

## Case Report

# IgG/IgA Pemphigus: Report of a Rare Variant of Atypical Pemphigus and a Review of the Literature

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## Abstract

First described as a distinct clinical entity in 1994, IgG/IgA pemphigus is a rare type of atypical pemphigus with a variety of clinical, histological, and immunological manifestations. Only 21 cases of this disease have been reported in the literature to date. We report a case of IgG/IgA pemphigus in a 54-year old female in which the diagnosis was delayed due to negative direct immunofluorescence results following two separate biopsies. The clinical and histological findings associated with this rare form of pemphigus will be discussed along with a review of the literature.

## INTRODUCTION

Pemphigus is an autoimmune blistering disease characterized by antibodies that target intercellular components of the epidermis. Several variants exist and can be broadly classified into typical and atypical pemphigus disorders. IgG/IgA pemphigus is a relatively new form of atypical pemphigus characterized by deposits of both IgA and IgG antibodies in the epidermis. Although a role for IgA in pemphigus was identified in 1987, the distinct disease entity was first described by Chorzelski et al. in 1994 [1]. The true incidence is unknown and to our knowledge, only 21 cases have been reported in the literature to date [2]. The immunopathologic and clinical features may vary, however, vesiculopustular eruptions demonstrating neutrophilic acantholysis upon biopsy is commonly observed [3]. Diagnosis must be confirmed with direct immunofluorescence identification of both IgG and IgA antibodies within the epidermis.

We present a case of IgG/IgA pemphigus and discuss the associated clinical, histological and immunological findings described in the literature. The clinical presentation of IgG/IgA pemphigus may vary significantly, therefore, proper biopsy technique and immunofluorescence testing is necessary for diagnosis and will also be discussed.

## METHODS

Review of the medical records provided information about patient history, biopsies and histological examination, including direct and indirect immunofluorescence. Direct

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immunofluorescence (DIF) was performed using polyclonal rabbit anti-human IgG, IgA, IgM and C3 Complement. Indirect immunofluorescence (IIF) was performed at dilutions of 1:10, 1:20, 1:40 with the patient's serum and monkey esophagus as the substrate using polyclonal rabbit anti-human IgG. A review of the literature was performed using PubMed/MeSH Database search. Available case reports and current review articles were investigated to provide up-to-date information about IgG/IgA pemphigus. Patient consent was obtained for photographs and appropriate clinical procedures.

## CASE REPORT

A 54-year-old Caucasian female was referred to our dermatology clinic for a 3-month history of a blistering disease associated with pruritis. Before her presentation to our clinic, she was seen and treated by two other dermatologists. Diagnoses considered included primary vesiculobullous disorders such as pemphigus vulgaris, pemphigus foliaceus, dermatitis herpetiformis and linear IgA bullous dermatosis. Other clinical concerns included subcorneal pustular dermatosis, acute generalized exanthematous pustulosis and bullous impetigo. Subsequently, she underwent a skin biopsy, by each dermatologist, separated by one month apart. The initial specimen was obtained from the left posterior arm and showed a spongiotic dermatitis with acantholysis and an intraepidermal pustule. The second biopsy was from the abdomen and showed a subcorneal vesicular dermatitis with eosinophilic spongiosis. Direct immunofluorescence (DIF) was also performed with each biopsy and was negative in both cases.

On presentation to our clinic, she described blisters that began on the upper back and gradually progressed to the trunk and extremities. The lesions were pruritic and sore. She denied mucosal involvement. She was treated with multiple courses of high dose oral prednisone which controlled the disease, although blisters rapidly reappeared with any attempt to taper her off corticosteroids. No new medications, travel, or recent exposures were elicited on history. Family history was negative for blistering or auto-immune disorders. She was otherwise healthy and review of systems was otherwise negative.

