Subcorneal Pustular Dermatosis Type of IgA Pemphigus in a 35-Year-Old Female: A Case Report

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ABSTRACT

Introduction: IgA pemphigus is a rare, distinct variant of Pemphigus characterized by vesiculopustular eruptions mediated by IgA autoantibodies targeting keratinocyte cell surface antigens, desmocollins 1-3 and sometimes desmogleins 1 and 3. Its classical features have been described in literature but atypical cases have also been documented. This report presents such case posing a diagnostic dilemma.

Case Report: A 35-year-old female presented with a 16-year history of intermittent eruptions of multiple hyperpigmented, annular and circinate, desquamating plaques and coalescing flaccid pustules on erythematous bases on the scalp, neck, trunk, and extremities. Histopathologic examination revealed subcorneal pustular dermatitis, and direct immunofluorescence was positive for granular intercellular IgG and IgA deposits in the epidermis. Antinuclear antibody test was negative and C3 level was normal. Antibody tests against desmogleins 1 and 3 were both negative. Topical potent corticosteroid therapy resulted in complete resolution of all lesions in three weeks.

Conclusion: Diagnostic dilemmas arise when laboratory results do not correlate with clinical findings. Findings of IgA autoantibodies in patients with pemphigus-like skin eruptions led to the diagnosis of subcorneal pustular dermatosis type of IgA pemphigus. Dapsone is the treatment of choice although topical potent corticosteroid alone may provide complete remission in some cases, avoiding the potential adverse effects of systemic therapy.

Keywords: IgA pemphigus, subcorneal pustular dermatosis, autoimmune blistering disease

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INTRODUCTION

IgA pemphigus is a rare, distinct variant of pemphigus with only approximately 70 cases reported until 2010.[1] It is characterized by vesiculopustular eruptions with subcorneal or intraepidermal blisters containing abundant neutrophils and evidence of IgA antibodies against keratinocyte cell surfaces. There are two types: subcorneal pustular dermatosis type and intraepidermal neutrophilic IgA dermatosis type. Clinically, it is impossible to distinguish between the two, and both histopathologic and immunofluorescence tests are necessary to ascertain the diagnosis.[2,3]

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The primary lesions of this disease are flaccid pustules on erythematous bases that easily rupture forming annular or circinate patterns. Frequently affected are the intertriginous areas but lesions may be generalized involving the scalp, trunk, and extremities.[4,5] The consistent feature, however, is the absence of mucosal involvement which helps differentiate it from other blistering diseases.[6] Histologic examination shows nonspecific subcorneal or intraepidermal pustules containing abundant neutrophils which may be found in a number of other conditions such as Sneddon-Wilkinson disease, pemphigus foliaceus, pustular psoriasis, acute generalized exanthematous pustulosis, and bullous impetigo.[7] The diagnosis of IgA pemphigus is confirmed by performing direct immunofluorescence (DIF) test which demonstrates positive intercellular IgA deposition over the upper or whole epidermis, instead of intercellular IgG pattern seen in classic pemphigus.[6,]

These classical features of IgA pemphigus are present in most reported cases, but for over 30 years now, atypical cases have also been documented.[3,8] The following report describes one such case posing a diagnostic dilemma.

CASE REPORT

A 35-year-old female presented at the Dermatology Outpatient Department with multiple hyperpigmented, annular and circinate desquamating plaques and coalescing flaccid pustules on erythematous bases on the scalp, neck, trunk, and extremities of ten-days-duration. She has had multiple recurrences of similar lesions over the past 16 years. Lesions would start as multiple erythematous, irregularly shaped plaques developing pustules on the scalp, spreading to the neck, trunk, upper extremities, and lower extremities. There were no associated symptoms such as pruritus and pain, and no systemic symptoms including fever, joint pains, and photosensitivity. There was no drug intake prior to onset and no personal or family history of psoriasis, lupus, or arthritis. Previous pustular eruptions persisted for a few months and spontaneously resolved despite no physician or dermatologist consult.

Three years prior, the patient sought dermatology consult due to generalized eruption of similar lesions. Skin punch biopsy showed subcorneal pustular dermatitis. Patient was managed with clobetasol propionate ointment, petroleum jelly, and hydroxyzine with note of resolution associated with post-inflammatory pigmentary change. Patient was advised to consult as needed.

