Mucous membrane pemphigoid (MMP), also known as cicatrical pemphigoid, constitutes a heterogeneous group of autoimmune blistering diseases that result from autoantibodies directed against epidermal basement membrane proteins.⁴ Although presentations vary, patients can have involvement of their conjunctiva, sometimes experiencing a progressive disease course resulting in vision loss.

Rituximab is a chimeric murine-human anti-CD20 monoclonal antibody that has demonstrated good efficacy in the treatment of refractory mucous membrane pemphigoid. However, not all cases of mucous membrane pemphigoid respond to rituximab. Herein we present a case of treatment-refractory mucous membrane pemphigoid and propose a mechanism to explain the lack of response to therapy.

Report of a Case
An older man presented to the Department of Dermatology, University of California, Davis, with generalized cutaneous bullae and oral erosions. A skin biopsy specimen underwent direct immunofluorescent examination of a biopsy sample from the patient’s perilesional skin demonstrated linear deposition of IgG and IgA along the dermoepidermal junction. After a multidrug immunosuppressive regimen that included rituximab, results of a second biopsy demonstrated only IgA along the dermoepidermal junction. This finding correlated well with flow cytometry data from the same patient that demonstrated a persistent population of IgA-secreting plasmablasts/plasma cells, despite depletion of CD20⁺ cells. In addition, results of immunohistochemical analysis of the perilesional skin remained positive for CD19 and CD138 immune cells (plasmablast/plasma cell markers).

CONCLUSIONS AND RELEVANCE These findings suggest that current available immunosuppressive medications, including rituximab, cannot eliminate IgA-secreting plasmablasts/plasma cells, which are likely central to the pathophysiology of IgA-mediated immunobullous diseases. Future studies are needed to develop alternative therapeutic strategies that target autoreactive IgA-secreting plasmablasts/plasma cells.

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mg/d), dapsone (100 mg twice daily), mycophenolate mofetil hydrochloride (1000 mg twice daily), and niacinamide (500 mg 3 times daily), resulting in minimal improvement. Rituximab (375 mg/m² of body surface area once weekly for 4 weeks), intravenous immunoglobulin (400 mg/kg daily for 5 days), and intravenous pulsed cyclophosphamide (15 mg/kg once monthly for 5 months) were sequentially added to his treatment regimen, again resulting in minimal improvement (Figure 1A). Results of peripheral blood CD19⁺ cell counts persisted at less than 1%, confirming rituximab activity. Disease progression continued and eventually resulted in worsening oral ulcerations, odynophagia, and significant ocular scarring (Figure 1B). The
Figure 2. Persistence of IgA-Secreting Plasmablasts/Plasma Cells After Aggressive Immunosuppressive Therapy

**A** B-cell population

CD3−CD14−CD19+ cells are depleted after rituximab treatment (0.1% vs 7.3% in healthy control sample; *P* < .002). Middle, CD20−CD27+ plasmablasts/plasma cells (red outline) represent a large proportion of the residual CD19+ cells after treatment (17.7% vs 0.7% in healthy control; *P* = .008). Right, Bar graphs illustrate changes in cell levels. PBMC indicates peripheral blood mononuclear cell.

**B** Levels of IgA-secreting cells (arrowhead) are increased in the CD20−CD19+CD27+ population (originating from the red outline in part A) after treatment.

**C** Levels of IgA-secreting cells are increased within the CD20+CD19+CD27+ population (originating from the blue outline in part A) after treatment.
patient developed macular edema, and prednisone eye drops were added to his treatment regimen. His therapy was also switched from mycophenolate mofetil to azathioprine sodium, and he received several additional cycles of intravenous immunoglobulin, again with minimal improvement. After the patient did not respond to rituximab, intravenous immunoglobulin, and cyclophosphamide, a second biopsy specimen was obtained for direct immunofluorescence. The results demonstrated deposition of linear IgA, sparse granular C3, but no IgG along the dermoeidermal junction (Figure 1C). Results of a second enzyme-linked immunosorbent assay confirmed resolution of autoreactive BP180- and BP230-specific IgG (ARUP Laboratories).

Given that the results of direct immunofluorescence studies demonstrated persistent deposition of autoreactive IgA, despite aggressive immunosuppressive therapy, peripheral blood was drawn for a detailed characterization of the treatment-resistant B cells. The medical ethics committee of the University of California, Davis, School of Medicine approved all aspects of this study according to the Declaration of Helsinki principles. Peripheral blood mononuclear cells were analyzed for expression of CD19, CD20, and CD27. In contrast to blood samples from healthy individuals, circulating CD20−CD19+CD27+ cells representative of the plasmablasts/plasma cell population (red outline) occupied a large proportion of the B-cell pool in the treated patient (17.7% vs 0.7%) (Figure 2A). Further analysis revealed that IgA-expressing cells were greatly expanded within the CD20−CD19+CD27+ plasmablast/plasma cell population after treatment, conservatively measured at 33.7% (Figure 2B). An increased population of CD20−CD19+CD27+ IgA-expressing memory B cells (blue outline) was also detected (25.9%) after treatment (Figure 2C). Thus, in our patient, IgA-expressing plasmablasts/plasma cells were strongly resistant to aggressive immunosuppressive therapy that included B-cell depletion with rituximab.

