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Case report

IgM ocular cicatricial pemphigoid: a unique insight into the immune system

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Abstract

A 42-year-old man with ocular erythema and scarring had a conjunctival biopsy revealing depostion of IgM and C3 without IgG at the epithelial basement membrane zone. Treatment with doxycyline, dapsone, and mycophenolate mofetil was unsuccessful and treatment with rituximab has led to partial remission of the conjunctival inflammation. He has undergone 4 cycles of rituximab treatment at intervals of 12 to 18 months.

Introduction

Cicatricial pemphigoid describes a group of autoimmune blistering diseases predominantly affecting the mucosae and associated with inflammation that may induce significant scarring [1]. The pathological feature that underlies these disorders is the presence of linear deposition of IgG and/or C3 in the epithelial basement membrane zone (BMZ) [1]. This is the first reported case of ocular cicatricial pemphigoid with linear deposits of IgM without IgG at the BMZ.

Case synopsis

A healthy 42-year-old man presented with a two-year history of redness, swelling, and a burning sensation of his right eye. He was previously diagnosed with chalazion and treated unsuccessfully with warm compresses, topical antibiotics, and oral doxycycline. Physical examination revealed bilateral erythema of the conjunctiva with symblepharon formation in the lateral cornea bilaterally, the right eye more affected than the left. Mild trichiasis was also noted in the right lateral eyelid. There were no cutaneous lesions present and no other mucous membrane involvement.

Biopsy of the right conjunctiva showed chronic non-granulomatous inflammation of the substantia propria with scarring. Direct immunofluorescence (DIF) of the right eye conjunctiva revealed linear deposition of IgM, C3, and fibrin at the BMZ. There was no IgG or IgA noted. Indirect immunofluorescence (IIF) using monkey esophagus showed linear deposition of IgM at the BMZ

without IgG or IgA. IIF using human saline split skin (SSS) demonstrated a linear deposition of IgM on the epidermal side of SSS without IgG at 1:5, 1:10, and 1:20 dilutions. Of note, heavy chain specific antibodies were used in the tests above. A year later, repeat IIF on monkey esophagus showed IgM deposition without IgG or IgA at the BMZ at 1:10 dilutions. Two years later, testing done at another laboratory showed trace amounts of IgM without IgG bound to the epidermal side of a SSS biopsy. During these years no commercial laboratory was found to test for IgM specific antibodies to any BMZ antigens (IKA personal communication).

Extensive workup for autoimmunity and malignancy was performed. No other autoimmune disorders, no malignancy, and no IgM monoclonal gammopathy were found. In addition to doxycyline, dapsone was given, which initially decreased the inflammation but was discontinued owing to development of bilateral hand neuropathy. Mycophenelate mofetil was initially helpful, but discontinued because of CNS side effects. Cyclophosphamide was not given owing to family history of bladder cancer. Treatment with rituximab initially followed the pemphigus protocol of Ahmed [2]. This consisted of rituximab 375/m^2 for three weekly infusions and IVIG 2 grams/kg in the fourth week for two months followed by monthly rituximab and IVIG infusions for 4 months. This regimen helped control the disease progression, but IVIG was discontinued after two cycles owing to development of aseptic meningitis. Each infusion cycle of rituximab was associated with significant improvement that lasted 12 to 18 months. He completed four cycles of rituximab. Other treatments included docycyline 100 mg twice daily, intermittent prednisolone eye drops, loteprednol eye drops, and eyelash epilation. He has had a fluctuating disease course over 8 years with no periods of complete remission.

Repeated IIF studies performed after rituximab treatment still demonstrated trace IgM deposition at the BMZ without any IgG involvement.