At the time of present consult, dermatologic examination showed multiple erythematous to hyperpigmented, irregularly shaped, well-defined, annular and circinate plaques, some topped with scales and some topped with coalescing flaccid pustules on the scalp, neck, trunk, and extremities (Figure 1). There were no lesions on the face, mucosal areas, palms, and soles. Nikolsky sign was negative. Hair and nail findings and general physical examination were unremarkable. The clinical impression was Sneddon-Wilkinson disease. Skin punch biopsies of a lesion and of perilesional skin were done on the left arm.

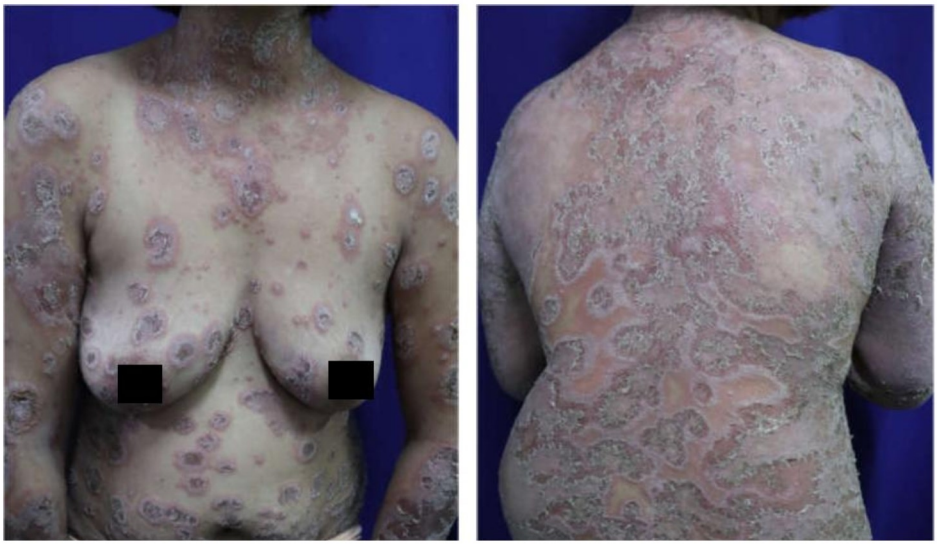

Figure 1. Multiple erythematous to hyperpigmented, irregularly shaped, well-defined, annular and circinate plaques, some topped with scales and some topped with coalescing flaccid pustules on the scalp, neck, trunk, and extremities.

Histopathologic examination showed subcorneal pustular dermatitis (Figure 2). DIF of perilesional skin revealed granular intercellular deposits of IgG, IgM and IgA in the epidermis and granular deposits of C3, IgM and IgA in the basement membrane zone (Figure 3). Complete blood count, creatinine, alanine transaminase, fasting blood sugar, glucose-6-phosphate dehydrogenase, chest x-ray, and urinalysis were all normal. Erythrocyte sedimentation rate was elevated. Antinuclear antibody (ANA) was negative and complement C3 was normal. Enzyme- linked immunosorbent assay (ELISA) for desmoglein 1 and 3 antibodies were both negative. The provisional diagnosis was Sneddon-Wilkinson disease, rule out IgA pemphigus. The patient was given clobetasol propionate ointment with petroleum jelly, oral antibiotics, tar shampoo, and cetirizine.

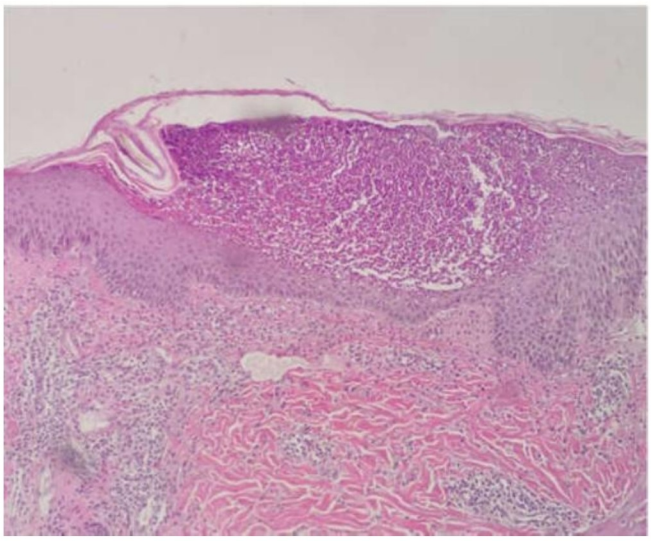

Figure 2. Subcorneal pustular dermatitis described as collections of neutrophils beneath the cornified layer and within the upper spinous cell layer. Perivascular infiltrates of lymphocytes and neutrophils are present in the papillary dermis (Hematoxylin-eosin stain, x100).