To gain further insight into the origin of the autoreactive IgA antibodies, the posttreatment perilesional skin biopsy specimen was reevaluated using immunohistochemical analysis for CD19 and CD138, which demonstrated the presence of CD19+ and CD138+ plasmablasts/plasma cells (Figure 1D). These immune cells are presumed to contribute to the pathogenic autoreactive IgA antibodies that were detected by direct immunofluorescence (Figure 1C). Furthermore, indirect immunofluorescence performed on a normal skin specimen with posttreatment serum using the salt split technique demonstrated IgA reactivity to the epidermal side of the split at a titer of 1:160 (ARUP Laboratories). No IgG was detectable via indirect immunofluorescence.

Discussion

Mei et al39 recently reported that rituximab fails to deplete self-replenishing IgA B cells of mucosal origin, although their study lacked patients with IgA-mediated autoimmunity. We speculate that the treatment-resistant peripherally circulating IgA-expressing plasmablasts/plasma cells in our patient are also derived from a self-sufficient population of tissue-resident B cells that are thought to be inherently resistant to anti-CD20 therapy.10,11 Our patient’s MMP did not respond to several additional immunosuppressive medications in addition to rituximab. We therefore hypothesize that his autoreactive IgA-secreting cells are very slowly regenerating or are a long-lived population. Otherwise, they should have been susceptible to the nitrogen mustard–alkylating agent, cyclophosphamide, which is especially toxic to proliferating cells.

Also noteworthy was the depletion of B cells longer than 1000 days after rituximab administration in our patient. This duration has been reported rarely in published studies.12 The patient is now being treated with combination therapy consisting of prednisone, 20 mg/d, leflunomide, 20 mg/d, and dapsone, 100 mg twice daily.

Conclusions

To our knowledge, this report is the first to show that autoreactive IgA-secreting B cells are resistant to multiple immunosuppressive medications, including rituximab. Our study, although limited to a single case, may explain why MMP resulting from autoreactive IgA and IgG manifests more severe disease when compared with MMP mediated by IgG alone.3 Future studies are needed to develop therapeutic strategies to target autoreactive rituximab-resistant IgA-expressing plasmablasts/plasma cells.


Archeological Sites and Dermatologic Medications
More Similar Than One May Think

Kara M. Trapp, BA; Scott A. Norton, MD, MPH

We noticed that names of medications often resemble names of ancient archeological sites. This may be a coincidence with no significance (a sphinx without a secret), but let’s see how well you can tell one from the other. Here’s your challenge: match the names of dermatologic medications and of Egyptian, Greek, and Mayan archeological sites with their appropriate descriptions (Figure).

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Medications and Ancient Archeological Sites

Quiz A

1. Oxyrhynchus  A. Mayan archeological site in Yucatán, Mexico
2. Oxybutynin   B. Humanized antibody used for the treatment of chronic idiopathic urticaria and moderate to severe persistent allergic asthma
3. Oxctuzcab    C. Medication used for the treatment of generalized hyperhidrosis
4. Omalizumab   D. Egyptian archeological site located in Upper Egypt
5. Obelisk    E. Medication used for the treatment of acute bacterial skin infections
6. Oritavancin  F. Egyptian archeological site in Aswan, Egypt

Quiz B

1. Epidaurus    A. Medication used for the treatment of facial hirsutism
2. Everolimus   B. Egyptian archeological site and island located in the Nile River
3. Etanercept  C. Medication used for the prevention of graft-vs-host disease
4. Elephantine D. Greek archeological site that was the home of Asclepius, the god of healing
5. Elopenthine E. Medication used for the treatment of psoriatic arthritis and plaque psoriasis
6. Efornithine F. Region of Greece that is rich in archeological sites

Quiz C

1. Ingenol    A. Medication used for the treatment of Raynaud phenomenon
2. Izamal   B. Medication used for the treatment of melanoma
3. Ixtonton  C. Mayan archeological site in Yucatán, Mexico
4. Isoxsuprine D. Mayan archeological site in the Petén Department of Guatemala
5. Izapa E. Medication used for the treatment of actinic keratosis
6. Ipilimumab F. Mayan archeological site in Chiapas, Mexico

Quiz A Answers: 1D, 2C, 3A, 4B, 5F, 6E

Quiz B Answers: 1D, 2C, 3F, 4B, 5D, 6A

Quiz C Answers: 1E, 2C, 3D, 4A, 5F, 6B