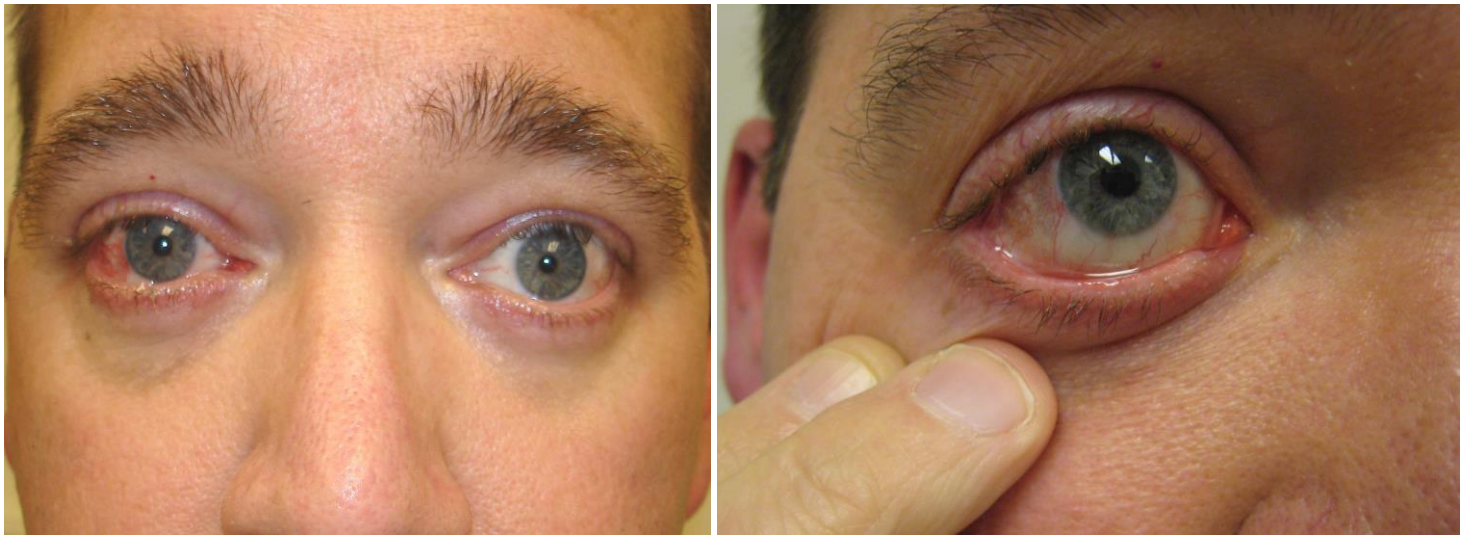

Figure 2. The patient has bilateral conjunctival injection and eyelid erythema with telangiectasias. **Figure 2.** Right eye erythema and symblepharon formation in the lateral cornea

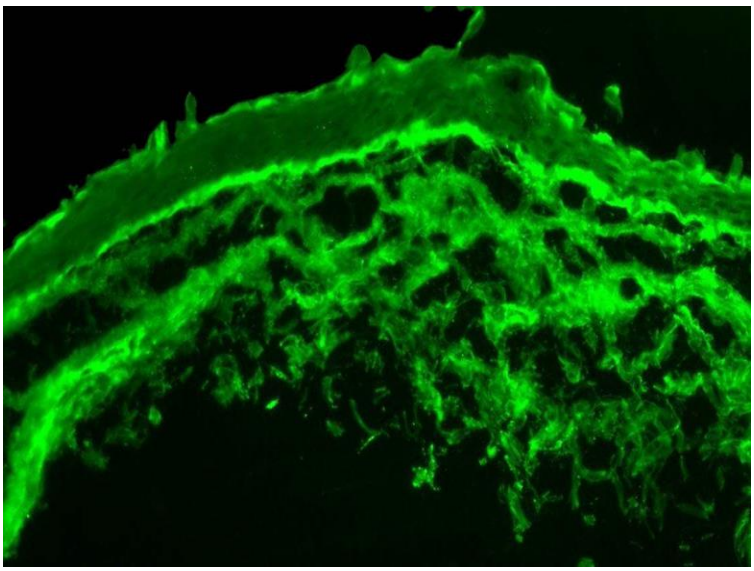

Figure 3. Direct immunofluorescence (DIF) of the right eye conjunctiva revealed linear deposition of IgM.

Discussion

Cicatricial pemphigoid, also called mucous membrane pemphigoid , describes a group of autoimmune blistering disorders primarily involving mucosal surfaces; cutaneous lesions involving the head and upper trunk may occasionally occur [1]. Mucous membrane inflammation develops in the oral mucosa most commonly followed by ocular, nasal, nasopharyngeal, anogenital, skin, laryngeal, and esophageal locations in descending order of involvement [1]. Mucous membrane involvement presents with erythema, erosions, and scarring. Ocular involvement usually appears with nonspecific conjunctival erythema, pain, or foreign body sensation; chronic inflammation may lead to scarring, shortening of fornices, symblepharon, ankyloblepharon, entropion, trichiasis, and loss of vision [1].

