EJCRIM
European Journal
of Case Reports
in Internal Medicine

ZOLEDRONIC ACID-INDUCED ORBITAL INFLAMMATION: A DIAGNOSTIC CHALLENGE

Tala Nasrini[1], Adam Bacon[2], Sharma Umesh[2]

[1] Department of Internal Medicine, Koç University School of Medicine, Istanbul, Turkey
[2] Department of Internal Medicine, Mayo Clinic Arizona, Scottsdale, USA

Corresponding author's e-mail: talanasrini@gmail.com

Received: 21/08/2025
Accepted: 26/08/2025
Published: 05/03/2026

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Written informed consent was obtained from the patient for publication of her clinical history and images.
Acknowledgments: The authors thank the ophthalmology and radiology teams for their support in patient care and data collection.
This article is licensed under a Commons Attribution Non-Commercial 4.0 License

How to cite this article: Nasrini T, Bacon A, Umesh S. Zoledronic acid-induced orbital inflammation: a diagnostic challenge. *EJCRIM* 2026;**13**:doi:10.12890/2026_005784

ABSTRACT

Introduction: Zoledronic acid is a bisphosphonate widely used for osteoporosis and other bone disorders. In rare cases, it can cause ocular inflammation mimicking orbital cellulitis.

Case description: A 52-year-old woman developed right eye pain and swelling within 24 hours of her first zoledronic acid infusion. Examination revealed conjunctival redness and mild eyelid swelling without proptosis, ophthalmoplegia, or vision loss. Laboratory markers were largely normal. Computed tomography scan and magnetic resonance imaging showed preseptal and postseptal inflammation without abscess formation. Treatment with corticosteroids and antibiotics resulted in complete symptom resolution within one week.

Conclusion: Zoledronic acid can induce rapid-onset orbital inflammation. Awareness of this rare adverse effect is essential to avoid misdiagnosis and ensure timely treatment.

KEYWORDS

Zoledronic acid, orbital inflammation, preseptal cellulitis, bisphosphonate adverse effects

LEARNING POINTS

- Bisphosphonate ocular toxicity may mimic common eye conditions but often resists standard treatment; clinicians should consider drug-induced causes in refractory cases.
- Temporal association with bisphosphonate therapy is crucial for diagnosis; rapid onset after infusion can indicate drug-induced orbital inflammation.
- Early corticosteroid therapy typically leads to full recovery, highlighting the importance of prompt recognition and management.

INTRODUCTION

Zoledronic acid is a nitrogen-containing bisphosphonate commonly used for managing osteoporosis, hypercalcemia of malignancy, Paget's disease, and metastatic bone disease[1,2]. Its efficacy and the convenience of an annual intravenous dosing regimen contribute to its widespread

EFIM
European Federation of Internal Medicine

Publisher
smc media srl

use. Ocular adverse effects associated with zoledronic acid are uncommon but clinically significant. The incidence of acute anterior uveitis following intravenous zoledronate infusion has been reported to be approximately 0.8% in randomized controlled trials[3,4]. More severe complications, including scleritis and orbital inflammation, are less frequently reported but can be vision-threatening and may lead to permanent complications if not promptly recognized and treated[3,5]. These manifestations are typically responsive to corticosteroid therapy and resolve completely if recognized early; however, delayed diagnosis may result in vision-threatening sequelae[4,6]. This case report underscores the importance of maintaining a high index of suspicion for drug-induced ocular inflammation in patients presenting with periocular symptoms following bisphosphonate administration.

CASE DESCRIPTION

A 52-year-old woman presented with a five-day history of progressively worsening right eye pain and swelling, associated with increased tearing. She had no history of trauma or infection. Two days prior, an ophthalmologic evaluation was unremarkable. Her past medical history included thymic tumour resection, recently diagnosed asthma, monoclonal gammopathy of undetermined significance, decreased bone density, and depression. Her medications included aripiprazole, atenolol, duloxetine, levothyroxine, and zoledronic acid. She had received her first intravenous zoledronic acid infusion one day before symptom onset.

On examination, she had bilateral conjunctival injection (right greater than left) and swelling of the right lateral eyelid. Mild discomfort occurred on eye movement, but there was no proptosis, ophthalmoplegia, diplopia, vision loss, or chemosis. Neck palpation was normal, with no goitre or nodules. She was afebrile. Laboratory tests revealed a mildly elevated erythrocyte sedimentation rate of 33 mm/hour, while the complete blood count, white blood cell count, serum creatinine, blood glucose, liver function tests, C-reactive protein, and lactate were normal. Blood cultures were negative.