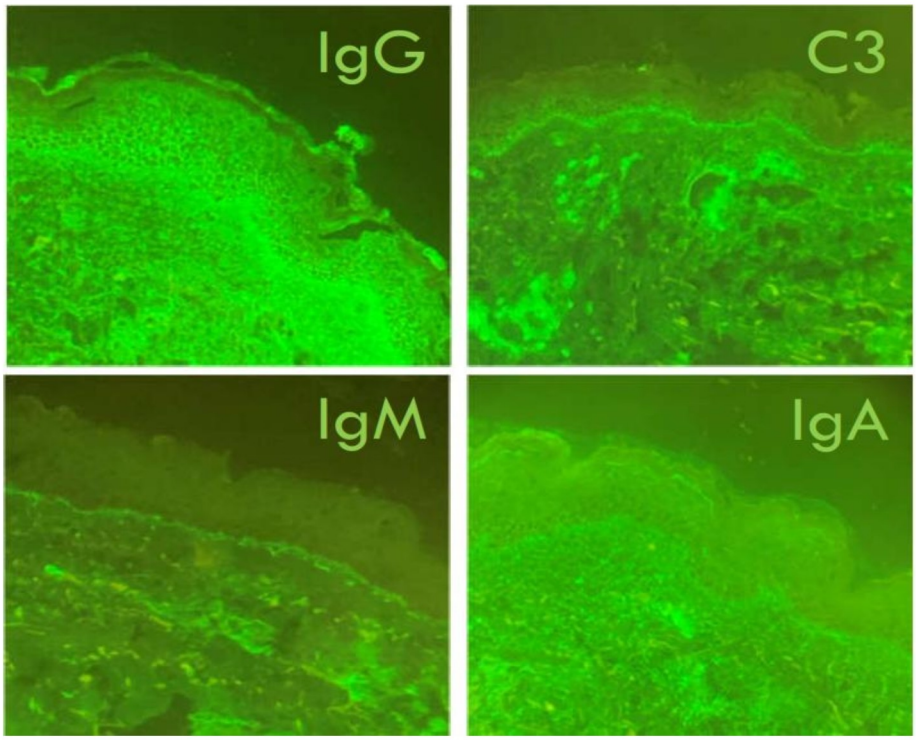

Figure 3. Granular intercellular IgG, IgM and IgA deposits in the epidermis and granular C3, IgM and IgA deposits in the basement membrane zone seen in direct immunofluorescence

After two weeks of topical steroid therapy, the patient presented with only few slightly erythematous patches and thin plaques topped with fine scaling. On the third week, lesions then healed with faintly hyperpigmented, smooth patches on the trunk and extremities (Figure 4). Topical steroid was discontinued. Until the fifth week, no recurrence was noted. Patient was advised regular monitoring for recurrence of lesions. A summary of the relevant past medical history and series of consults of the patient at the dermatology outpatient department is provided in Table 1.

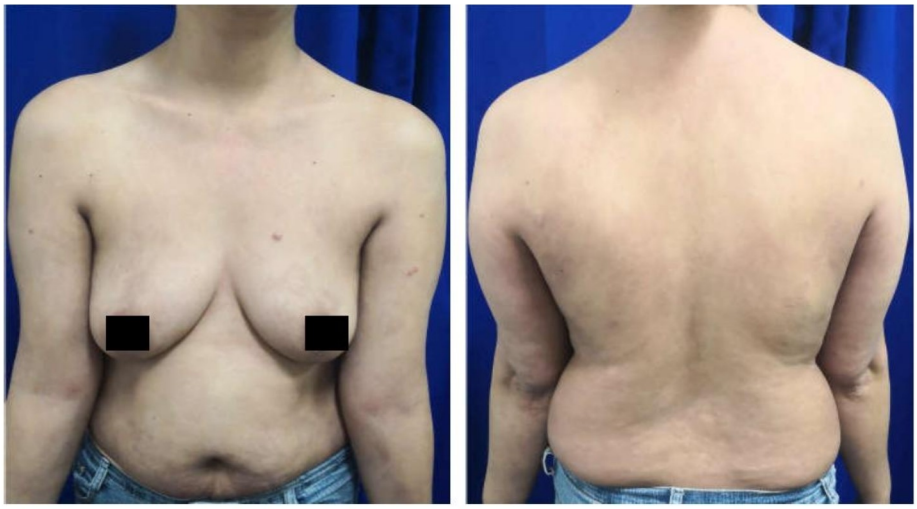

Figure 4. Few faintly hyperpigmented, smooth patches on the trunk and extremities after three weeks of topical potent corticosteroid therapy.

