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Severe unilateral hypopyon uveitis secondary to zoledronate infusion masquerading as endophthalmitis

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Introduction

Bisphosphonates are predominantly used to treat osteoporosis and metastatic bone disease. Ocular inflammation, although rare, is a known adverse effect. The reported incidence of uveitis after zoledronate varies between 0.07%-0.8%.[1-3] We present a unique case of severe hypopyon-associated anterior and intermediate uveitis in an 81-year-old female 48 hours after her first intravenous (IV) zoledronate dose for osteoporosis, with clinical presentation initially concerning for endogenous endophthalmitis.

Case Report

An 81-year-old female with hypertension, chronic kidney disease, and osteoporosis presented to the emergency room with 2 days of worsening floaters and vision loss in the left eye. Past ocular history was notable for a remote history of cataract surgery in both eyes and tube shunt surgery several years earlier in the right eye. She was taking dorzolamide 2% twice daily (BID) and latanoprost 0.005% at bedtime in both eyes.

On presentation, visual acuity (VA) was 20/30 in the right eye and hand motion (HM) in the left eye. The pupil in the right eye was briskly reactive; the left eye was pharmacologically dilated with no afferent pupillary defect by reverse. Intraocular pressures were 9 in the right eye and 23 in the left eye. Slit-lamp and dilated fundus examination (DFE) in the right eye was unremarkable except for pseudophakia and anterior chamber (AC) tube shunt. Slit lamp examination in the left eye showed 3+ conjunctival injection, corneal edema, 4+ AC cells (>50 cells per standardization of uveitis nomenclature criteria) with a 1-mm layered hypopyon, and 3+ anterior vitreous cells. DFE in the left eye revealed 3+ vitreous haze obscuring the posterior pole (Figure 1A). B-scan ultrasonography demonstrated moderate vitreous hyperechoic opacities and sclerouveal thickening (Figure 1B).

The patient denied recent illnesses, hospitalizations, or travel. She reported receiving her first IV zoledronate infusion for osteoporosis 2 days before symptom onset. With this presentation, possible endogenous endophthalmitis was considered, though zoledronic acid-associated uveitis was also in the differential diagnosis. A vitreous tap and intravitreal administration of vancomycin and ceftazidime in the left eye were performed. She was started on topical prednisolone 1% every hour while awake and atropine 1% BID in the left eye. She was admitted for an inpatient endogenous endophthalmitis work-up. Complete blood count with differential, comprehensive metabolic panel, QuantiFERON gold, rapid plasma reagin, *Treponema pallidum* screen, serum toxoplasmosis immunoglobulin G and immunoglobulin M titers, blood and urine cultures, and serum angiotensin converting enzyme levels were all unremarkable. A chest x-ray was unrevealing, and no valvular vegetations were identified on echocardiography. Vitreous tap showed a few white blood cells but no organisms on Gram stain, and there was no microbial growth on culture. Polymerase chain reaction (PCR) testing for herpes simplex virus, varicella zoster virus, cytomegalovirus, and toxoplasmosis DNA was negative. Given the unrevealing work-up, 3 days after initial presentation, oral prednisone 40 mg/day was started, and topical prednisolone 1% hourly and atropine 1% BID in the left eye were continued.

Two weeks later, VA in the left eye improved to 20/400 with 1+ AC cell and resolved hypopyon. There was 2+ vitritis with a hazy posterior pole and no retinal lesions (Figure 1C). One week later, VA in the left eye improved to 20/100 with resolution of AC cell, trace vitreous cell, and an improved posterior view (Figure 1D). Given continued improvement, oral prednisone was tapered by 10 mg/week to cessation, and topical prednisolone 1% was tapered from QID by 1 drop/week to cessation. At 2-month follow-up, there was no recurrent AC or vitreous inflammation; however, cystoid macular edema developed with VA of 20/200 in the left eye (Figure 1E). Topical ketorolac 0.5% QID and prednisolone 1% 6x/day in the left eye were started. At the most recent follow-up, 3 months after initial presentation, cystoid macular edema had decreased (Figure 1F) with improvement in VA in the left eye to 20/70. Topical ketorolac and prednisolone were continued in the left eye. Avoidance of future bisphosphonate use was recommended.