While on a daily dose of prednisone 60 mg, physical examination revealed numerous erythematous papules and plaques with overlying erosions and small vesicles located on the trunk and proximal extremities (Figure 1). Some lesions were arciform and annular in arrangement with overlying serum crusting. Her conjunctiva and oral mucosa were without lesions on initial presentation. A complete blood count, comprehensive metabolic panel, and urinalysis were within normal limits except for mild leukocytosis (13.0 K/uL) with an elevated neutrophil count (11.3, N 1.6-7.3) and mildly elevated liver enzymes (AST 110 U/L, ALT 178 U/L). Anti-nuclear antibody titer was positive at 1:160.

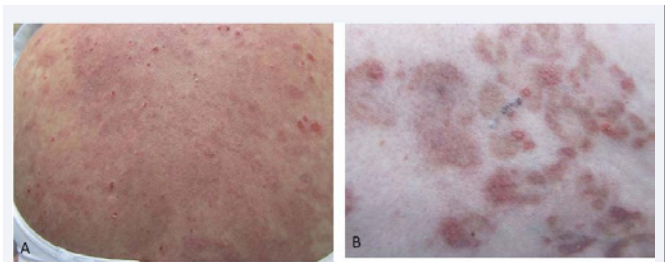
Though there were two previous pathological reports of negative DIF testing, clinical suspicion for an autoimmune blistering disorder was high. Sneddon-Wilkinson disease was also considered. Two perilesional 4-mm punch biopsies were performed on the patient's back. Routine histopathological examination was significant for an acantholytic dermatitis with neutrophilic aggregates in the superficial epidermis (Figure 2). Direct immunofluorescence was positive for intercellular deposits of IgG and IgA in the epidermis (Figure 3). C3 was also positive in the lower portion of the epidermis. Subsequent serum indirect immunofluorescence (IIF) on monkey esophagus did not demonstrate intercellular fluorescence with IgG or IgA.

The patient was continued on 60 mg of prednisone daily while starting systemic dapsone and colchicine. Her systemic corticosteroids have been slowly tapered and she has achieved complete control of her symptoms with dapsone 100 mg daily and colchicine 0.6 mg twice daily. Of note, during her treatment course, she developed oral erosions involving the posterior pharynx.

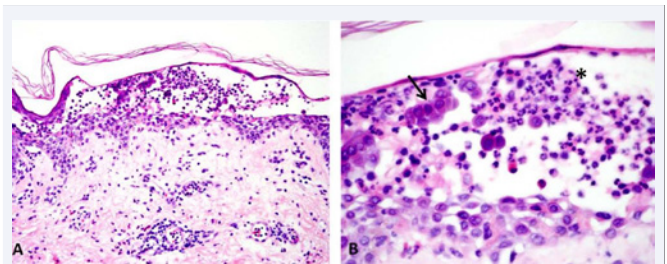
The patient has had all age appropriate cancer screenings. Upon the diagnosis, a chest X-ray and serum protein electrophoresis were obtained and found to be within normal limits. She continues to be followed closely in our clinic.

## DISCUSSION

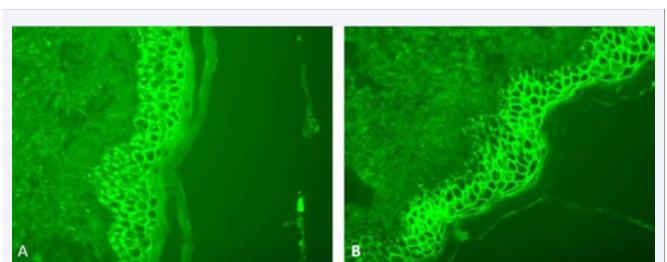
IgG/IgA pemphigus is considered a rare atypical variant of pemphigus vulgaris. It was first described in 1994 and is a relatively new clinical-pathological disease entity [1]. Only 21 cases have been reported to date. Five cases are incompletely described and not included in the table. Table 1 summarizes data available for the remaining 16 cases. As a result, little is known regarding the true incidence and demographics of IgG/IgA pemphigus. Much variation exists in the clinical, histological, and immunological features adding to the difficulty in diagnosis and evidence based management [3].



