

## CLINICAL REPORT

# IgA Pemphigus: The First Two Scandinavian Cases

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**IgA pemphigus is a rare neutrophilic acantholytic skin disorder with only approximately 70 cases reported in the indexed literature to date. Here we describe two patients with IgA pemphigus (subcorneal pustular dermatosis type and intraepithelial neutrophilic type) that to our knowledge are the first Scandinavian patients with this disease. Initially, both patients were misdiagnosed as subcorneal pustular dermatosis of Sneddon and Wilkinson and only subsequent careful immunofluorescence studies (in one case with confocal laser scanning microscopy) led to the correct diagnosis. Apart from the expected IgA depositions on epidermal cell surfaces, both patients demonstrated some degree of intercellular IgG-specific immunofluorescence. No circulating IgA autoantibodies were detected. One patient was treated with the standard regime comprising dapsone and prednisolone, whereas in the other case a novel methotrexate and prednisolone combination treatment showed marked clinical efficacy. Key words: IgA pemphigus; immunofluorescence; confocal microscopy; methotrexate.**

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IgA pemphigus, first described in 1982 by Wallach et al. (1), is a newly recognized neutrophilic and acantholytic disorder. Clinically, the patients present with pruritic eruption comprising erythematous, slightly infiltrated plaques with clusters of vesicles, often at the periphery of the lesions with central crusting. Any part of the body can be affected, but the sites of predilection are groins, axillas, lower trunk and proximal parts of the extremities (2). The disease usually occurs in middle-aged to elderly persons with a slight female preponderance (2, 3), but a childhood variant has been described (4–6).

Histopathologically, pustular lesions are often found surrounded by neutrophil infiltrations and accompanied by minimal spongiosis. In the subcorneal pustular dermatosis (SPD) type, the histological alterations are mostly localized in the upper epidermis, whereas in the

intraepithelial neutrophilic (IEN) variant the lower or entire dermis is affected (2, 3, 7–9).

The pathogenesis is considered to be analogous to that of the classic, IgG-mediated pemphigus with IgA autoantibodies against desmosomal proteins causing acantholysis, blistering and neutrophilic inflammation (7, 10). This scenario has been supported by immunofluorescence findings, where fine, intraepithelial, pemphigus-like depositions of IgA have been reported (10–12). In the SPD variant, the IgA deposition is predominantly in the upper epidermal layers, whereas in the IEN variant the depositions are found throughout the entire epidermis or concentrated in its lower part (3, 7, 8, 13–16). Circulating antibodies are found in less than 50% of patients on standard substrates (7, 10, 17, 18). The titres are usually low and their clinical significance of antibody titre is unknown (17, 19).

The target antigens in IgA pemphigus have not been completely elucidated. Desmoglein 3 and desmocollin 1 have been proposed as possible target antigens in the IEN and SPD types, respectively (15, 17, 19–23), but other adhesion proteins are almost certainly involved (2, 3, 10 and unpublished data herein). The acantholysis is probably complement-independent, since complement depositions are only rarely found in affected skin (14, 18).

The disease is extremely rare. To date, over 70 cases of IgA pemphigus have been reported, mostly in the USA, Japan and France. It is possible that the incidence of this disease is underestimated and misdiagnosed as subcorneal pustular dermatosis, Sweet's syndrome, fungal infections or even pustular psoriasis. We report the first two Scandinavian cases of IgA pemphigus of SPD and IEN types.