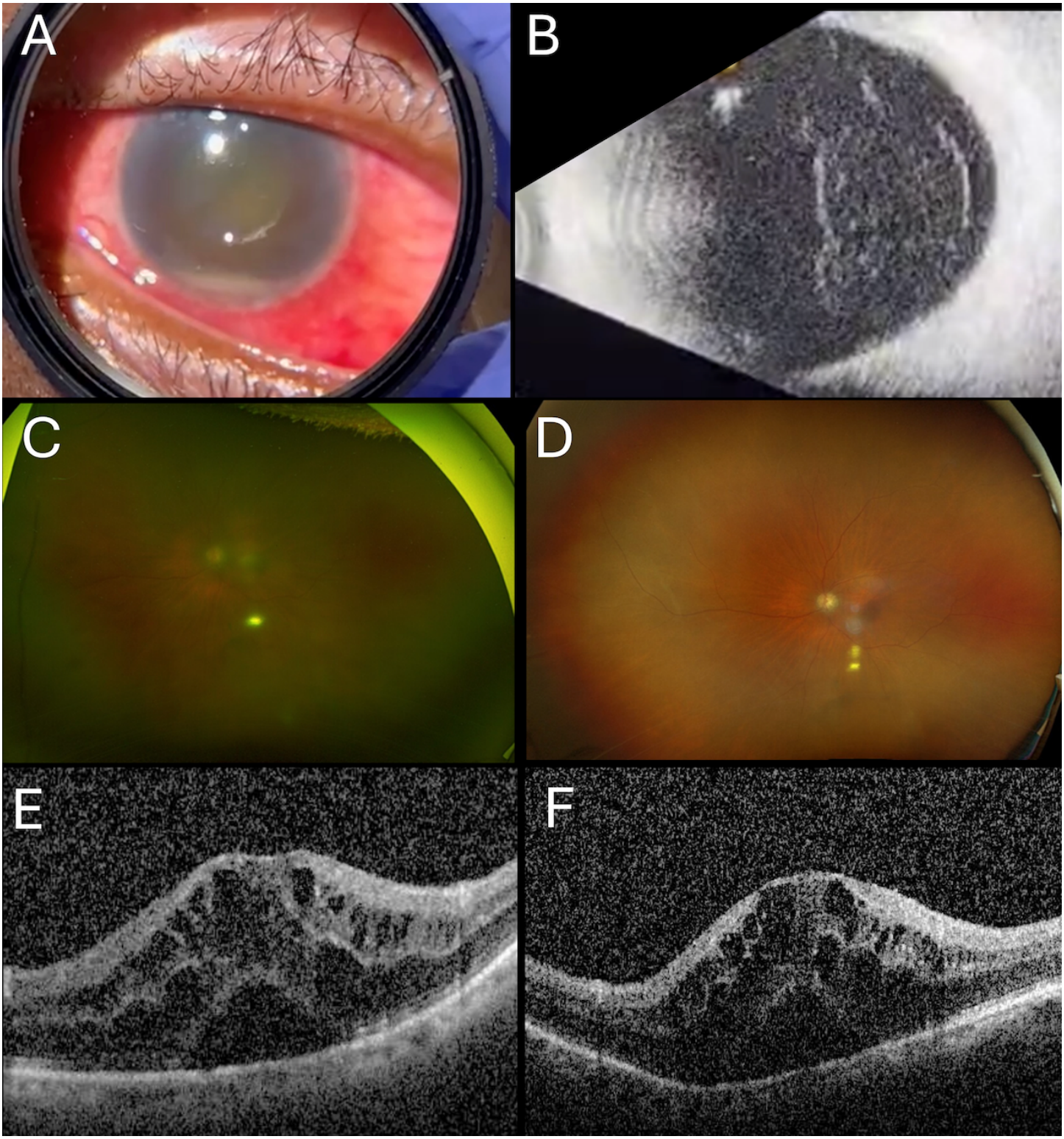

Figure 1. A. Magnified anterior view of the left eye at presentation was notable for diffuse conjunctival injection, diffuse corneal edema, and a layering hypopyon, B. B-scan ultrasonography of the left eye on presentation demonstrated moderate vitreous opacities, C. Ultra-widefield fundus photo of the left eye at 2-week follow-up demonstrated an improved, albeit still hazy, view secondary to vitritis and no apparent retinal lesions, D. Fundus photo of the left eye at 3 weeks revealed significantly improved vitritis and no retinal lesions, E. Optical coherence tomography (OCT) at the 2 month follow-up revealed new cystoid macular edema

and subretinal fluid. There was no recurrence of anterior chamber or vitreous inflammation, F. At the 3-month follow-up visit, OCT showed improved cystoid macular edema while on topical prednisolone 1% and ketorolac 0.5% eye drops. Subretinal fluid remained.

Discussion

Ocular inflammatory side effects following bisphosphonate use are rare but previously reported. In a large clinical trial, the incidence of acute anterior uveitis was 0.8% after the first zoledronate intravenous infusion.[3] A lower rate of 0.07% was reported for uveitis in a US veterans' cohort within 6 months of bisphosphonate use.[2] Among 44 reported cases of zoledronate-associated anterior uveitis (Table), 32 were unilateral, 11 bilateral, and one unspecified. The average patient age was 64.7 years (standard deviation 8.3), and the median time from bisphosphonate administration to symptom onset was 2 days (range 0 days - 3 years) with 79.5% reporting symptoms within 3 days. Mean initial VA was logMAR 0.45, or ~20/123 Snellen equivalent. Of 28 patients with documented slit lamp examinations, 27 had conjunctival injection, 10 had keratic precipitates, 25 had AC cell, 17 had AC flare, 10 had AC fibrin, and 3 had hypopyon. Fundus examination was reported in 19 patients, of which 17 were unremarkable, one had cystoid macular edema, and one had mild vitreous haze with blurred optic disc margins. Uveitis symptoms and findings typically resolved with topical anti-inflammatory and bisphosphonate cessation; 3 patients were re-challenged with bisphosphonate and did not redevelop uveitis.[4]

