

IgG/IgA pemphigus with differing regional presentations



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INTRODUCTION

Immunoglobulin (Ig) A pemphigus is rare. Principal variants include subcorneal pustular dermatosis-type and intra-epidermal neutrophilic-type. Novel subtypes are increasingly being recognized. Herein, we report a case of IgG/IgA pemphigus, an unusual form of pemphigus that has features in common with IgA pemphigus. Emphasis is made on the unique clinical and immunopathologic characteristics pertinent to this patient.

CASE REPORT

A 36-year-old Chinese woman with a history of atopic eczema presented with 3 months' history of skin blisters and scalp scaling, onset of which was 1 and 2 months, respectively, after the consumption of herbal medicine. Physical examination revealed pustular eruptions with peri-vesicular erythema and pustules over the trunk and proximal part of the limbs (Fig 1, A). Pityriasis amiantacea-like lesions were noted over the scalp midline (Fig 1, B and C). Anti-skin antibody serology was negative. Biopsy of a truncal blister revealed a predominantly subcorneal splitting and marked acantholysis. The inflammatory infiltrates consisted predominantly of neutrophils and occasional eosinophils. Direct immunofluorescence (DIF) was reported as negative. The condition was managed as subcorneal pustular dermatosis, with pustular drug eruption as the major differential diagnosis. Discontinuation of

Abbreviations used:

DIF:	direct immunofluorescence
ELISA:	enzyme-linked immunosorbent assay
Ig:	immunoglobulin

the herbal medicine and administration of dapsone 50 mg once daily resulted in remission. Dapsone was successfully tapered 6 months later. Two months after the stopping of dapsone, the vesicles and pustules recurred. Repeated skin biopsy showed similar histopathologic findings (Fig 2, A). DIF over the peri-vesicular skin showed a granular, intercellular positivity of IgA and IgG (Fig 2, B and C). The features were those of IgA pemphigus, with additional IgG immunoreactant. Dapsone was resumed at a dose of 25mg daily, and all the blisters subsequently resolved.

Antidesmoglein 1 IgG and antidesmoglein 3 IgG autoantibody titres from patient serum were determined by performing enzyme-linked immunosorbent assay (ELISA; Euroimmun) at the Clinical Immunology Laboratory of Queen Mary Hospital. Antidesmoglein 1 IgG was approaching the upper limit of the normal range (19.6 RU/mL; cutoff value, <20 RU/mL), whereas the test for antidesmoglein 3 IgG was negative (<2 RU/mL; cutoff value, <20 RU/mL). Meanwhile, ELISA for antidesmoglein IgA and antidesmocollin IgA and IgG were not available in our locality.

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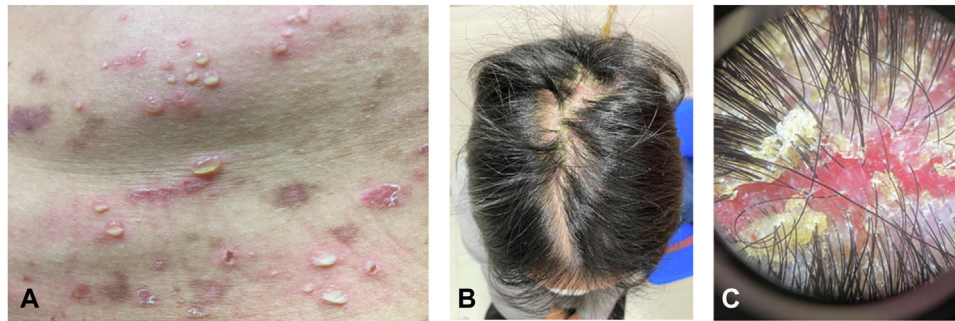


Fig 1. **A**, The truncal blisters taken at the upper abdomen. The blisters were large and tense, scattered throughout the truncal region and involved the proximal parts of the four limbs. Peri-blistery erythema was evident. Hypopyon formation was seen in some of the blisters. Some of the blisters had already resolved, leaving behind post-inflammatory hyper-pigmentation. Scarring was not seen. **B**, There were scaling and erythema localized over the scalp midline, extending antero-posteriorly. Despite an extensive involvement, there was no scarring alopecia or appreciable hair shedding. The scalp condition was entirely asymptomatic. **C**, A dermoscopic view of the thick scale that entangled the base of the hair shafts. The underlying scalp surface was erythematous, friable and moist. Abnormal vascular pattern, surface erosion and ulceration were not found. There was no evidence of tinea capitis.