Table 1. Timeline of the patient's relevant past medical history and series of consults at the dermatology outpatient department (OPD).

Date	Relevant Past Medical History		
16 years prior to consult	Recurrent vesiculopustular eruptions Interventions: traditional healers, unrecalled oils, soaking in seawater, observation only Outcome: spontaneous resolution with/out intervention		
3 years prior to consult	Recurrence of vesiculopustular eruption Interventions: skin punch biopsy, clobetasol ointment, petroleum jelly, hydroxyzine Outcome: resolution of lesions		
Date	**Summary of findings**	**Diagnostics**	**Management**
Initial consult	Multiple erythematous to hyperpigmented, annular and circinate plaques, some topped with scales and some with coalescing flaccid pustules, (-) pruritus/pain	skin punch biopsy, CBC, creatinine, ALT, FBS, ESR	Clobetasol ointment + petroleum jelly Oral antibiotics
1 week after	Few slightly erythematous patches and thin plaques topped with fine scaling Histology: subcorneal pustular dermatitis Normal lab results except ↑ ESR	G6PD	Clobetasol ointment + petroleum jelly Tar shampoo Cetirizine
3 weeks after	Faintly hyperpigmented, smooth patches DIF: (+) epidermal intercellular IgG, IgM, IgA; (+) granular C3, IgM, IgA in BMZ G6PD: not done	G6PD, CXR, urinalysis, ANA, C3, Dsg 1 and 3 ELISA	Emollient
5 weeks after	No recurrence of lesions Normal and negative lab results	None	Advised regular monitoring

CBC = complete blood count; ALT = alanine aminotransferase; FBS = fasting blood sugar; ESR = erythrocyte sedimentation rate; G6PD = glucose-6-phosphate dehydrogenase; DIF = direct immunofluorescence; BMZ = basement membrane zone; CXR = chest x-ray; ANA = antinuclear antibody; Dsg = desmoglein; ELISA = enzyme-linked immunosorbent assay.

DISCUSSION

Based on the clinical history and presentation of the patient at the time of consult, the primary consideration was Sneddon-Wilkinson disease versus subcorneal pustular dermatosis (SPD) type of IgA pemphigus. Both disorders manifest flaccid pustules that coalesce into annular or circinate patterns and desquamating plaques that form from ruptured pustules. The mucous membranes are not affected and systemic symptoms are usually absent,[6,7,9] as in the patient's case. Meanwhile, the histopathology showing a subcorneal neutrophilic infiltrate and perivascular mixed infiltrates is also compatible with these two conditions. However, as these are nonspecific findings, DIF is essential to establish the diagnosis. In classic SPD or Sneddon- Wilkinson disease, DIF is negative. In contrast, DIF of IgA pemphigus shows intercellular IgA deposition in the epidermis.[6,7,10]

DIF of the patient's perilesional skin revealed both intercellular IgG and IgA deposits in the epidermis, with weaker IgA staining compared to IgG. The intercellular IgG pattern is consistent with the pemphigus group of diseases, which includes pemphigus vulgaris, pemphigus foliaceus, pemphigus vegetans, pemphigus erythematosus, and drug-induced pemphigus.[11-13] Intercellular IgA deposits may be also seen but only as secondary deposits. In IgA pemphigus, typical cases show exclusive IgA

deposition in the epidermis. IgG or C3 may also sometimes be deposited but with weaker staining than IgA.[3,14] Meanwhile, multiple granular deposits in the basement membrane zone is suggestive of lupus erythematosus (LE) or pemphigus erythematosus.[11,12] Antibody ELISA for both desmogleins 1 and 3, however, turned out negative, ruling out the classic pemphigus disorders mentioned above. The absence of symptoms and signs of LE, negative ANA, normal C3, and other normal laboratory findings also make the diagnosis of LE or pemphigus erythematosus unlikely.