Diagnostic criteria include DIF microscopy or immunohistochemistry examinations on perilesional mucosal biopsies demonstrating continuous deposits of either individual or combinations of IgG, IgA, and/or C3 in the BMZ [1]. CP is associated with autoantibodies to one or more components of the basement membrane zone [1, 2, 4, 5)]. Antibodies to beta-4 integrin have been associated with ocular CP and antibody titers correlated with disease activity [1, 2, 4, 5]. Other identified antigens include bullous pemphigoid (BP) 180 and several ectodomains of BP180, BP 230, and laminin 332 [4, 5]. Our patient presented with clinical signs and symptoms consistent with CP along with DIF evidence of linear deposits of IgM and C3 bound to the epithelial BMZ, suggesting a diagnosis of CP. However, unlike other cases of CP documented in the literature, our patient showed anti-BMZ IgM without any evidence of IgG or IgA present. Although this might be expected early in the course of an autoimmune disease, our patient's DIF results remain stable after many years. A literature search revealed one case of disseminated cutaneous cicatricial pemphigoid with only IgM deposition at the BMZ [6]. Cutaneous cicatricial pemphigoid affecting predominately the head, neck, and scalp – a form known as Brunstig-Perry cicatricial pemphigoid — occurs without or with only mild mucosal involvement [7, 8]. IgM at the BMZ may be detected in these patients, but always in association with IgG and IgA [7]. Disseminated cicatricial pemphigoid is rare, affects the head, the trunk, and extremities, may be preceded by the Brunstig-Perry localized form, and is associated with deposition of linear IgG, IgA, and C3 at the BMZ [9]. In a review of the diagnostic value of IgM deposition at the dermal-epidermal junction in 200 patients, more than half were associated with lupus erythematosus, and the others associated with a wide spectrum of cutaneous disorders, none showing any known specific association except for history of sun exposure [10]. No other cases of isolated linear anti-BMZ IgM positive CP with mucosal involvement were identified.

However, there are reported cutaneous disorders that include papules, plaques, or blisters with linear depostion of IgM at the BMZ, all in association with IgM Waldenstrom macroglobulinemia [11-14]. Isolated IgM positivity that is unrelated to a monoclonal gammopathy appears to be related to the antigen that is inducing the reaction – and it is likely to be a polysaccharide part of a glycoprotein and not a protein itself. Immunoglobulin class switching requires an interaction between a CD4+ T cell and the antigen specific B cell. This patient has no immunoglobulin deficiency or IgM gammopathy to explain this failure to class switch. Antibody formation against polysaccharide components, however, is T cell independent; B-cells are directly activated and so class switching from IgM to IgG is not seen [15]. In the cases of IgM monoclonal gammopathy-associated cutaneous disorders, the antigens varied and were present on both sides of the split in SSS [11,12] or on the dermal side alone [13,14] but did not react with collagen type VII or laminin 332 [14].

Further investigation into the antigens that precipitate the autoimmune response seen in IgM cicatricial pemphigoid is warranted and may provide further insight into the etiology of this disease.

Table I. Linear IgM Dermatosis

	Mucous Membrane	Cutaneous	Subepidermal blister	DIF linear IgM IIF	Circulating and/or monoclonal IgM	Treatment
Our patient	Eyes	No	No	Positive Positive	Negative	Doxycycline, dapsone, cellcept, prednisone, rituximab, IVIg
Braun-Falco 1981	No	Occipital, trunk, extremities	Yes	Positive Negative	Negative	Bactrim, dapsone, azathioprine
Cobb 1992	No	Pruritic papules	No	Positive Positive	IgM Kappa anti BMZ binds to both sides of salt split skin	PUVA
Whitttaker 1996	No	Bullous disorder with skin fragility	Yes	Positive Positive	IgM Kappa bind to both sides of salt split skin	Prednisone, Azathioprine
Peck 1997	No	Papules and plaques	No	Positive Positive	IgM Kappa on dermal side of BMZ	Chemotherapy
Chattopadhyay 2013	No	Bullae	Yes	Positive Positive	IgM on dermal side of salt split skin	Rituximab, cytoxan, prednisolone

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