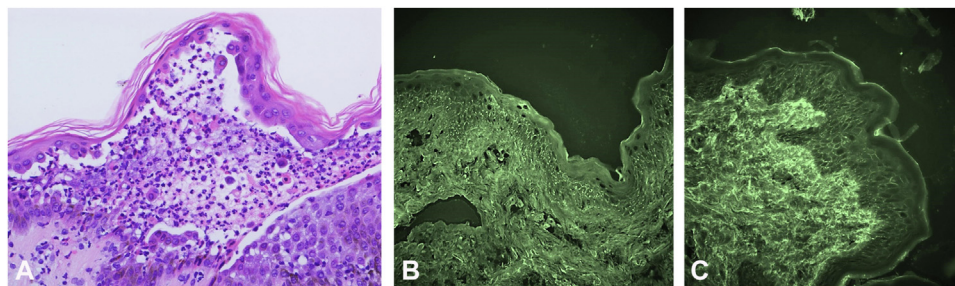


Fig 2. **A**, Truncal blister skin biopsy, featuring intra-epidermal acantholysis, dense neutrophilic and occasional eosinophilic infiltrates. There was no interface dermatitis, pigmentary incontinence, viral cytopathic effect or fungal hyphae. (H&E stain, 400 \times). **B**, The second skin biopsy for direct immunofluorescence, IgA with fluorescein isothiocyanate. Note the intercellular net-like positivity over the lower one- to two-thirds of the epidermis. Non-specific background staining was noted in the dermal collagen bundles. (Direct immunofluorescence microscopy, $\times 100$). **C**, The second skin biopsy for direct immunofluorescence, IgG with fluorescein isothiocyanate. Note the intercellular net-like positivity throughout the entire epidermis. Non-specific background staining was noted in the dermal collagen. (Direct immunofluorescence microscopy, $\times 100$).

Empirical treatment of the scalp lesions with potent topical steroid was ineffective. Work-up, including Wood lamp examination and microbiological studies, was negative. Diagnostic scalp biopsy was therefore arranged to investigate if the scalp lesion represented a *bona fide*, classic IgA-type pemphigus. Punch biopsy revealed marked acantholysis, involving both the epidermis and hair follicular epithelium, and dense neutrophilic infiltrates (Fig 3, A). There was no follicular miniaturization or elevated telogen ratio. DIF showed granular intercellular positivity for IgG, IgA (Fig 3, B and C), and C3. The overall clinico-pathologic features favored a diagnosis of IgG/IgA pemphigus, with

concurrent truncal and scalp involvement. Prednisolone at a dosage of 30 mg daily was added on top of dapsone 25 mg daily, which resulted in complete resolution of her scalp condition within 10 weeks. Further blood tests and positron emission tomography/computed tomography of the whole body excluded hematological and solid organ malignancy. The prednisolone-dapsone combination was well tolerated.

DISCUSSION

Ever since the initial descriptions by Wallach et al in 1982, the spectrum of IgA pemphigus continues to expand.¹ Advances in immunopathologic