## CASE REPORTS

### Case 1

An 84-year-old man was admitted to hospital because of generalized pustular skin eruption. His previous medical history was unremarkable except for the diagnosis of arterial hypertension treated with amlodipin. Three years before admission, the patient developed non-itchy, erythematous, slightly infiltrated plaques with superficial, flaccid pustules in the genito-femoral area. Skin biopsies showed subcorneal pustules and superficial perivascular neutrophilic and lymphocytic infiltrates. The direct immunofluorescence was interpreted as negative. The diagnosis of subcorneal pustulosis

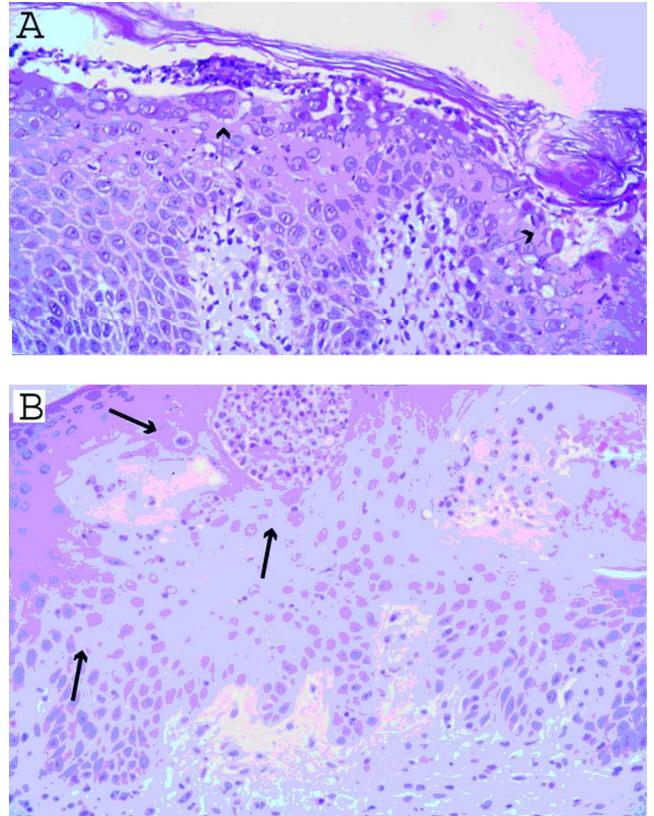
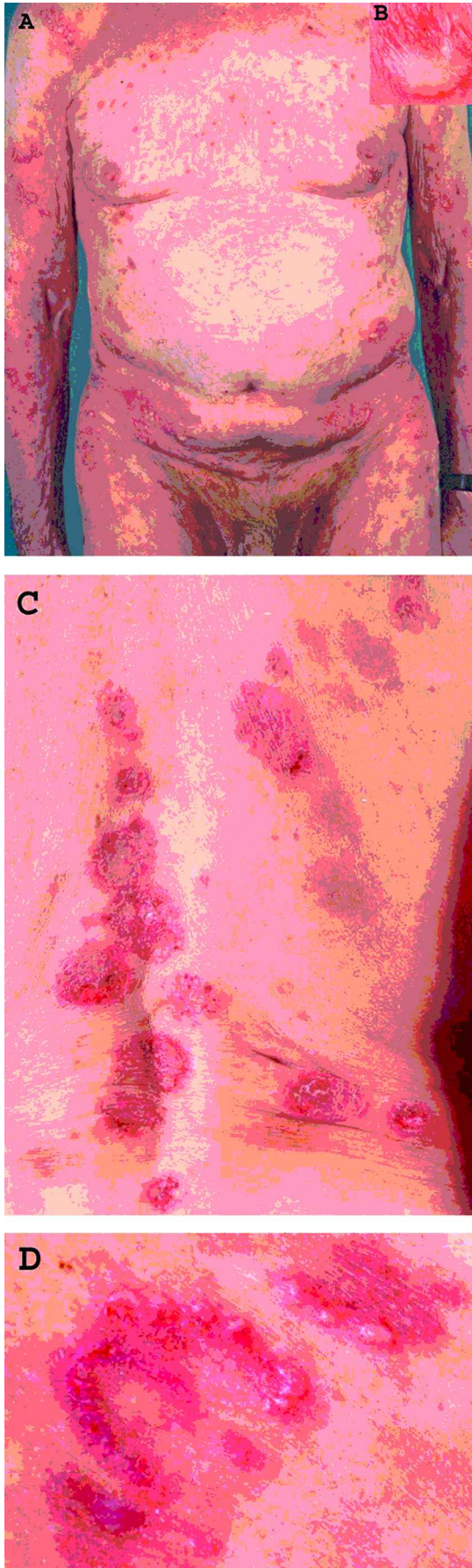