**Figure 1** IgG/ IgA Pemphigus. (A) Numerous erythematous papules and plaques with overlying erosions and small vesicles involving the trunk and proximal extremities. Serum crust is present. (B) Magnified view of papules and plaques.



**Figure 2** IgG/IgA Pemphigus. (A) Intraepidermal vesicle with acantholysis in the superficial epidermis and neutrophilic aggregates. H&E stain, 10x magnification. (B) Magnified view demonstrating intact acantholytic keratinocytes (black arrow) and neutrophilic aggregates (asterisk). H&E stain, 40x magnification.



**Figure 3** IgG/IgA Pemphigus. Direct immunofluorescence testing for IgA and IgG performed following a perilesional biopsy. (A) Intercellular deposits of IgA. (B) Intercellular deposits of IgG showing greater staining intensity with IgG compared to IgA. Intercellular C3 deposition is seen in the lower portion of the epidermis. Direct Immunofluorescence stain, 40x magnification.

The pemphigus spectrum disorders are autoimmune blistering diseases that have antibodies directed against the intercellular surface components of keratinocytes [2,4,5]. The traditional classification of pemphigus includes pemphigus foliaceus, pemphigus erythematosus, pemphigus vulgaris, and pemphigus vegetans [6]. The more recently described and atypical pemphigus spectrum disorders include herpetiform pemphigus, paraneoplastic pemphigus, and IgA pemphigus. IgA pemphigus is further subdivided into subcorneal pustular dermatosis and intraepidermal neutrophilic IgA dermatosis [4,6]. IgG/IgA pemphigus appears to be a unique and separate variant of atypical pemphigus with distinct and variable, clinical and histological manifestations.

IgG/IgA pemphigus is a neutrophilic acantholytic skin disorder that reveals intercellular deposits of both IgA and

**Table 1:** Reported Cases of IgG/IgA Pemphigus.

Patient	Clinical	DIF	Antibody targets	Histology	Treatment	Malignancy	References
81 yo female	Vesiculobullous erythema, trunk and extremities	IgG IgA C3	Desmoglein1	Acantholytic cells, neutrophil infiltration	Dapsone	Gallbladder carcinoma	[7]
33 yo female	Vesiculobullous erythema, pustules	IgG IgA	Desmoglein1	Superficial bullae with neutrophil infiltration	Dapsone, Prednisone	Ovarian carcinoma	[6]
25 yo female	Vesicles, annular erythematous plaques with erosions	IgG IgA	Desmoglein1	Acantholytic cells, neutrophilic intraepidermal pustules	Topical clobetasol dipropionate	--	[2]
70 yo male	Erythematous annular plaques, vesicles and pustules	IgG IgA	Desmoglein1	Subcorneal pustules and vesicles, acantholytic cells	Acitretin, methylprednisolone	Pancreatic carcinoma	[2]
43 yo female	Flaccid bullae, crusted erosions, oral mucosa involvement	IgG IgA C3	Desmoglein1 Desmoglein3	Acantholytic bullae with lymphocytic and neutrophilic infiltrate	Oral prednisone, topical betamethasone valerate	--	[4]
48 yo male	Vesicles, erythematous macules with erosions	IgG C3	Desmoglein1 Desmoglein3 (circulating IgA antibodies identified on ELISA)	Dyskeratosis, acantholysis, neutrophilic infiltration, microabscesses	Dapsone	--	[3]
42 yo female	Annular erythema with peripheral vesicles, erosions with crusting	IgG IgA C3	Desmoglein1	Acantholytic bullae, neutrophilic infiltrate	Prednisone, minocycline, topical betamethasone valerate	--	[5]
39 yo female	Vesicles, pustules, central erosions and crusts, flaccid bullae	IgG IgA	Desmocollin1	Neutrophilic pustules, acantholysis	Dapsone	--	[10]
11 yo male	Flaccid pustules, bullae, vesicles and erosions of mucous membranes, conjunctivitis	IgG IgA	Desmoglein3	Acantholysis, neutrophilic infiltrate	Dapsone, prednisone	--	[8]
48 yo female	Erosive stomatitis, conjunctivitis, exudative erythema multiforme-like lesions	--	Desmocollin3 Desmocollin2 BP180 Envoplakin Periplakin	Suprabasilar acantholysis, dense inflammatory infiltrate	High-dose prednisolone.	B-Cell non-Hodgkin's Lymphoma	[13]
5 patients*	Atypical pemphigus features in 3 cases, PV-like appearance in one case and PF-like appearance in one case.	--	Desmoglein1 Desmoglein3 **	--	--	--	[18]
78 yo female	Annular erythema, vesicles, pustules, peripheral erosions; esophageal erosions	--	Desmoglein 1 Desmoglein 3	Neutrophilic spongiosis with eosinophilic infiltrate, intraepidermal pustules	Prednisolone	--	[12]
42 yo male	Erythematous plaques with vesicles, pustules and crust; PH-like appearance	--	Desmoglein 1 Desmocollin 3	Vesicles with neutrophilic and eosinophilic infiltrate, acantholysis	Prednisolone, dapsone	--	[11]
60 yo female	Erythematous vesicles and pustules; PF-like appearance	IgG IgA	--	Acantholysis, neutrophilic blisters	Dapsone	--	[14]

