

JAMA Ophthalmology Clinical Challenge

Acute-Onset Orbital Inflammation in a Patient With Multiple Myeloma

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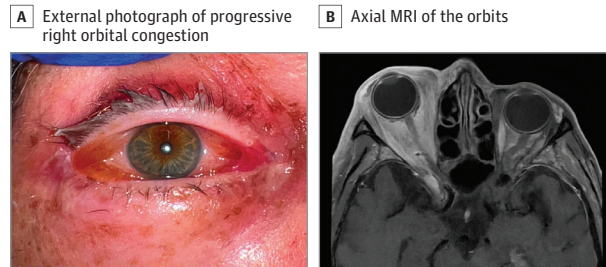


Figure 1. A, External photograph of the right eye demonstrating periocular edema, conjunctival injection, and chemosis. B, Axial T1 fat-suppressed postcontrast magnetic resonance imaging (MRI) demonstrating proptosis of the right eye with optic nerve straightening, diffuse enhancement of the right intraconal and extraconal fat, and periorbital tissues.

A 72-year-old male patient presented with 2 days of conjunctival injection in the right eye, chemosis, eyelid edema, and pain with eye movements. His medical history included hypothyroidism, psoriasis, and recent diagnosis of multiple myeloma, and he was taking daratumumab and zoledronic acid. He denied eye trauma, dental surgery, or sinus disease. Examination of the right eye was notable for visual acuity of 20/50, reduced ocular motility in all gazes, proptosis, and chemosis. There was no afferent pupillary defect. Examination of the left eye was unremarkable. Computed tomography of the orbits with contrast demonstrated right preseptal edema and intraorbital fat stranding of the extraconal and intraconal fat without sinus disease. Nasal endoscopy performed by the otolaryngology service showed no evidence of invasive fungal sinusitis. The patient received a single dose of intravenous vancomycin and ceftriaxone, then was transitioned to ampicillin-sulbactam for presumed orbital cellulitis. After 48 hours, motility, proptosis, and chemosis worsened (Figure 1A).

Magnetic resonance imaging of the orbits with and without contrast (Figure 1B) was remarkable for proptosis with optic nerve straightening, enhancement of the intraconal and extraconal fat, edema and enhancement of the right extraocular muscles, new thickening of the left sphenoid sinus with internal air-fluid level, and new inflammation of the left masticator space. A follow-up computed tomography of the sinus with contrast showed no evidence of osseous structure destruction to suggest invasive fungal sinusitis. Under guidance from the infectious disease service, antibiotics were broadened back to vancomycin and ceftriaxone with continued worsening.

WHAT WOULD YOU DO NEXT?

- A. Start antifungal therapy
- B. Sinus biopsies
- C. Start corticosteroids
- D. Orbital biopsy

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Diagnosis

Zoledronic acid-induced orbital inflammation

What to Do Next

- C. Start corticosteroids

Discussion

This patient with multiple myeloma presented with acute unilateral orbital congestion and ophthalmoplegia and was initially treated for presumed orbital cellulitis. His condition worsened despite treatment with broad-spectrum intravenous antibiotics, thus raising suspicion for an alternative etiology. Although invasive fungal sinusitis was considered on the differential diagnosis due to his immunocompromised state, neither bedside nasal endoscopy nor com-

puted tomography of the sinus was suggestive of the disease. Therefore, antifungals were not started (choice A), and sinus biopsies were not pursued (choice B).

An inflammatory etiology was considered, given the multifocal involvement observed on imaging (right orbit, left sphenoid sinus, masticator space). On further probing, the patient reported he received his first infusion of zoledronic acid, a bisphosphonate, as part of his treatment for multiple myeloma 3 days prior to presentation. Given the acute onset of symptoms within 72 hours of the first zoledronic acid infusion, a diagnosis of orbital inflammatory disease due to bisphosphonate infusion was suspected. Treatment with intravenous pulse methylprednisolone was initiated (choice C). Due to the suspected etiology and the acute nature of the presentation, an orbital biopsy would not be the best next option (choice D).

