Pemphigus Improving with Gluten-free Diet

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Sir,

Serum IgA class anti-endomysial antibodies (EMA) are markers of coeliac disease and dermatitis herpetiformis (DH) and are useful in monitoring compliance to diet. Their overall sensitivity for the diagnosis of DH is about 80% and their specificity around 96% (1). As anti-gliadin antibodies (AGA) have already been reported in pemphigus (2, 3), the presence of AGA in another patient with pemphigus may not surprise, but the finding of IgA-EMA in yet another, and the response of both patients to a gluten-free diet treatment are worthy of attention.

CASE REPORTS

Patient 1

An 82-year-old woman presented with a 20-day history of a bullous eruption. She had not been taking any drug and had previously been in good health. She exhibited vesiculobullous lesions on the trunk and eczematous lesions on the thighs. There were no mucosal or scalp lesions.

Histopathology showed spongiosis and lymphocytic exocytosis. Oedema and a modest inflammatory infiltrate were present in the superficial dermis. The infiltrate was perivascular and interstitial, with prevalence of eosinophils.

Direct immunofluorescence disclosed a pemphigus-like deposition of IgA in the epidermal intercellular space (ICS). No other immunoglobulins or complement components were deposited.

Circulating anti-ICS IgA was also demonstrated by indirect immunofluorescence on monkey oesophagus (Alfabiotec, Rome, Italy) at a titre of 1:40 together with IgA-EMA (+). ELISA showed circulating IgG-AGA (++) and IgA-AGA (+). The liquid from bullae did not contain anti-ICS IgA, but it was strongly positive for IgA-EMA. Anti-transglutaminase antibodies were absent in the serum. Immunoblotting performed on keratinocyte extracts showed circulating antibodies directed to an aspecific band at 140-kDa, both with anti-total Ig and anti-IgA.

Full blood count, erythrocyte sedimentation rate, liver function tests, electrolytes and total IgE were within normal limits. No monoclonal IgA was found by immunoelectrophoresis.

Even in the absence of DH features, either in histology or in direct immunofluorescence, IgA-EMA, IgG-AGA and IgA-AGA prompted us to introduce a gluten-free diet. Twenty days later the lesions had cleared. Interruption of the diet caused clinical lesions to relapse promptly.

Patient 2

An 18-year-old woman presented with a 1-month history of vesiculobullous eruption on the chest. On examination, the bullae were tense and arose on erythematous skin. Gradually, they extended centrifugally from the breast to the abdomen, neck and lumbar regions, and then to the limbs and arms. No other abnormality was observed.

Full blood count, erythrocyte sedimentation rate, liver function tests, electrolytes, antinuclear antibodies, serum levels of immunoglobulins and complement components were within normal limits.

Histological examination of lesional skin showed a subcorneal bullous lesion. There was acantholysis and spongiosis with eosinophilic exocytosis. Oedema and a perivascular infiltrate of eosinophils and lymphocytes were seen in the upper dermis.

Direct immunofluorescence of the lesional skin revealed a deposition of IgG and C3 in ICS. Indirect immunofluorescence on monkey oesophagus revealed circulating IgG anti-ICS (1:160). ELISA showed IgG-AGA (+++) and IgA-AGA (++) in the serum. Circulating IgA-EMA and anti-transglutaminase antibodies were absent. Serum immunoblotting on keratinocyte extracts reacted at 160-kDa antigen, typical of pemphigus foliaceus. ELISA confirmed the presence of serum antibodies directed to the 160-kDa antigen.

The presence of IgG-AGA prompted us to introduce a gluten-free diet, even in the absence of any clinical, histological and further immunological evidence of coeliac disease. One month later, lesions had cleared and the IgG-AGA titre abated, in spite of IgG anti-ICS having increased up to 1:160.

DISCUSSION

The various test results of the two patients are shown in Table I. The patients had IgA pemphigus and

Table I. *Summary of immunoserological results*

		Circulating antibodies				Blister fluid
Patient no.	DIF	IIF	ELISA	IB	TG Ab	IIF
1	IgA in ICS	IgA anti-ICS 1:40 IgA-EMA +	IgG-AGA ++ IgA-AGA +	140 kDa	Negative	IgA-EMA+++
2	IgG and C_3 in ICS	IgG anti-ICS 1:160 IgA-EMA	IgG-AGA +++ IgA-AGA ++	160 kDa	Negative	ND

DIF, direct immunofluorescence; IIF, indirect immunofluorescence; IB, immunoblotting; Ab, antibody; ICS, intercellular substance; AGA, antigliadin antibody; EMA, antiendomysial antibody; ND, not done; TG, transglutaminase.

pemphigus foliaceus, respectively. This was confirmed by direct immunofluorescence. Both shared two interesting features, the presence of serological markers of glutensensitive enteropathy and the impressive response to a gluten-free diet.

IgA-AGA and/or IgG-AGA mark coeliac disease and DH, but are also encountered in other disorders including psoriasis (4, 5), SLE (6) and pemphigus/pemphigoid (2). In fact, their prevalence in the population at large is as high as 5.7% (7).

IgA-EMA has a higher degree of specificity for DH and coeliac disease, although their prevalence in the population at large is 1.2% (7) and their sensitivity may be disappointing (8). IgA-EMA have never been reported in patients with pemphigus or pemphigoid (9).

Coeliac disease has an extremely polymorphic nature. Atypical or subclinical cases affecting several organs, without gastrointestinal symptoms, must be common, especially as cases with normal mucosal architecture of the bowel exist (8). Unfortunately, an accurate estimation of the incidence of these cases is lacking. In Italy, a recent survey disclosed that almost half of the diagnosed patients had a subclinical/silent form. The most frequent extra-intestinal marker of the subclinical cases were iron-deficiency anaemia (28%), alopecia and DH (11%), osteoporosis (7%) and recurrent aphthous stomatitis (6%), while first-degree relatives (30%), Basedow's disease (25%) and insulin-dependent diabetes (20%) were the most frequent associations in silent forms (10).

In our patients, the presence of both markers of coeliac disease suggests an underlying subclinical coeliac disease without diarrhoea, steatorrhoea, anaemia or low weight. The response to the gluten-free diet and the relapse that followed its withdrawal both strongly support the proposition that the patients had a silent gluten sensitivity. Unfortunately, both the patients refused duodenal biopsies.

Examples of a successful gluten-free diet in other cutaneous diseases exist, however. Psoriasis patients with high levels of IgA- and IgG-AGA improved with such a regimen even in the absence of IgA-EMA and of high numbers of intra-epithelial lymphocytes in duodenal mucosa (11). Alopecia areata occurs in 1.6% of patients with DH (12), but the effect of the diet is controversial (13–15). Although dapsone is regarded as the first-line therapy in IgA pemphigus (16) (possibly just because of a concomitant subclinical coeliac disease), a gluten-free diet has never been used before to treat pemphigus.

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