Fig. 2. Histology of IgA pemphigus. a) subcorneal acantholysis and pustules in case 1. b) Intraepidermal pustules and vesicles in case 2. Arrows show acantholytic cells.

was made and dapsone 100 mg daily was started. Unfortunately, the treatment was terminated owing to the development of profound haemolytic anaemia and methemoglobinaemia. The patient was then treated briefly with 25 mg acitretin daily (terminated because of unacceptable side effects (pseudotumor cerebri)) and with colchicine, which failed to improve the disease. Finally, prednisolone at a dose of 10 mg daily was instituted with a partial improvement of skin symptoms.

At admission, the patient presented with a mainly intertriginous, symmetric eruption comprising erythematous, slightly infiltrated plaques with clustered vesicles and flaccid pustules (Fig. 1a, b). The mucosal membranes were not affected. Ophthalmologic examination was normal. Haematology, plasma electrolytes, liver and kidney function tests, albumin and immunoglobulin fractions were normal. M-protein and Bence-Jonck protein were absent. Antinuclear antibodies were negative and chest X-ray was normal. Bone marrow examination was normal.

A skin biopsy revealed subcorneal pustules with acantholysis (Fig. 2a). Direct immunofluorescence of the perilesional, erythematous skin showed slight intercellular deposits of IgA and fainter deposits of IgG localized mostly in the outer epidermis (Fig. 3a). However, this finding was present in only two out of a total of four biopsies. Immunofluorescence of

Fig. 1. Clinical features of IgA pemphigus. a, b (inset). Subcorneal pustular dermatosis type (case 1). Note irregular, erythematous plaques with a predilection for the intertriginous regions with pustules, vesicles and crusting. The level of pus in a flaccid pustule is shown in (b). c, d. Intraepithelial neutrophilic type (case 2), discrete, confluent erosions with crusting. Annular pattern of vesicles and pustules is shown in (d).

