

REFERENCES

1. Lattman J, Massry GG, Hornblass A. Pseudomonal eyelid necrosis: clinical characteristics and review of the literature. *Ophthalm Plast Reconstr Surg*. 1998;14:290–4.
2. Comaish I, Thaller V, Newman P. Necrosis of the lid due to *Pseudomonas aeruginosa*. *Eye*. 2000;14:387–9.
3. Kreger AS. Pathogenesis of *Pseudomonas aeruginosa* ocular diseases. *Rev Infect Dis*. 1983;5:S931–5.
4. Kronish JW, McLeish WM. Eyelid necrosis and periorbital necrotizing fasciitis. *Ophthalmology*. 1991;98:92–8.
5. Lazzeri D, Lazzeri S, Figus M, et al. Periorbital necrotizing fasciitis. *Br J Ophthalmol*. 2010;94:1577–85.
6. Rodriguez-Gonzalez F, Marrero-Saavedra D, Rutllan-Civit J, Cabrera-Vargas E, Martinez-Qintana E. Ocular necrotizing fasciitis due to *Pseudomonas aeruginosa* in a non-neutropenic patient. *Saudi J Ophthalmol*. 2013;27:281–2.
7. Prendiville KJ, Bath PE. Lateral cantholysis and eyelid necrosis secondary to *Pseudomonas aeruginosa*. *Ann Ophthalmol*. 1988;20:193–5.
8. Zeligowski AA, Peled U, Wexler MR. Eyelid necrosis after spider bites. *Am J Ophthalmol*. 1986;101:254–5.
9. Jordan DR, Ziai S, Gilberg SM, Mawn LA. Pathogenesis of canicular laceration. *Ophthalm Plast Reconstr Surg*. 2008;24:394–8.
10. Reifler DM. Management of canicular laceration. *Surv Ophthalmol*. 1991;36:113–32.
11. Kenneth TC, Balabanova M. Vasculitis in systemic lupus erythematosus. *Clin Dermatol*. 2004;22:148–56.

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Intravenous rituximab for the treatment of relapsing adult-onset asthma with periocular xanthogranuloma



In 1993, Jakobiec et al. first reported adult-onset asthma with periocular xanthogranuloma (AOAPOX) in 6 patients, who were treated with oral and inhaled steroids.¹ Clinically, these patients present to the ophthalmologist with bilateral, yellowish-orange, elevated, and indurated xanthomatous eyelid mass lesions.¹ The anterior orbital fat, extraocular muscles, lacrimal gland, and optic nerve may eventually get involved. The onset of asthma may occur concurrently, precede, or follow the periocular/orbital lesions.^{2,3} Hence, a timely systemic workup is crucial to identify coexisting severe morbidities like asthma, paraproteinemias, and lymphomas.²

The histopathology and immunohistochemistry features eosinophilic infiltrates with dendritic cells, xanthoma cells, lymphocytes, and high CD8 and CD20 positivity.^{2–5} A magnetic resonance imaging (MRI) of the orbits is preferred over a computed tomography before planning an incisional biopsy, as MRI provides better soft-tissue delineation, picks up subtle infiltrations and helps in differentiating orbital inflammatory disorders.⁶

The primary treatment for AOAPOX is medical. The corticosteroids, methotrexate, and rituximab have been tried as monotherapies or in combination therapies with satisfactory success.^{1,2,7,8} Recently, rituximab monotherapy successfully treated bilateral orbital necrobiotic xanthogranuloma with CD20 predominance.⁹ Pomponio et al. used rituximab as first-line monotherapy in AOAPOX associated with IgG4-related disease and reported a sustained (1 year) clinical response after its single course of 2 g in 2 doses.¹⁰ We report 2 patients of AOAPOX who relapsed after stopping oral deflazacort and showed long-term remission after intravenous rituximab therapy.

CASE DESCRIPTIONS

Case 1

A 43-year-old male complained of painless, slowly progressive swellings of both upper eyelids of 2 years' duration. He was a known case of bronchial asthma and was currently on inhalational steroids. He was referred to us with a diagnosis of bilateral orbital lymphoma. On examination, the best corrected visual acuity was 6/6 in both eyes with normal intraocular pressures. Both superior orbital sulci were full with medial and central prominences (Fig. 1A–C). He had bilateral upper blepharoptosis with restricted elevation (Fig. 1D) and no proptosis. The overlying eyelid skin appeared healthy and was freely mobile. On palpation, the superior orbital mass lesions were indurated, nontender, and measured 40 × 25 mm. The anterior and posterior segment was within normal limits (WNL).

