: 353–359.
3. Ishii K, Amagai M, Komai A, Ebihara T, Chorzelski TP, Jablonska S, et al. Desmoglein 1 and desmoglein 3 are the target autoantigens in herpetiform pemphigus. Arch Dermatol 1999; 135: 943–947.
4. Wallach D, Cottenot F, Pelbois G, Cavelier B, Didierjean L, Saurat JH. Subcorneal pustular dermatosis and monoclonal IgA. Br J Dermatol 1982; 107: 229–234.
5. Hashimoto T, Kiyokawa C, Mori O, Miyasato M, Chidgey MA, Garrod DR, et al. Human desmocollin 1 (Dsc1) is an autoantigen for the subcorneal pustular dermatosis type of IgA pemphigus. J Invest Dermatol 1997; 109: 127–131.
6. Yasuda H, Kobayashi H, Hashimoto T, Itoh K, Yamane M, Nakamura J. Subcorneal pustular dermatosis type of IgA pemphigus: demonstration of autoantibodies to desmocollin-1 and clinical review. Br J Dermatol 2000; 143: 144–148.
7. Hashimoto T, Inamoto N, Nakamura K, Nishikawa T. Intercellular IgA dermatosis with clinical features of subcorneal pustular dermatosis. Arch Dermatol 1987; 123: 1062–1065.
8. Hashimoto T, Komai A, Futei Y, Nishikawa T, Amagai M. Detection of IgA autoantibodies to desmogleins by an enzyme-linked immunosorbent assay: the presence of new minor subtypes of IgA pemphigus. Arch Dermatol 2001; 137: 735–738.
9. Harman KE, Holmes G, Bhogal BS, McFadden J, Black MM. Intercellular IgA dermatosis (IgA pemphigus) – two cases illustrating the clinical heterogeneity of this disorder. Clin Exp Dermatol 1999; 24: 464–466.
10. Hashimoto T, Yasumoto S, Nagata Y, Okamoto T, Fujita S. Clinical, histopathological and immunological distinction in two cases of IgA pemphigus. Clin Exp Dermatol 2002; 27: 636–640.
11. Chorzelski TP, Beutner EH, Kowalewski C, Olszewska M, Maciejowska E, Seferowicz E, et al. IgA pemphigus foliaceus with a clinical presentation of pemphigus herpetiformis. J Am Acad Dermatol 1991; 24: 839–844.
12. Hashimoto T. Recent advances in the study of the pathophysiology of pemphigus. Arch Dermatol Res 2003; 295 (suppl 1): S2–S11.
13. Oiso N, Yamashita C, Yoshicka K, Amagai M, Komai A, Nagata Y, et al. IgA/IgG pemphigus with IgG and IgA anti-desmoglein 1 antibodies detection by enzyme-linked immunosorbent assay. Br J Dermatol 2002; 147: 1012–1017.
14. Kozlowska A, Hashimoto T, Jarzabek-Chorzelska M, Amagai A, Nagata Y, Strasz Z, et al. Pemphigus herpetiformis with IgA and IgG antibodies to desmoglein 1 and IgG antibodies to desmocollin 3. J Am Acad Dermatol 2003; 48: 117–122.
15. Chorzelski TP, Hashimoto T, Nishikawa T, Ebihara T, Dmochowski M, Ismoil M, et al. Unusual acantholytic bullous dermatosis associated with neoplasia and IgG and IgA antibodies against bovine desmocollins I and II. J Am Acad Dermatol 1994; 31: 351–355.