Computed tomography (CT) scan *(Fig. 1)* and magnetic resonance imaging (MRI) *(Fig. 2)* of the orbits demonstrated bilateral preseptal and postseptal inflammatory changes, more pronounced on the right side, without evidence of abscess formation. Both globes were intact and symmetric, and the left orbit appeared normal. There were no signs of orbital fractures, foreign bodies, or trauma-related changes. Importantly, no proptosis, optic nerve compression, or extraocular muscle involvement was observed, helping to distinguish drug-induced orbital inflammation from infectious or infiltrative aetiologies. Imaging findings were atypical for bacterial orbital cellulitis, which commonly presents with abscess formation, fat stranding, or subperiosteal collections. These studies helped rule out orbital tumours, thyroid eye disease, and idiopathic orbital inflammation, supporting a drug-related aetiology in the context of recent zoledronic acid infusion. The patient was treated with intravenous methylprednisolone 250 mg every 6 hours for 24 hours, followed by oral prednisone 60 mg daily, tapered gradually. Amoxicillin-clavulanate 875 mg twice daily was administered for seven days. Marked improvement was observed within 48 hours, and symptoms resolved completely by one week.

Ocular condition	Common symptoms	Indicators of bisphosphonate-Induced aetiology	Recommended management	Bisphosphonate therapy considerations
Conjunctivitis	Redness, gritty sensation, tearing; vision usually normal	Symptoms 2–3 days post-infusion; poor antibiotic response	Usually mild; topical steroids may help; resolves after stopping drug	Therapy may continue; often requires discontinuation if persistent[6,7]
Episcleritis	Mild irritation, photophobia, localized redness	Similar timing; limited antibiotic response	Corticosteroids beneficial; ophthalmology referral depending on severity	Stop or switch therapy if severe; rechallenge possible with prophylaxis
Anterior Uveitis (Iritis)	Eye pain, photophobia, blurred vision, ciliary injection, possible hypopyon	Hours–days post-infusion; no antibiotic response	Urgent ophthalmology referral; corticosteroids essential; resolves after stopping drug	Bisphosphonate must be stopped; rechallenge contraindicated
Keratitis	Eye pain, redness, decreased vision, possible corneal ulcers	Temporal relation to drug; no antibiotic response	Urgent referral; corticosteroids needed; resolves after stopping drug	Therapy cessation advised[9,10]
Scleritis	Severe pain, tenderness, scleral redness	Onset soon after infusion; corticosteroid responsive; high recurrence risk	Immediate ophthalmology referral; corticosteroids required	Bisphosphonate must be stopped; rechallenge not recommended

Table 1. Summary of ocular conditions associated with bisphosphonate use, common symptoms, indicators of drug-related aetiology, and management considerations.

Differential diagnosis

Orbital cellulitis was considered but deemed unlikely given the patient's afebrile status, normal inflammatory markers, absence of proptosis, ophthalmoplegia, or visual impairment, and imaging demonstrating no abscess formation[5,6].

Preseptal cellulitis was a potential consideration due to mild preseptal thickening on imaging; however, the bilateral involvement and absence of systemic symptoms made this diagnosis less probable[2,4].

Drug-induced orbital inflammation was strongly suspected, given the temporal relationship to the first intravenous zoledronic acid infusion, rapid onset of symptoms within 24 hours, and imaging findings of bilateral pre- and postseptal inflammation without abscess formation[5].

Other causes such as idiopathic orbital inflammatory syndrome, thyroid eye disease, and allergic reactions were excluded based on clinical presentation, normal thyroid function tests, unremarkable neck examination, and imaging features[3,4].

DISCUSSION

Zoledronic acid is a potent nitrogen-containing bisphosphonate commonly used to manage osteoporosis and metastatic bone disease due to its high affinity for bone mineral and long skeletal half-life[1–3]. While generally well tolerated, it has been associated with a spectrum of adverse effects, including rare orbital and ocular inflammatory reactions[4,5].

The precise mechanism of bisphosphonate-induced orbital inflammation is not fully elucidated, but an immune-mediated reaction has been proposed. Activation of γδ T cells and subsequent release of pro-inflammatory cytokines, particularly interleukin-1 and interleukin-6, are thought to drive inflammation in periocular tissues[6,7]. This immune response resembles the acute-phase reaction commonly observed following intravenous bisphosphonate administration[8].

In the present case, symptoms developed within 24 hours of zoledronic acid infusion, consistent with prior reports indicating onset within 24 to 48 hours[7,8]. The clinical presentation mimicked infectious orbital cellulitis; however, the absence of fever, normal systemic inflammatory markers, bilateral involvement, and rapid response to corticosteroid therapy strongly supported a drug-induced aetiology rather than infection[6,7].