60 yo female	Vesicles and erythema followed by development of pustules; PF-like appearance	IgG IgA	140 kD protein	Acantholysis, neutrophilic blisters	Dapsone, then betamethasone	--	[17]
63 yo male	Erythematous plaques with erosions and crusts	IgG IgA	Desmocollin 1 Desmocollin 2	Subcorneal acantholytic bullae with neutrophils	Dapsone	Lung cancer	[1]
DIF = direct immunofluorescence; PV = pemphigus vulgaris; PF = pemphigus foliaceus; PH = pemphigus herpetiformis *patient demographics not reported **no specific antigens identified in 3 of the reported cases							

IgG antibodies within the epidermis [7]. Age of onset is highly variable and ranges from 11 years to 81 years [7,8]. Eleven of the 16 cases (69%) of IgG/IgA pemphigus, including our patient, were reported in women. Interestingly, IgA pemphigus has also been reported more commonly in women [9].

The clinical presentation is variable, sometimes making diagnosis difficult. Our patient had erythematous papules and plaques with vesicles, erosions and crusting (Figure 1). This presentation, though non-specific, is similar to the clinical findings of other known cases [2,3,5,6,10-12]. The annular configuration of some lesions seen in our patient was reported in at least 4 other patients [2,5,12]. Pustules were also commonly identified. Pruritus and tenderness were also common presenting complaints [3,6,13]. The location of the lesions varied, however, the trunk and extremities were most commonly involved [7,12,14]. Mucosal involvement has been reported [4,13] with esophageal involvement was seen in one patient [12]. No other reports of posterior pharyngeal involvement exist to our knowledge.

Abnormalities in lab work are not common in this disorder unless associated with an underlying malignancy. Our patient had a mild leukocytosis likely due to chronic systemic corticosteroid use. The elevation in liver enzymes could be a sign of an underlying malignancy of hepatic origin [15], however, in our patient further work-up revealed non-alcoholic steatohepatitis. The positive anti-nuclear antibody titer is of indeterminate significance.

A paraneoplastic association with IgG/IgA pemphigus has been suggested [1,2]. The mechanism is unknown, however, anti-desmoglein 1 antibodies were identified in several cases and may be associated [2]. Malignant diseases reported with IgG/IgA pemphigus include lung cancer [1], pancreatic adenocarcinoma [2], carcinoma of the gallbladder [7], lymphoma [13], and ovarian carcinoma [6]. The small number of patients reported with IgG/IgA pemphigus limits our ability to conclude that a relationship between this rare type of pemphigus and malignancy truly exists although age appropriate cancer screening is indicated.