The working diagnosis of orbital lymphoma and orbital xanthogranuloma was kept. The laboratory investigations were requested, and the complete blood counts, peripheral blood film, lipid profile, and renal and liver function tests were WNL. MRI orbits showed bilateral, ill-defined, hyperintense mass with diffuse soft-tissue infiltration in superior orbits, on both T1W and T2W images (Fig. 1E,F). Bilaterally, the lacrimal glands appeared to be involved, and the extraocular muscles were enlarged. A bilateral incisional biopsy from the superior orbit was performed and detailed histopathology with immunostaining was requested. The biopsy results showed dense nodular collections of xanthoma cells in perivascular and periadenexal locations. The foamy histiocytes were highlighted by CD68 immunostain, which was consistent with features of a diffuse xanthomatous lesion.

Oral deflazacort was started at a dosage of 30 mg/day, 18 mg/day, and 6 mg/day for the first, second, and third month, respectively, with a satisfactory response. After 3 months of stopping steroids, he had an ophthalmic and pulmonary relapse. Intravenous rituximab (375 mg/m²) was prescribed weekly for 4 weeks followed by a monthly dose for 3 months. At 14 months follow-up after cessation of rituximab (Fig. 2),

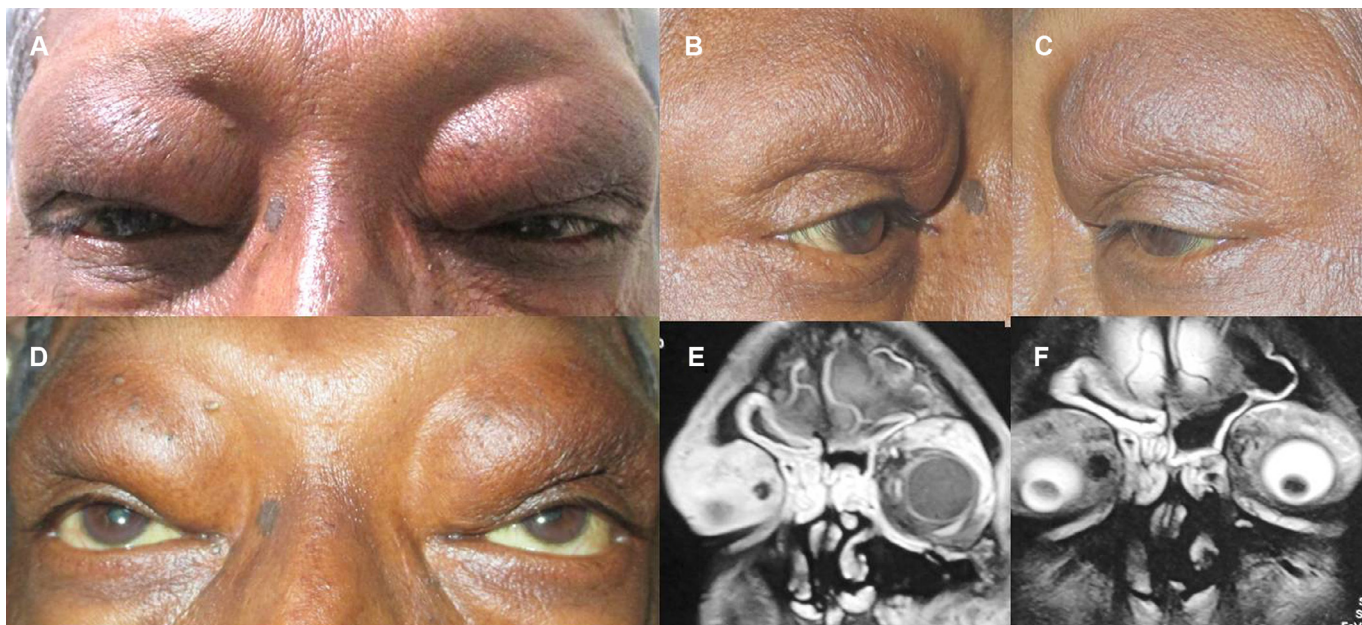


Fig. 1—A, The fullness of bilateral superior orbital sulci (medial and central predominance) with mild blepharoptosis (left > right). The conjunctiva and cornea appears normal. **B,** Right lateral view shows the prominent forward extension of superior orbital mass and no proptosis. **C,** Left lateral view shows similar features with blepharoptosis. **D,** Bilateral markedly restricted elevation. **E,** MRI coronal scan (T1W) shows bilateral diffuse and hyperintense masses in superior orbits and neighboring ethmoid sinuses. **F,** MRI coronal scan (T2W) shows reduced and patchy hyperintensity within the masses in both superior orbits and neighboring ethmoid sinuses.