Bisphosphonates are commonly used in osteoclast-mediated bone loss due to osteoporosis, Paget disease of bone, bone metastases, hypercalcemia of malignancy, and multiple myeloma.¹ Bisphosphonate-induced orbital and ocular inflammation is uncommon and has been described in both case reports and case series. With widespread use of bisphosphonates, orbital and sinus inflammation is becoming an increasingly recognized adverse effect.² Ocular adverse effects include anterior uveitis, scleritis, and optic neuritis.³ Orbital inflammation can be severe and occurs acutely, usually within 72 hours of medication administration when given intravenously and within 2 to 3 weeks when given orally.^{2,4-7}

The close temporal association between the infusion of zoledronate and the onset of orbital inflammation in this patient is consistent with prior reports. Prompt administration of corticosteroids was associated with good response.^{2,4-7} Corticosteroids are the mainstay of therapy, but the ideal dosing strategy and taper schedule is unclear. Discontinuation of bisphosphonates is recommended; in most reported cases, the bisphosphonate was discontinued. There is 1 report of a patient who continued monthly bisphosphonate therapy without recurrence of orbital inflammation.⁵ Further studies are needed to clarify the likelihood of recurrence if patients continue taking bisphosphonates.

Patient Outcome

This patient received intravenous solumedrol, 500 mg, daily for 2 days with immediate marked clinical improvement (Figure 2).

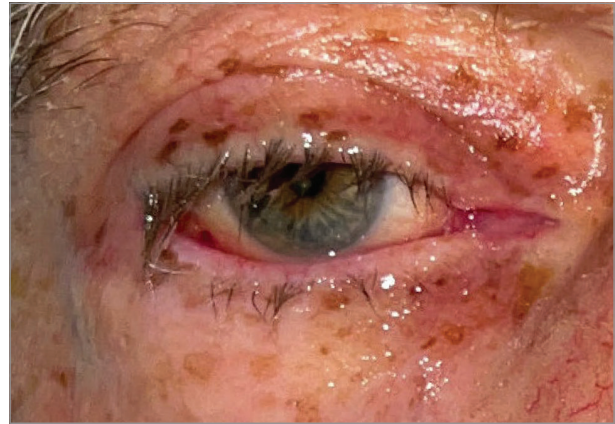


Figure 2. External photograph after 2 days of intravenous methylprednisolone demonstrating clinical improvement in orbital congestion.

He received 1 more dose of intravenous solumedrol, 250 mg, and was transitioned to an oral prednisone taper. He was examined 2 weeks after discharge with complete resolution of all orbital symptoms: he had no chemosis, conjunctival injection, proptosis, or double vision. The oncologist discontinued zoledronate and prescribed denosumab. At 3-month follow-up, none of the presenting symptoms had recurred and uncorrected visual acuity in the right eye had improved to 20/25 OD.

ARTICLE INFORMATION

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REFERENCES

1. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. *Mayo Clin Proc*. 2008;83(9):1032-1045. doi:10.4065/83.9.1032
2. Khalid MF, Micieli J, DeAngelis D, Micieli JA. Zoledronic acid-induced orbital inflammation. *BMJ Case Rep*. 2021;14(8):e245359. doi:10.1136/bcr-2021-245359
3. Wolpert LE, Watts AR. Zoledronate-induced anterior uveitis, scleritis and optic neuritis: a case report. *N Z Med J*. 2021;134(1537):91-94. <https://journal.nzma.org.nz/journal-articles/zoledronate-induced-anterior-uveitis-scleritis-and-optic-neuritis-a-case-report>
4. Pirbhai A, Rajak SN, Goold LA, et al. Bisphosphonate-induced orbital inflammation: a case series and review. *Orbit*. 2015;34(6):331-335. doi:10.3109/01676830.2015.1078380
5. Phillips PM, Newman SA. Orbital inflammatory disease after intravenous infusion of zoledronate for treatment of metastatic renal cell carcinoma. *Arch Ophthalmol*. 2008;126(1):137-139. doi:10.1001/archophthol.2007.17
6. Herrera I, Kam Y, Whittaker TJ, Champion M, Ajlan RS. Bisphosphonate-induced orbital inflammation in a patient on chronic immunosuppressive therapy. *BMC Ophthalmol*. 2019;19(1):51. doi:10.1186/s12886-019-1063-8
7. Peterson JD, Bedrossian EH Jr. Bisphosphonate-associated orbital inflammation—a case report and review. *Orbit*. 2012;31(2):119-123. doi:10.3109/01676830.2011.648818