Histological findings in all reported cases demonstrate a neutrophilic infiltrate [3,4]. Acantholysis is commonly described but not seen in all cases [3]. Nakajima et al. suggest that both dyskeratosis of acantholytic cells and neutrophil infiltration into the epidermis could be considered diagnostic indicators of IgG/IgA pemphigus [3].

A few target antigens strongly associated with pemphigus disorders have been well established, including desmoglein 3 for pemphigus vulgaris and desmoglein 1 for pemphigus foliaceus

[6]. IgG/IgA pemphigus is associated with a variety of antigens. IgA and IgG antibodies targeting both desmogleins 1 and 3 as well as desmocollins 1, 2 and 3 have all been identified to date [2-8,10,13]. This variation in target antigens may account for the clinical and histological variety seen with IgG/IgA pemphigus. It has also been suggested that the coexistence of IgA and IgG antibodies seen in this rare form of pemphigus could be transient, representing a transition period within a single disease or between two pemphigus disorders [6].

The above case described presented some difficulty in diagnosis due to a negative DIF on two separate occasions leading the patient to go undiagnosed for several months even after seeing multiple dermatologists in the past. The initial two biopsies were performed at outside facilities. While speculative, poor biopsy technique or technical difficulties encountered in laboratory processing may have caused the negative DIF results. It is also possible that recent treatment could have caused the repeated false negatives. Finally, misinterpretation by the dermatopathologist in cases with substantial background staining may result in a false negative. The reported sensitivity of DIF in pemphigus disorders is 88% [16]. It is a reliable diagnostic test for pemphigus that becomes positive early in the course of disease and remains positive for long periods after clinical remission [17]. In approximately 50% of cases, IIF detects IgA autoantibodies [18]. Immunofluorescence testing is absolutely necessary for increased detection of those variants of pemphigus, including IgG/IgA pemphigus, that are considered rare [16]. This highlights the importance of proper biopsy technique when autoimmune bullous disorders are suspected.

A perilesional punch biopsy should be obtained. Lesions identified as new by the patient and/or those appearing active on clinical examination should be targeted for biopsy. Biopsy of more than one lesion can be considered, particularly if the lesions have various clinical appearances indicating different stages in the autoimmune disease process. Technical faults and/or treatment-induced changes are often to blame for false negative results, therefore, biopsy should be obtained before beginning the patient on therapy [16]. Our patient had been referred to us already on a daily dose of prednisone 60 mg daily. Moreover, at the time the serum IIF was obtained, the patient had been appropriately treated. This may explain the negative result of the IIF. In addition to immunofluorescence studies, ELISA can be performed to identify the specific IgA and IgG target antigens involved.

The treatment for IgG/IgA pemphigus typically includes a course of high-dose systemic corticosteroids. Oral prednisone (or



prednisolone) can be used to induce remission, but in some cases was required for maintenance as well [4-6,8,11-13]. Successful treatment and maintenance therapy with sulfonamides, including dapsone have also been reported [1,3,8,10,11,14,19]. Topical steroids were successful in one case [2], but may also be used in combination with oral agents to help control disease.

## CONCLUSION

IgG/IgA pemphigus is a rare and relatively newly identified form of atypical pemphigus. The clinical and histological findings are variable. Erythematous papules and plaques with vesicles, pustules and erosions are typical clinical findings. Intraepidermal neutrophils and acantholysis are the hallmark findings on histology. Definitive diagnosis is obtained via DIF testing which shows intercellular IgA and IgG antibodies directed against the cell surface of keratinocytes. Recent recognition of IgG/IgA pemphigus as a separate disease entity in addition to the small number of reported cases available highlight the need for further studies.

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