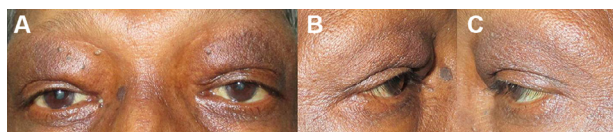


Fig. 2—A, The 12 months' postrituximab follow-up shows a marked reduction in the size and extent of the superior orbital mass. The blepharoptosis is also reduced. **B,** Right lateral view shows the minimal fullness of superior orbital sulcus. **C,** Left lateral view shows similar reduction with reduction of ptosis.

the orbital masses had significantly reduced with correction of blepharoptosis, extraocular movements, and stabilization of asthmatic complaints.

Case 2

A 45-year-old male presented with yellowish patches and swellings over both upper eyelids since 2 years. He was on irregular asthma treatment for the last 1 year. He was misdiagnosed as xanthelasma by a dermatologist and was advised to undergo transcutaneous laser-based therapy. The routine ophthalmic examination was WNL. The clinical features are shown in Figure 3. The Hertel's exophthalmometry reading was 24 mm for both eyes. Keeping AOAPOX as the working diagnosis, the systemic investigations were requested. The thyroid function tests were WNL, and blood film showed eosinophilia.

The MRI orbits showed diffuse, bilateral, hyperintense masses in the superior pre- and retroseptal region. The incisional biopsy revealed orbital xanthogranuloma with B-cell predominance (CD20+). He responded satisfactorily to oral deflazacort but showed a relapse after 2 months of discontinuing steroids. Intravenous rituximab was administered in a similar dosage mentioned above. At 12 months follow-up after stopping rituximab, the yellowish eyelid plaques and swellings had minimized significantly with sustained remission.

DISCUSSION

The differential diagnosis for bilateral orbital masses in adults includes orbital lymphoma, nonspecific orbital inflammatory disease, metastasis, histiocytic lesions, amyloidosis, multiple myeloma, and orbital xanthogranuloma.² The AOAPOX may present with conjunctival and eyelid involvement responsive to systemic immunosuppression.¹¹ Usually xanthogranuloma patients first present to an ophthalmologist, which renders its awareness an imperative necessity.

Cavallazzi et al. postulated a role of eosinophil recruitment and activation for causing the associated asthma in AOAPOX.¹² Hayden et al. successfully treated orbital xanthogranuloma using methotrexate (10–20 mg/week) and postulated its



Fig. 3—A, Bilateral superior and inferior orbital sulci appear full with yellow-orange discoloration/plaques (left > right) with medial and central prominence. The left eye has 15 degree exotropia with bilateral proptosis. **B,** Right lateral view shows proptosed eyeball with lower eyelid retraction. **C,** Left lateral view shows similar features.

anti-inflammatory effect due to stimulation of adenosine release and reduced cytokine production.^{7,12} Satchi et al. published the first report of treating AOAPOX with rituximab in 3 patients with a complete and sustained response (>12 months).⁸ Those patients showed a moderate and incomplete response to methotrexate and steroids. They concluded that the B-cell predominant (CD20+) disease better responds to anti-CD 20 molecule, i.e. rituximab. The immunohistochemistry of our patients showed CD68 and CD20 positivity and showed a satisfactory response to rituximab, making this target-specific treatment a better option than steroids. With rituximab, a better and long-term remission can be obtained as compared to steroids.^{8–10} We believe that an intravenous route is better for administering rituximab in AOAPOX patients as it provides both orbital and systemic remission. A proportionately higher cost of rituximab treatment remains the only concern, which can be a limitation for its use in developing countries.

In conclusion, an adequate awareness, appropriate imaging (MRI), and timely histopathological diagnosis with CD cell specificity helps in better management of AOAPOX. The current trend also shows an inclination toward first-line monotherapy with rituximab for patients with AOAPOX. The authors would like to recommend the use of intravenous rituximab as a primary first-line monotherapy for orbital xanthogranulomas.