Differential diagnosis for acute orbital inflammation is broad and includes both infectious and non-infectious causes. Infectious aetiologies encompass bacterial orbital cellulitis, tuberculosis, syphilis, endophthalmitis, herpes simplex virus, varicella-zoster virus, *Bartonella henselae*, and toxoplasmosis. Non-infectious conditions include granulomatosis with polyangiitis, thyroid orbitopathy, sarcoidosis, Behçet's disease, idiopathic orbital inflammation, orbital metastasis, and primary ocular malignancy[4,9]. Careful clinical evaluation supported by orbital imaging, such as CT scan or MRI, is crucial to exclude alternative diagnoses[5,6].

Epidemiologically, most bisphosphonate-associated orbital inflammation cases are unilateral, approximately 77%, and occur predominantly in women, reflecting the higher use of bisphosphonates for postmenopausal osteoporosis[3,4,6]. Intravenous administration is associated with earlier and more frequent onset, typically within hours to 14 days, compared with oral formulations, where onset ranges from 15 to 45 days[2,6,7]. Underlying inflammatory or autoimmune conditions, including seronegative rheumatoid arthritis, Sjögren's syndrome, ankylosing spondylitis, and pulmonary sarcoidosis, may increase susceptibility[7,10].

A literature review identified 44 published cases of zoledronic acid-related ocular inflammation from 2010 to 2023. The average patient age was 64.5 years (range 45–87), with 79% female. Orbital inflammation occurred in 45.5 %, anterior uveitis in 38.6 %, and both manifestations in 15.9 %[10]. Anterior uveitis and bilateral involvement were reported in approximately one-third of cases, which helps differentiate bisphosphonate-related inflammation from idiopathic orbital inflammatory syndrome, typically unilateral and associated with ocular motility restriction or optic nerve compression[5,7].

Management relies on prompt recognition and initiation of corticosteroids, which results in rapid resolution in nearly all reported cases[8,9]. Oral corticosteroids are generally effective, though intravenous administration may be required in severe presentations. Rechallenge with zoledronic acid can be considered under corticosteroid prophylaxis but must be individualized, weighing potential benefits and risks[9,10]. Ocular conditions associated with bisphosphonate therapy, their typical presentation, and recommended management strategies are summarized in *Table 1*, highlighting the clinical patterns that may help distinguish drug-induced inflammation from infectious or idiopathic aetiologies.

Given the risk of corticosteroid-induced bone loss, guidelines recommend bone-protective measures, including minimizing steroid exposure, promoting weight-bearing activity, optimizing calcium and vitamin D intake, and addressing modifiable risk factors such as smoking or alcohol use[10].

REFERENCES

1. Lewiecki DEM. Safety of long-term bisphosphonate therapy for the management of osteoporosis. *Drugs* 2011;**71**:791–814. doi: 10.2165/11585470-000000000-00000
2. Fraunfelder FW, Fraunfelder FT. Adverse ocular drug reactions recently identified by the National Registry of Drug-Induced Ocular Side Effects. *Ophthalmology* 2004;**111**:1275–1279. doi: 10.1016/j.ophtha.2003.12.052
3. Sharma NS, Ooi J-L, Masselos K, Hooper MJ, Francis IC. Zoledronic acid infusion and orbital inflammatory disease. *N Engl J Med* 2008;**359**:1410–1411. doi: 10.1056/NEJMc0803366
4. Peterson JD, Bedrossian EH. Bisphosphonate-associated orbital inflammation—a case report and review. *Orbit* 2012;**31**:119–123. doi: 10.3109/01676830.2011.648818
5. Ryan PJ, Sampath R. Idiopathic orbital inflammation following intravenous pamidronate. *Rheumatology* 2001;**40**:956–7. doi: 10.1093/rheumatology/40.8.956
6. Erickson BP, Lee WW. Orbital Cellulitis and Subperiosteal Abscess: A 5-year Outcomes Analysis. *Orbit* 2015;**34**:115-120. doi: 10.3109/01676830.2014.950286
7. Benderson D, Karakunnel J, Kathuria S, Badros A. Scleritis complicating zoledronic acid infusion. *Clin Lymphoma Myeloma* 2006;**7**:145–147. doi: 10.3816/CLM.2006.n.053
8. Faryal, Rehman, Amjad Hayat. Keeping an eye on bisphosphonate therapy in myeloma: a case report of ocular inflammation post-zoledronic acid infusion. *Case Rep Hematol* 2021;**2021**:6647277. doi: 10.1155/2021/664727
9. Banal F, Briot K, Ayoub G, Dougados M, Roux C. Unilateral anterior uveitis complicating zoledronic acid therapy in prostate cancer. *J Rheumatol* 2008;**35**:2458–2459. doi: 10.3899/jrheum.080273
10. Durnian JM, Olujohungbe A, Kyle G. Bilateral acute uveitis and conjunctivitis after zoledronic acid therapy. Eye (Lond). 2005;**19**:221–222. doi: 10.1038/sj.eye.6701461