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Acute unilateral anterior uveitis following zoledronic acid infusion: A case report

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Abstract

Bisphosphonates are widely used to treat several clinical conditions. Zoledronic acid is one of this class, commonly used for the treatment and prevention of osteoporosis, hypercalcemia of malignancy, Paget's disease, and multiple myeloma. A variety of ocular side effects associated with bisphosphonates therapy has been reported but are uncommon and readily treatable. Most of these ocular inflammatory conditions are associated with other bisphosphonates such as pamidronate but rarely reported with zoledronic acid. Acute anterior uveitis associated with zoledronic acid is rare. We describe a 75-year-old female who presented with features of acute unilateral non-granulomatous anterior uveitis which developed within 24 h following the first dose of intravenous infusion of zoledronic acid administered to treat post-menopausal osteoporosis. She was treated with topical steroids and made an uneventful recovery in 2 weeks.

Keywords

Zoledronic acid, anterior uveitis, bisphosphonate

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Introduction

Zoledronic acid is a bisphosphonate, commonly used as a treatment for several medical conditions such as post-menopausal osteoporosis, hypercalcemia of malignancy, multiple myeloma, and Paget's disease.[1] Unlike many other bisphosphonates, zoledronic acid is administrated intravenously. This increases the bioavailability, mitigates gastrointestinal side effects, and lowers the frequency of dosing.[2] Although zoledronic acid is generally well tolerated, frequent side effects include transient low-grade fever, fatigue, arthralgia, myalgia, nausea, and increased bone pain.[3] These are similar to those reported with other bisphosphonates and are usually mild and transient.[1] An acute-phase reaction characterized by fever and headache manifesting within 3 days following injection is a common phenomenon (42.4%).[3] Cases of ocular inflammatory conditions following exposure to bisphosphonates have been reported since 1960s.[4] A number of ocular inflammatory side effects such as uveitis, episcleritis, and scleritis have been reported as complications of bisphosphonates therapy especially with pamidronate but only rarely with zoledronic acid.[5] The national osteoporosis foundation has recommended reporting any ocular inflammation associated with bisphosphonates therapy to healthcare providers as soon as possible.[6] Herein, we describe a 75-year-old female presented with features of acute unilateral non-granulomatous anterior uveitis following intravenous infusion of zoledronic acid given to treat osteoporosis.

Case presentation

A 75-year-old Sri Lankan female with a background of hypertension and ischemic heart disease presented with a history of pain, blurring of vision, photophobia, and redness of her left eye of about 6-h duration. She admitted that she received the first dose of zoledronic acid 4 mg in 100 mL normal saline intravenously over a period of 15 min on the previous day. She denied any history of trauma, fever, or headache.

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She was diagnosed with post-menopausal osteoporosis 2 years ago after having a dual-energy X-ray absorptiometry (DEXA) scan when she presented with mechanical lower back pain. She was initiated on oral alendronate 70 mg weekly along with calcium and vitamin D supplements. She had been taking them regularly since then without reporting any side effects. In spite of good adherence to treatment, she failed to be symptom free and had continued to experience intermittent mechanical lower back pain. Subsequently, she underwent a repeat DEXA scan which showed a T-score of −5.1 over her lower lumbar vertebra with no significant improvement compared to the previous T-score. Accordingly, the clinical team decided to switch her to zoledronic acid as a substitution for oral alendronate and she was given 4 mg of zoledronic acid in 100 mL of normal saline as an intravenous infusion over a period of 15 min on the day before admission.

Physical examination revealed a hyperemic conjunctiva on the left eye with best corrected visual acuity of 6/9 and 6/6 on left and right eye, respectively. Intraocular pressure was 14 mmHg in the right eye and 10 mmHg in the left eye. Slit-lamp examination of left eye revealed conjunctival hyperemia, fine few keratic precipitates, cells and flare in the anterior chamber (Figure 1) with normal posterior segment. Her right eye was normal. There was no evidence of proptosis, periorbital edema, ptosis, or ophthalmoplegia. Rest of the general and systemic clinical examinations was unremarkable with a blood pressure of 130/80 mmHg. Her initial investigations showed elevated C-reactive protein (CRP) (84.4 mg/L) and erythrocyte sedimentation rate (ESR) (65 mm at the first hour) with no significant abnormalities detected in rest of the basic investigations. A diagnosis of acute non-granulomatous anterior uveitis of the left eye secondary to zoledronic acid was made and she was started with topical prednisolone. She was also evaluated for any other conditions that may cause acute anterior uveitis. Subsequent investigations (complete blood count, angiotensin-converting enzyme level, X-ray chest, rheumatoid factor, human leukocyte antigen B27 (HLA-B27), perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA), cytoplasmic ANCA (c-ANCA), and serology for infective causes, namely, Epstein–Barr virus, Cytomegalovirus (CMV), human immunodeficiency virus (HIV), Venereal Disease Research Laboratory test (VDRL), and polymerase chain reaction (PCR) for Varicella zoster) did not show any abnormalities.

She responded well clinically to the treatment and achieved complete resolution of symptoms by the end of 2 weeks along with the normalization of CRP to 3.1 mg/L. Thereafter, she had been followed at the ophthalmologic clinic for 6 months, during which she never experienced recurrence of any similar episodes. At the 6-month review, she was asymptomatic and findings on ophthalmological examination showed persistent and complete resolution of ocular signs (Figure 2).