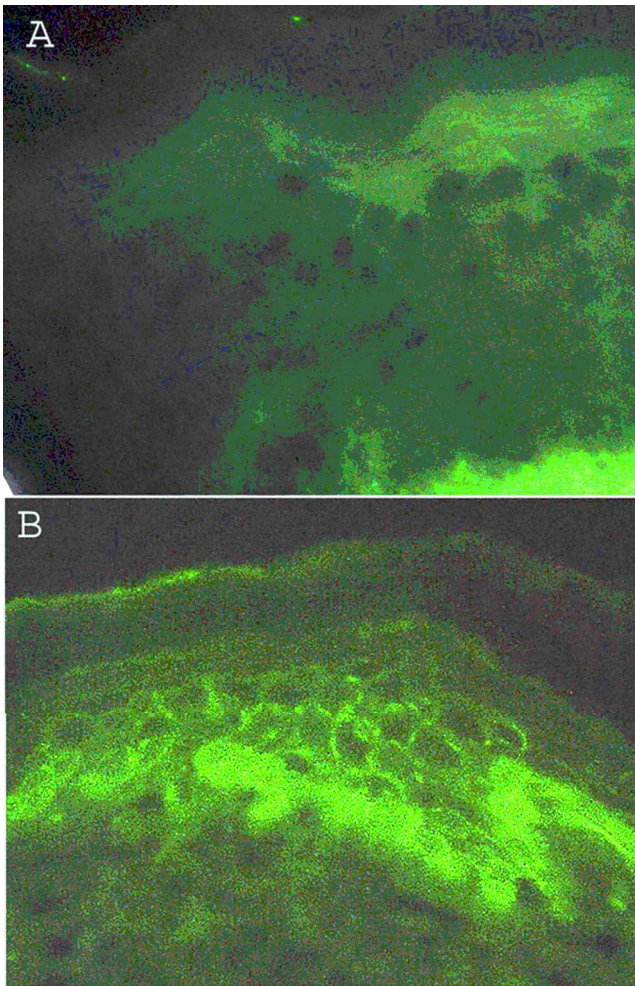


Fig. 3. Direct immunofluorescence in IgA pemphigus in case 1 (a) and case 2 (b).

clinically normal skin appeared negative. To determine whether the deposits represented an unspecific phenomenon, confocal laser scanning microscopy was performed. This method confirmed the presence of intercellular IgA and IgG (but not IgM or C3 complement component) in subcorneal region (Fig. 4). Moreover, faint intercellular IgA (but not IgG) deposits were found in the upper epidermis in non-lesional skin (Fig. 4), reinforcing the diagnosis of IgA pemphigus SPD type. Indirect immunofluorescence for circulating IgA and IgG antibodies on guinea pig lip substrate was negative.

The patient was treated successfully with prednisolone 40 mg daily combined with 10 mg daily acitretin. After 2 months the acitretin was discontinued owing to increased intracranial pressure and the disease flared shortly afterwards. Methotrexate 2.5 mg daily for 4 days/week was initiated and full remission was obtained, which allowed the prednisolone dose to be tapered to 20 mg over 6 months and further to the maintenance dose of 5 mg over an additional 7 months.

#### Case 2

A 60-year-old man presented with an itchy vesicopustular skin eruption on the trunk and extremities. He was treated with carbamazepine because of the history of epilepsy but was otherwise healthy. Five months before admission, subcorneal

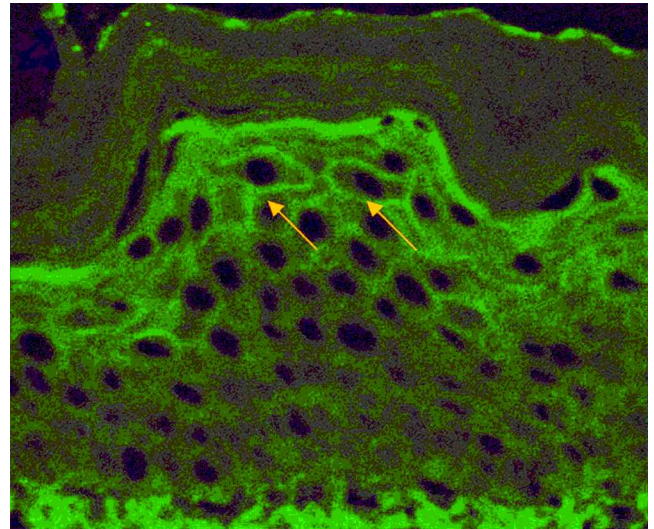


Fig. 4. Confocal microscopy, direct immunofluorescence with FITC-conjugated anti-IgA antibody in case 1. The material was prepared using standard techniques (as for Fig. 3) and scanned using  $\times 40$  dry objective in an Olympus confocal microscope using krypton-argon laser at 488 nm as an excitation source. Intercellular IgA deposits in the upper epidermis in the perilesional skin are marked with yellow arrows. This sample was scored negative in classic immunofluorescence.

pustular dermatosis (Sneddon-Wilkinson) had been diagnosed based on clinical criteria and on the presence of subcorneal pustules in the skin biopsy. The immunofluorescence investigation was not performed at that time and the patient was treated with 50 mg daily dapsone and potent topical glucocorticoid. He was referred to the hospital department because of an insufficient response to treatment.