There are reports of atypical cases of pemphigus with presence of both intercellular IgA and IgG deposits in the epidermis. Some have classified them as IgG/IgA pemphigus, although there is no consensus yet on whether this is a variant of IgA pemphigus or a unique form of pemphigus.[8,15] On the other hand, IgA pemphigus is considered to be a distinct clinical entity that includes two subtypes, namely subcorneal pustular dermatosis and intraepidermal neutrophilic dermatosis (IEN).[16] Histologically, SPD type shows subcorneal neutrophilic infiltrates while IEN type shows neutrophils mainly in the lower epidermis or throughout the epidermis. Another difference between the two is that the target autoantigen of SPD type is desmocollin 1; while for IEN type, the exact autoantigen is still unknown, but with desmogleins 1 and 3 demonstrated in a few reports.[2,17] Therefore, for cases of IgA pemphigus, antibody testing for desmocollin should be performed aside from desmoglein antibody tests to elucidate the unique feature of the disease and strengthen the diagnosis. This is ideal but unfortunately, the test is not available in the local setting.

Desmocollin and desmoglein are major desmosomal glycoproteins that belong to the cadherin superfamily of cell adhesion molecules. They constitute the adhesive core of desmosomes which facilitate adhesion between keratinocyte cell surfaces.[6,16] In autoimmune blistering disorders of the pemphigus group, autoantibodies preferentially target specific isoforms of these desmosomal proteins. For instance, in pemphigus vulgaris, IgG autoantibodies against desmoglein 3 are present whereas pemphigus foliaceus is characterized by IgG autoantibodies against desmoglein 1.[18,19] Binding of autoantibodies to their target antigens induces loss of epidermal adhesion, leading to blister formation.[2,18] In SPD type of IgA pemphigus, antibodies to desmocollin are found instead of antibodies to desmoglein. Desmocollin has three isoforms, desmocollins 1-3, which are expressed in a differentiation- specific manner: desmocollin 1 shows strong expression in the upper spinous layers; desmocollin 2 shows similar expression to desmocollin 1 but is most strongly expressed at the base of the rete ridges; and desmocollin 3 is most strongly expressed in the basal layers.[16] As previously mentioned, desmocollin 1 is the autoantigen of SPD type of IgA pemphigus, which results in the subcorneal blistering and concentration of IgA deposits in the upper epidermis found in histopathology and DIF, respectively.[2] In the case of the patient, subcorneal pustule formation but with intercellular deposits of IgA throughout the epidermis may be due to the presence of autoantibodies to all three types of desmocollin and not just to desmocollin 1.[16] However, this hypothesis could only be confirmed once testing for these antibodies is done.

Diagnostic dilemmas arise when laboratory results do not correlate with clinical findings. However, considering the clinical presentation of the patient, all the diagnostic and laboratory test results available, and the relatively benign course of the lesions, a diagnosis of SPD type of IgA pemphigus was made.

Unlike classic pemphigus, IgA pemphigus has a milder, limiting clinical course, although it is known to be recurrent and associated with diseases such as monoclonal IgA gammopathy, rheumatoid arthritis, and Sjögren syndrome.[2,6] With timely and appropriate treatment, IgA pemphigus heals without scarring.

Although dapsone is the treatment of choice,[2,20] in the patient's case, the current lesions, as well as previous lesions three years ago, successfully resolved with topical corticosteroid alone. One case report cited that the use of topical corticosteroids in a patient with IgA pemphigus provided only slight improvement, and dapsone had to be started to achieve complete remission.[17] If the patient's lesions did not demonstrate a good response to the initial treatment, dapsone may be given at a dose of 50-200 mg daily. Once the disease has been controlled, it is then tapered to the minimum effective dose and usually continued long-term to avoid recurrence.[7-9] Fortunately, the patient did not require dapsone; hence, potential adverse effects of this drug such as hemolysis and methemoglobinemia were avoided.[6,10] Few reports also mentioned the use of oral corticosteroids, colchicine, systemic retinoids, adalimumab, mycophenolate mofetil, PUVA, and a combination of these for IgA pemphigus.[6,21]

In conclusion, IgA pemphigus is a rare, autoimmune blistering disease with epidermal intercellular IgA deposition seen in DIF. Atypical cases with both IgG and IgA antibodies against keratinocyte cell surfaces are more rare, that for over 30 years now, there is still no consensus on how these should be classified. When diagnostic test results are not clear-cut, correlation of the clinical with the laboratory findings is done to commit to a diagnosis and plan the appropriate management of patients. Dapsone is the treatment of choice for IgA pemphigus, but topical potent corticosteroid alone may also be effective in some cases, thereby avoiding the potential adverse effects of this systemic drug.

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