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REFERENCES

1. Jakobiec FA, Mills MD, Hidayat AA, et al. Periocular xanthogranulomas associated with severe adult-onset asthma. *Trans Am Ophthalmol Soc.* 1993;91:99–125. discussion 125–9.
2. Davies MJ, Whitehead K, Quagliotto G, Wood D, Patheja RS, Sullivan TJ. Adult orbital and adnexal xanthogranulomatous disease. *Asia Pac J Ophthalmol (Phila).* 2017;6:435–43.
3. Hammond MD, Niemi EW, Ward TP, Eiseman AS. Adult orbital xanthogranuloma with associated adult-onset asthma. *Ophthalm Plast Reconstr Surg.* 2004;20:329–32.
4. Sivak-Callcott JA, Rootman J, Rasmussen SL, et al. Adult xanthogranulomatous disease of the orbit and ocular adnexa: new immunohistochemical findings and clinical review. *Br J Ophthalmol.* 2006;90:602–8.
5. Guo J, Wang J. Adult orbital xanthogranulomatous disease: review of the literature. *Arch Pathol Lab Med.* 2009;133:1994–7.
6. Miszkil KA, Sohaib SA, Rose GE, Cree IA, Moseley IF. Radiological and clinicopathological features of orbital xanthogranuloma. *Br J Ophthalmol.* 2000;84:251–8.
7. Hayden A, Wilson DJ, Rosenbaum JT. Management of orbital xanthogranuloma with methotrexate. *Br J Ophthalmol.* 2007;91:434–6.
8. Satchi K, McNab AA, Godfrey T, Prince HM. Adult orbital xanthogranuloma successfully treated with rituximab. *Ophthalmology.* 2014;121:1664–5.
9. Sagiv O, Thakar SD, Morrell G, Tetzlaff MT, Esmali B. Rituximab monotherapy is effective in treating orbital necrobiotic xanthogranuloma. *Ophthalmic Plast Reconstr Surg.* 2018;34:e24–7.
10. Pomponio G, Olivari D, Martioli M, et al. Sustained clinical response after single course of rituximab as first-line monotherapy in adult-onset asthma and periocular xanthogranulomas syndrome associated with IgG4-related disease: a case report. *Medicine (Baltimore).* 2018;97:e11143.
11. Shams PN, Rasmussen SL, Dolman PJ. Adult-onset asthma associated with simultaneous conjunctival, eyelid, and orbital xanthogranulomatosis responsive to systemic immunosuppression. *Ophthalmic Plast Reconstr Surg.* 2015;31:e162–3.
12. Cavallazzi R, Hirani A, Vasu TS, et al. Clinical manifestations and treatment of adult-onset asthma and periocular xanthogranuloma. *Can Respir J.* 2009;16:159–62.

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A modified technique for bedside amniotic membrane application to the eyelid margins for Stevens-Johnson syndrome



Amniotic membrane (AM), the innermost layer of the placenta, is commonly used as a graft and dressing to promote healing and ocular surface reconstruction. It has been used successfully in the treatment of various ocular surface conditions, such as Stevens-Johnson syndrome (SJS) and toxic epidermolysis necrolysis (TEN) to protect the ocular surface.^{1,2} Amniotic membrane application typically takes place in the operating room, unless the patient is too unstable for transport. The technique described by Shamma et al. involves suturing the amniotic membrane over the eyelid margin, then pushing the membrane into the fornix with a muscle hook.³ We report a streamlined technique of amniotic membrane application that can be rapidly performed at the bedside under local anaesthetic.

METHODS

The procedure is performed with local and topical anaesthesia without intravenous sedation. For each eyelid, a 3.5 cm × 3.5 cm cryopreserved amniotic membrane (AmnioGraft and Prokera Bio-Tissue, Miami, Fla.) was used. First, a Prokera device was placed, and then attention was directed toward placement of the free amniotic membranes to the eyelid margins and

palpebral conjunctiva (Fig 1). The cryopreserved AM is packaged with a paper backing. The AM was partially peeled off of the paper backing, and the partial attachment to the backing helps with orientation and minimizes folding of the AM onto itself (Fig 1). The membrane was placed with the stromal surface against the ocular surface. Two 6-0 double armed prolene sutures were preplaced in each leading corner of the amniotic membrane. This ensures that when the amniotic membrane is pulled into the fornix, the stromal side is in contact with the healing eyelid margin. With the eyelid distracted from the globe by a Desmarre retractor, the double-armed sutures were placed deep into the fornix and externalized through the skin. Traction was applied to the externalized sutures, which subsequently draws the amniotic membrane deep into the fornix. With the paper backing still partially attached, the membrane remains in proper orientation. As the surgeon pulls the membrane into the fornix, an assistant carefully peels the remaining membrane off the paper backing. The trailing edge of the amniotic membrane is then folded over the eyelid margins and draped over the Prokera, which also folded the eyelashes away from the eye. This technique therefore negates the need for eyelash trimming, which may actually create a more abrasive surface for the amniotic membrane. The externalized sutures were then passed through the folded amniotic membrane and tied off with foam bolsters for support. The identical procedure was repeated for the remaining 3 eyelids. Fig 2 shows a patient who underwent AM placement who presented with TEN.