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Immunoglobulin M bullous pemphigoid: An enigma



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INTRODUCTION

Bullous pemphigoid is an autoimmune blistering disease characterized by pruritus, tense blisters and erosions of the skin or mucosae, subepidermal splitting, and linear IgG or complement deposition along the epidermal basement membrane zone (BMZ), directed against the hemidesmosomal proteins BP180 and BP230.¹ Deposition of IgA in conjunction with IgG is regularly found in bullous pemphigoid, whereas deposition of only IgA along the epidermal BMZ is known as linear IgA disease.

The presence of only immunoglobulin M (IgM) deposition in pemphigoid has rarely been described and the relevance of IgM in the pathomechanism of autoimmune blistering diseases is still debated.² In this case report, we describe a peculiar case involving a patient with bullous pemphigoid clinically, in which exclusively tissue bound and circulating IgM subclass antibodies were present, even after many years of disease activity and follow-up. This case provides more insight toward the possible role of IgM in the pathomechanism of bullous pemphigoid.

CASE REPORT

A healthy 49-year-old woman presented with a 6-year history of spontaneous blisters on the lower extremities, which later extended to her whole body. Pruritus was not present. The patient originated from North Africa, and there were no family members with a similar skin disorder.

Physical examination revealed multiple tense bullae on erythematous skin on the left shoulder

Abbreviation used:

IgM: immunoglobulin M

and neck (Fig 1, A). The lesions healed with hyperpigmentation, without scarring or milia. The buccal mucosa showed purpura and bullae (Fig 1, B).

Two 4-mm biopsies were taken from perilesional and healthy (nonsun-exposed) skin for direct immunofluorescence microscopy and a blood sample was taken for serologic examination. The biopsies showed a strong linear n-serrated deposition of IgM along the epidermal BMZ together with complement C3, without the presence of IgG or IgA (Fig 1, C). Indirect immunofluorescence microscopy on salt-split skin showed a strong epidermal staining (roof) for IgM, whereas IgG and IgA results were negative (Fig 1, D). The immunoblot result for BP180 and BP230 (IgG) was negative. In accordance with the clinical presentation, a diagnosis of IgM bullous pemphigoid was made. In the following years, multiple biopsies and serologic tests were performed, repeatedly showing deposition of complement C3 and IgM subclass antibodies only, without IgA and IgG. Additional laboratory investigation showed no aberrant findings; more specifically, an infection, immunoglobulin deficiency, and IgM monoclonal gammopathy were ruled out.

At presentation, the patient had already been treated with high doses of prednisone, azathioprine,

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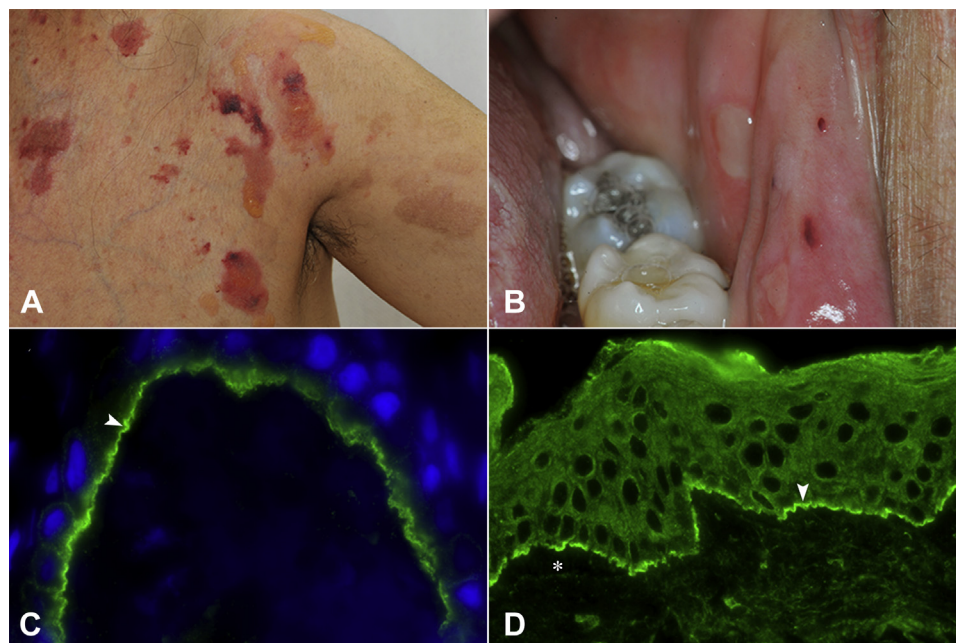