In comparison, we present a unique case of unilateral severe hypopyon anterior and intermediate uveitis secondary to zoledronate that was associated with severe vision loss (HM) and initially presented with greatest concern for endogenous endophthalmitis. The severe vitreous inflammation and vision loss on presentation separates our case from the 3 other case reports of zoledronate-associated mixed hypopyon and hyphema anterior uveitis previously reported. The first case was a 68-year-old woman who presented with sclerouveitis 12 hours after the first IV zoledronate for osteoporosis.[5] Presenting VA was 20/50 with 4+ AC cell, 2+ flare, and a hypopyon mixed with hyphema. The patient initially worsened with topical steroids and oral non-steroidal anti-inflammatory drugs alone, then improved with a single dose of 1 g of IV methylprednisone followed by 60 mg of daily oral prednisone. The second case involved an 80-year-old female with anterior uveitis and hypopyon in the right eye 24 hours after the first zoledronate dose.[6] Presenting VA was 20/120, and AC was notable for a 1 mm blood-tinged hypopyon. The patient initially worsened with topical prednisolone acetate 1% every 30 minutes, then symptoms resolved after subconjunctival betamethasone injection. The third patient was a 62-year-old female with hypopyon anterior uveitis in the right eye 24 hours after the first dose of zoledronate.[7] Visual acuity was 20/67 with medium AC cell and flare and 2 mm bloody hypopyon. The patient's symptoms resolved after 3weeks of topical hydrocortisone and dexamethasone. Our patient similarly presented after her first dose of zoledronate, with rapid onset of symptoms. However, our patient presented 4 days after zoledronate infusion and 2 days after symptom onset. The delayed presentation may have contributed to the more severe vitreous inflammation and vision loss compared to other cases in literature. Moreover, our patient had chronic kidney disease, which may reduce clearance of bisphosphonate and lead to greater drug exposure. Like 2 of the reported cases, our patient required escalation of anti-inflammatory treatment beyond topical drops to achieve quiescence.

The pathophysiology underlying bisphosphonate-induced ocular inflammation is not well understood. However, there are several proposed mechanisms. Bisphosphonates increase M1 macrophage polarization, altering the ratio of proinflammatory M1 to anti-inflammatory M2 macrophages.[8] Alternatively, aminobisphosphonates activate gamma delta T-cells and trigger release of proinflammatory IL-6, IL-17, TNF-alpha, and IFN-gamma.[9] Moreover, due to their large molecular size, bisphosphonates contribute to inflammation through immune complex deposition.[10]

Conclusion

We present a unique case of unilateral hypopyon-associated anterior and intermediate uveitis secondary to IV zoledronate, initially concerning for endogenous endophthalmitis, which may have been exacerbated by the delayed presentation and chronic renal disease. Although ocular inflammation is uncommon following bisphosphonate use, ophthalmologists, prescribing physicians, and patients should recognize this potential adverse event and its variable severity. Our case highlights the importance of a thorough history and medication review when evaluating eyes with uveitis and emphasizes the need to rule out infectious etiologies prior to initiating aggressive anti-inflammatory medications. Prompt recognition of bisphosphonate-associated ocular inflammation may facilitate diagnosis, drug cessation, and early treatment to help optimize long-term outcomes.

Table. Demographic and clinical characteristics of intravenous zoledronate-associated anterior uveitis cases previously reported in literature through May 1, 2025.		
Clinical feature	**Category**	**Frequency (Proportion)**
Age in years, mean (standard deviation)		64.7 (8.3)
Time to onset in days, median (interquartile range)		27.3 (2.0-3.0)
Laterality*	Unilateral Right eye Left eye Bilateral	32 (74.4%) 16 (37.2%)[1-13] 13 (30.2%)[9,14-21] 11 (25.6%)[5,9,22-29]
Visual acuity, mean (standard deviation)	logMAR Snellen	0.45 (0.40) 20/123
Slit lamp examination (SLE)	Total number reporting SLE Conjunctival injection Keratic precipitates AC cell AC flare AC fibrin Hypopyon	28[1-7,10,12-19,21-30] 27 (96.4%)[1-7,10,12-16,18,19,21-30] 10 (35.7%)[5,7,14,15,18,22,26-28] 25 (89.3%)[1-4,6,7,10,12-19,21-30] 17 (60.7%)[2,4-6,10,12-16,18,24,26-28] 10 (35.7%)[1,4-6,14,18,19,22,23,26] 3 (10.7%)[6,10,12]
Posterior exam	Total number reporting DFE Normal exam Macular edema Blurred disc	19[3-5,7,13,15-19,21-28] 17 (89.5%)[3-5,7,13,15,16,18,19,21-27] 1 (5.3%)[28] 1 (5.3%)[17]

*One case did not report laterality.

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Statement of Ethics

This case series adheres to patient confidentiality and ethical principles in accordance with the guidelines of the Declaration of Helsinki and relevant local regulations. Consent was obtained from the patient for the publication of this case report.

Conflict of Interest Statement

BTC, SZ, BPH, MC, JSK, TB, FAB, SM, JPD: None.

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