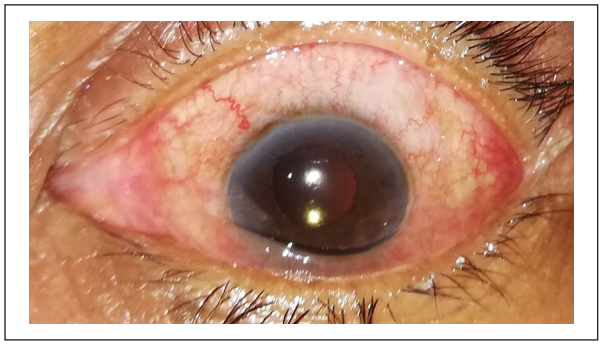

Figure 1. Slit lamp showing (anterior segment) conjunctival hyperemia and anterior chamber haze due to cells and flare (before treatment).

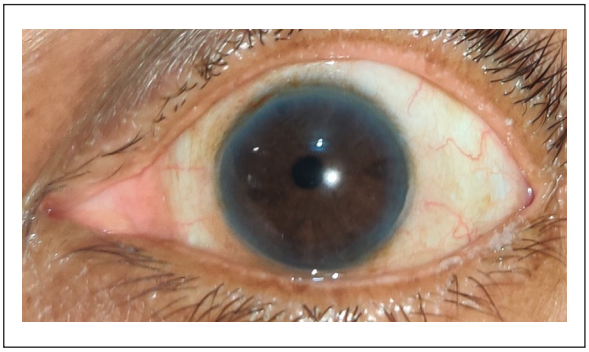

Figure 2. Slit lamp showing complete resolution of ocular signs at review in 6 months.

Discussion

Zoledronic acid belongs to a class of drugs known as bisphosphonates which act primarily via the effective inhibition of osteoclast-mediated bone resorption.[7] Bisphosphonates have been shown to be effective for increasing bone mineral density and decreasing the risk of fractures[4] and used to reduce the incidence of skeletal complications significantly in patients with benign skeletal diseases such as osteoporosis and Paget's disease as well as malignant conditions such as multiple myeloma. In addition, they are also used in hypercalcemia associated with malignancy due to their potent antiresorptive activity.[7]

Zoledronic acid is administered as a single yearly infusion when used in patients with osteoporosis who are either intolerant or demonstrate a lack of response to oral bisphosphonates. The frequently reported adverse events include bone pain, osteonecrosis of the jaw (ONJ), transient flu–like symptoms such as nausea, myalgia, arthralgia, and low-grade fever, emesis, constipation, headache, and fluctuations in serum electrolytes (magnesium, calcium, and phosphorus).[8]

Most of the case reports describe that symptoms related to ocular side effects start within 48 h of the initial infusion and are accompanied by acute-phase systemic symptoms in

nearly half the patients. Presentation can be either unilateral or bilateral with two-third of cases reporting only unilateral involvement.[4,6] There are several ocular side effects including conjunctivitis, scleritis, episcleritis, keratitis, eyelid edema, optic neuritis, periorbital edema, anterior uveitis, macular edema, and ophthalmoplegia which have been reported with different bisphosphonates including zoledronate, alendronate, pamidronate, etidronate, and risedronate.[6,9] Of those, keratitis and scleritis have a greater risk of long term visual loss.[4] Furthermore, serious complication, such as acute retinal pigmented epithelitis, has also been reported following intravenous administration of bisphophonates.[10] Most of the cases of acute anterior uveitis following exposure to bisphosphonates were published in patients who had received alendronate and pamidronate.[11–14] Only a few cases of bilateral and unilateral anterior uveitis after the infusion of zoledronic acid have been reported.[8,15–17]

The exact mechanism of zoledronic acid associated uveitis is unclear, but it appears to be an inflammatory response to zoledronic acid. Nitrogen-containing bisphosphonates are more potent inhibitors of bone resorption than simple bisphosphonates and are known to cause elevated levels of proinflammatory cytokines including tumor necrosis factor (TNF) alpha and interleukin 1 and interleukin 6.[18,19] It was proposed that orbital fibroblasts react more to the cytokines during orbital inflammation as they express more sensitivity to it.[19] Having shared structural homology between bisphosphonates such as pamidronate and zoledronic acid and several T-cell ligands, bisphosphonates activate antigen receptors, thereby causing cytokine release. It indicates the possibility of immune-mediated mechanisms which play a key role in bisphosphonate associated ocular toxicities.[5]

Most of the ocular complications related to bisphosphonates therapy were successfully treated with a topical ocular steroid and only a few required systemic steroids.[6,20] In a review of previous reports, bisphosphonates have been successfully used with or without protection of steroid in five patients who had developed ocular toxicity after the initial exposure. There were no ocular side effects reported with subsequent infusions. Therefore, re-administration of bisphosphonates to patients who developed ocular inflammation after initial therapy should not be considered as an absolute contraindication.[6]

The close temporal relationship between zoledronic acid infusion and onset of classical symptoms of ocular involvement with the absence of other secondary causes confirm the diagnosis of zoledronic acid–induced acute non-granulomatous anterior uveitis in our patient. It is further supported by prompt response to steroids and the absence of any recurrences during follow-up.

Conclusion

Zoledronic acid–induced acute anterior uveitis is a rare complication manifesting usually within 24 h following infusion. Patients being prescribed zoledronic acid should be informed of the possibility of ocular side effects. This case also emphasizes the importance of ocular examination in any patient undertaking bisphosphonate treatment to ensure early diagnosis and prompt treatment.

Author contributions

All three authors were involved in the assessment and management of the patient; collected and analyzed data; and read and approved the final article.

Availability of data

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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Informed consent

Written informed consent was obtained from the patient for the anonymized information to be published in this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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