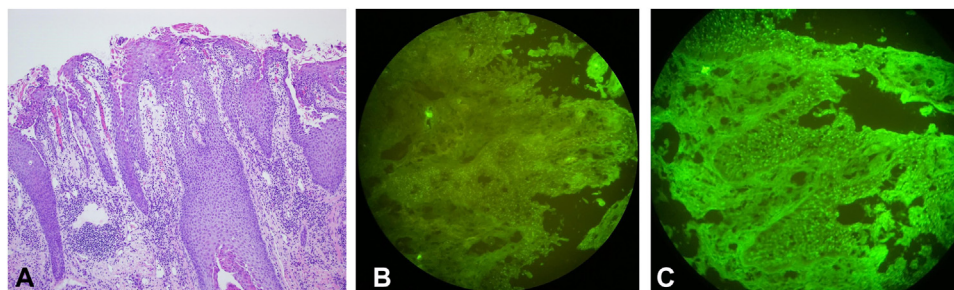


Fig 3. **A**, Medium power view of the scalp biopsy. Note the extensive intra-epidermal and intra-follicular splitting secondary to the acantholysis. There was no interface dermatitis, thickening of basement membrane or keratinocytic viral cytopathic effect. The papillary dermis was oedematous and capillaries markedly engorged. The inflammatory infiltrates comprised mainly of neutrophils, rarely eosinophils and lymphocytes. (H&E stain, 100 \times). **B**, Scalp punch biopsy for direct immunofluorescence, IgA with fluorescein isothiocyanate. Note the intercellular net-like positivity over the epidermis. There was a non-specific background staining within the dermal collagen bundles. (Direct immunofluorescence microscopy, $\times 40$). **C**, Scalp punch biopsy for direct immunofluorescence, IgG with fluorescein isothiocyanate. Note the intercellular net-like positivity over the entire epidermis. There was a non-specific background staining within the dermal collagen bundles. (Direct immunofluorescence microscopy, $\times 40$).

techniques help clarify the pathophysiology and continue to unveil novel pemphigus subtypes.² IgG/IgA pemphigus is exceedingly uncommon, with fewer than 50 cases reported so far.³ The target antigens appear to be heterogeneous, and the laboratory findings have varied across studies.⁴ Whether it represents an intermediate form of pemphigus, a distinctive pemphigus variant arising from inflammation-associated epitope spreading, or a novel entity secondary to antibody class-switching within an altered immunological milieu remains uncertain.^{3,5-7} Intertriginous distribution, pustular lesions, acantholysis, and intercellular C3 deposition in the epidermis were reported as features common to IgG/IgA pemphigus.⁵ Circulating autoantibodies against the desmoglein and desmocollin isoforms could be demonstrated by ELISA.⁶

Major differential diagnoses include bullous impetigo, subcorneal pustular dermatosis, pemphigus foliaceus, linear IgA bullous dermatosis, and paraneoplastic pemphigus. In our patient, the negative anti-skin antibody serology, negative DIF of the first skin biopsy, and superb therapeutic response to dapsone lead to an initial working diagnosis of subcorneal pustular dermatosis. An IgA immune complex is notoriously unstable and prone to degradation.⁸ This may be the reason for the apparently negative DIF in the first skin biopsy, as the circulating or tissue-bound IgA level may either be absent initially or below the detection limit of the DIF. The borderline-positive antidesmoglein IgG 1 titre gave clue to the possible nature of the treatment-recalcitrant scalp condition, which called for the

subsequent scalp biopsy. This somewhat atypical serologic profile illustrated the heterogeneous immunologic nature of IgG/IgA pemphigus.

Immune-mediated acantholysis was the responsible mechanism for blistering in pemphigus. The peculiar absence of an intact scalp blister in our patient was probably attributed to region-specific anatomical differences. Closely-spaced terminal hair follicles provided a framework that precluded and resisted acantholysis-induced epidermal disruption. The grossly visible pityriasis amiantacea-like lesions were made up of dislodged fragments of parakeratosis generated from the acantholytic process. It was unusual that the severity of intra-follicular acantholysis did not result in significant hair loss or hair cycle abnormality. We cannot offer any satisfactory explanations for this observation.

Suppression of auto-reactive antibody production is the cornerstone of treatment in pemphigus. The treatment of choice for IgG/IgA pemphigus is dapsone monotherapy.^{3-5,9} Systemic steroid administration can be considered as an alternative or add-on therapy.^{3-5,9,10} Addition of prednisolone was eventually required for the scalp disease in our patient, suggesting the contribution of pathogenic IgG over this region. Other therapeutic options reported to be efficacious included acitretin, colchicine, mycophenolate mofetil, and adalimumab.^{4,9} There is a lack of good-quality evidence regarding the association of IgG/IgA pemphigus with malignancy. Studies are needed to elucidate their relationship.^{3-5,9}

Conclusion

We highlighted a case of IgG/IgA pemphigus, with a unique combination of findings across different anatomical regions. Definitive diagnosis required a holistic consideration of clinical and immunopathologic data. In our case, ELISA helped ascertain the contribution of IgG to the scalp disease and facilitate clinical correlation, diagnosis, and management. The encounter also highlighted the utility and pitfalls of DIF microscopy in the management of IgG/IgA pemphigus. Awareness of these issues will improve the clinical outcome.

Conflicts of interest

None disclosed.

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