At admission, the patient presented with a symmetric eruption accentuated centrifugally on the trunk and lower extremities. The eruption comprised annular and nummular erythematous plaques with central erosions and crusts and peripheral vesicles and pustules (Fig. 1c, d). There was no mucosal involvement. Extensive laboratory investigations including haematology, plasma electrolytes, liver and kidney function tests, M-protein and Bence-Jones protein, immunoglobulin fractions, chest X-ray and abdominal ultrasound did not reveal any abnormalities.

The first biopsy specimen showed a normal epidermis with scant perivascular lymphocytic infiltration in the upper dermis. The second biopsy, taken after 3 weeks, showed the same changes, whereas in the biopsy sampled 2 months later there were intraepidermal pustules, mostly in the spinous zone with focal, sparse acantholysis (Fig. 2b). In the superficial dermis, a mixed interstitial and perivascular inflammatory cell infiltrate with lymphocytes, polymorphonuclear granulocytes and scattered eosinophils was seen. Direct immunofluorescence showed intercellular IgA deposits in both involved and clinically normal skin throughout the epidermis, with fading of fluorescence intensity in the subcorneal region (Fig. 3b). Weakly fluorescent intercellular IgG deposits were also noted. There were no depositions of IgM, IgE or C3 and the indirect immunofluorescence for circulating IgA and IgG antibodies on a guinea pig lip as a substrate was negative.

The diagnosis of IgA pemphigus, IEN type, was made and the patient was treated with dapsone at a dose of 100 mg/day combined with prednisolone 15 mg daily. The lesions gradually disappeared and the dose of prednisolone

was tapered over 10 months. Attempts to reduce dapsone resulted in a marked exacerbation of the disease.

## DISCUSSION

Although the clinical changes were suggestive of IgA pemphigus, the diagnosis was established after a considerable time lag in both patients. IgA pemphigus should always be considered in a patient with a non-infectious intraepithelial pustular disease, and differentiated from pemphigus foliaceus, subcorneal pustular dermatosis of Sneddon and Wilkinson, Sweet syndrome, atypical forms of pyoderma gangrenosum and the monoclonal gammopathy-associated neutrophilic dermatoses (24).

It is likely that, as with other neutrophilic dermatoses, IgA pemphigus may sometimes be associated with monoclonal gammopathy (16, 24). Although extensive laboratory studies did not reveal evidence of gammopathy in our patients it seems prudent to evaluate all patients with IgA pemphigus for the presence of this condition and the associated haematological myeloproliferative disorder.

Since the acantholysis in IgA pemphigus is minimal and sometimes even absent (10) it can be argued that immunofluorescence should be employed early in the diagnostics of patients with widespread pustular eruptions. The example of case 1 shows that immunoglobulin depositions in IgA pemphigus may be weak, especially in the SPD type. Several biopsies should be taken from affected and non-affected skin to rule out this autoimmune disorder, since IgA depositions may be absent in some samples. As shown in our cases, pemphigus-like IgG depositions may be present in the skin in IgA pemphigus patients, but their intensity is usually lower than those of IgA and they are usually present only in lesional skin. Chorzelski et al. (23) observed a similar double IgA/IgG intercellular staining in the outer epidermis in their case of allegedly paraneoplastic IgA pemphigus. In difficult cases, where intensity of the direct immunofluorescence is weak and hard to interpret, confocal laser scanning microscopy can be considered to enhance the visualization of intercellular IgA deposits (Fig. 4), especially in the clinically normal skin.

Dapsone is usually considered to be a drug of choice, but should be administered at relatively high doses (100 mg daily) (2). This drug was used together with low-dose prednisolone to control the disease in case 2. However, neither dapsone nor the second-line drug, acitretin, was possible in case 1 because of severe side effects. Colchicine, the efficacy of which was reported in IgA pemphigus (25), was not effective. The novel management with prednisolone and methotrexate reported here was efficacious in this case and may provide an alternative treatment option in patients who

cannot be controlled with dapsone and/or systemic glucocorticoids.

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