Fig 1. Clinical and immunopathologic findings of a patient with IgM bullous pemphigoid. **A**, Bullae and vesicles on erythematous skin on the upper body, partly hemorrhagic, with hyperpigmented maculae. **B**, Mucosal involvement with vesicles and purpura on the buccal mucosa. **C**, Direct immunofluorescence microscopy of perilesional skin showing linear deposition of IgM in an n-serrated pattern (arrowhead). **D**, Indirect immunofluorescence microscopy on salt-split skin showing a strong staining of IgM along the epidermal side (arrowhead); the artificial subepidermal blister is depicted by an asterisk.

minocycline, nicotinamide, methotrexate, mycophenolate mofetil, doxycycline, and cyclophosphamide. Because of insufficient result, infusion of human intravenous immunoglobulin was started (50 g intravenously per day during 3 consecutive days per month). For 1 year she received monthly human intravenous immunoglobulin infusions, which resulted in complete remission, but after cessation of the therapy the blisters returned. After this period, she was treated with mycophenolate mofetil (500 mg twice a day) and prednisone (7.5-15 mg/day) for almost a year, which had to be stopped because of the adverse effects of headache, dizziness, and malaise. Consequently, the human intravenous immunoglobulin infusions were restarted, combined with mycophenolate mofetil (500 mg twice a day), and resulted in complete remission within a short period. After treatment for 4 years with human intravenous immunoglobulin infusions, the therapy was changed to rituximab (1000 mg intravenously twice a month). While the patient was being treated with rituximab, new blisters developed. After 5 months, the human intravenous immunoglobulin infusions

(50 g intravenously per month) were restarted, and she is currently in remission.

DISCUSSION

In this case report, we describe a peculiar case involving a patient with bullous pemphigoid, with both complement C3 and tissue bound and circulating IgM subclass antibodies only. Even more unusual is that this patient after years of disease activity and follow-up still demonstrated (circulating) antibodies exclusively from IgM subclass, without any evidence of class switching. The presence of complement C3 supported the diagnosis of bullous pemphigoid because complement is thought to be an important factor in the pathogenesis of bullous pemphigoid by the attraction and activation of inflammatory cells, normally initiated by IgG antibodies.^{1,3,4} Although the reacting antigen could not be proven, because ELISA against BP180 NC16a and BP230 is unsuitable for IgM, we believe this IgM must be directed against one of the hemidesmosomal components and may be responsible for the activation of complement in this patient. The first clue was the n-serrated pattern

of the IgM deposition in the biopsy, which corresponded with binding to autoantigens located above the sublamina densa zone.^{1,5} Second, the epidermal staining (roof) in the indirect immunofluorescence microscopy on salt-split skin also pointed to BP180 and BP230 as the involved antigens.^{1,6,7}

A literature search revealed several case reports of patients with IgM epidermolysis bullosa acquisita (Supplemental Table I; available at <http://www.jaad.org>).⁸⁻¹⁰ In our case, epidermolysis bullosa acquisita was ruled out by the absence of scarring and the presence of linear deposition of IgM along the epidermal side in indirect immunofluorescence microscopy on salt-split skin, and because the linear deposition showed an n-serrated pattern. The presence of IgM-only positivity has also been reported in a case with ocular pemphigoid, in which solely the ocular mucosa was involved (Supplemental Table I).¹¹ However, the presence of an IgM-mediated entity was debated by Velthuis et al.² In their article, 25 patients were described with linear staining of IgM along the epidermal BMZ, but because of the heterogeneity of the clinical presentation, the existence of a linear IgM dermatosis was eventually denied. One patient in that cohort was thought to have a form of IgM-mediated bullous pemphigoid and seemed to match the profile of our case, with clinically bullous pemphigoid, linear deposition of IgM and complement C3 along the BMZ, and the presence of circulating IgM and complement C3 against BMZ components. Besides the reported 25 cases by Velthuis et al,² other cases with deposition of IgM antibodies at the BMZ have been reported, particularly in pregnant women (Supplemental Table I).

Why no immunoglobulin class switching has occurred in our patient with bullous pemphigoid after years of disease activity is unclear because no evidence was found for a monoclonal IgM gammopathy or immunodeficiency. The existence of a cryoglobulinemia or hyper IgM syndrome was ruled out as well. A possible explanation for the persistence of high IgM titers would be that long-lived plasma cells are responsible for the production of the IgM antibodies. This theory is supported by the fact that infusion with rituximab

did not result in remission, whereas use of human intravenous immunoglobulin did.^{12,13} The mechanism of action of human intravenous immunoglobulin is not fully understood, but its therapeutic effect seems to result from a combination of mechanisms, in which B cells are involved.¹³

In conclusion, although the pathogenic role of IgM could not be proven, we believe these IgM antibodies must play an important role in the pathogenesis of bullous pemphigoid in this patient.

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