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CASE REPORT

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Posterior scleritis following a single infusion of zoledronate for osteoporosis: A case report and literature review

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Key Clinical Message

The most frequently reported adverse reaction to zoledronic acid is an acute phase reaction resembling influenza. While rarer adverse events such as osteonecrosis of the jaw and atypical femoral fractures have gained significant recognition, the ocular adverse effects, particularly scleritis, are not yet fully comprehended. Here, we present the case of a 75-year-old female patient with osteoporosis who developed bilateral redness and intense eye pain 48 h after receiving a 5 mg intravenous dose of zoledronic acid. Clinical presentation suggested bilateral conjunctivitis, but treatment with levofloxacin eye drops and acyclovir ophthalmic gel exacerbated the symptoms over 2 days, predominantly affecting the left eye. Ocular ultrasonography revealed thickening of the left eyeball wall with a "T" sign, while an orbital CT scan showed increased thickness of the left sclera. Treatment with methylprednisolone 80 mg intravenous infusion twice daily led to gradual symptom improvement and eventual resolution of inflammation. This report, based on a review of relevant literature, investigates the treatment and outcomes of zoledronic acid-induced scleritis, emphasizing the importance for clinicians to promptly identify and manage this rare and serious ocular adverse reaction.

KEYWORDS

bisphosphonates, drug adverse reactions, scleritis, zoledronic acid

1 | INTRODUCTION

After more than half a century of continuous development, bisphosphonates have emerged as the primary treatment for osteoporosis. Furthermore, they are utilized in conditions like hypercalcemia, Paget's disease, osteogenesis imperfecta, and malignant bone metastases. These drugs exhibit overall favorable safety profiles, with the primary adverse reactions being fever and muscle pain resembling flu-like symptoms. Less frequent adverse effects include renal impairment and hypocalcemia, whereas rare adverse reactions like jaw osteonecrosis and atypical femoral fractures are widely recognized in clinical practice.[1] However, their ocular adverse effects remain inadequately understood. This study reports a severe ocular adverse drug reaction, posterior scleritis, following

intravenous administration of zoledronic acid in a patient with primary osteoporosis and offers a review of pertinent literature to increase physician awareness of potential adverse drug reactions.

2 | CASE HISTORY AND EXAMINATION

The patient, a 75-year-old female, was admitted to our hospital on December 6, 2021, for a history of "chronic generalized bone pain." In 2019, she presented to the hospital after a fall resulted in a left forearm fracture, which was managed with manual reduction and immobilization using a plaster cast. Since then, the patient has inconsistently self-administered calcium carbonate and vitamin D3 without experiencing recurrent fractures. She reported persistent whole-body bone pain and a progressive loss of height, amounting to a 5 cm reduction upon admission. She has had type 2 diabetes mellitus for 9 years and denies any history of gastrointestinal, chronic kidney, or urologic disorders. Her long-term medication regimen includes metformin extended-release tablets (0.5 g twice daily) and 9 units of insulin glargine administered subcutaneously before bedtime for glycemic control, which has been effective. She does not smoke or drink alcohol, consumes minimal dairy products, and enjoys outdoor activities.

During the physical examination, the patient was measured to be 150 cm tall, weighing 50 kg, with a BMI of 22 kg/m^2. Chest and spine examinations showed no deformities, and there were no restrictions in spinal or limb movements. There was no tenderness upon chest or pelvis compression, while mild tenderness was noted upon percussion of the lumbar vertebrae. Moreover, tenderness was observed on the spinous processes ranging from the 7th thoracic vertebra to the 4th lumbar vertebra. Neurological assessment did not reveal any abnormalities.

Auxiliary examination: (1) 25-hydroxyvitamin D3 level was 23 ng/mL (reference range: 30–70 ng/mL). (2) HbA1c level was 6.9% (reference range: 4.2%–5.9%). (3) Fasting blood glucose was 6.39 mmol/L (reference range: 3.90–6.10 mmol/L). (4) Abdominal ultrasound indicated fatty liver, hepatic cysts, and left renal cysts. (5) Ophthalmological examinations showed bilateral cataracts, suspected incipient cataracts, bilateral vitreous opacities on ocular ultrasound, mild venous tortuosity in the bilateral fundus, suspected hemorrhage spot in the left eye, and no significant edema in macular optical coherence tomography (OCT).

The patient's medical history revealed a previous forearm fracture. DXA scans showed T-scores of ≤ -2.5 in the lumbar spine and proximal femur, indicating severe osteoporosis. Additional tests, including blood biochemistry and bone metabolism markers, were conducted to exclude secondary osteoporosis and confirm primary osteoporosis. The patient was educated on standard lifestyle practices for osteoporosis management and prescribed calcium supplements and vitamin D3. Without contraindications for zoledronic acid, the patient received their first intravenous dose of 5 mg on December 10th for osteoporosis treatment. The patient developed typical flu-like symptoms later that afternoon. On December 12th, the patient presented with severe swelling of the eyelids, significant redness in the conjunctiva, increased discharge, and a hypersensitive pupillary light reflex.

3 | METHODS

Following an ophthalmological consultation, a preliminary diagnosis of bilateral conjunctivitis was made. Consequently, a treatment regimen of levofloxacin eye drops and acyclovir ophthalmic gel was prescribed. However, after 2 days of treatment, there was no significant improvement in symptoms.

On December 14th, worsening redness and swelling around the eyelids and eyes resulted in difficulty in opening the eyes, especially the left one, accompanied by pain radiating towards the head and occasional tearing. Despite these symptoms, the body temperature remained within normal limits. Upon a subsequent consultation with the ophthalmology department, findings revealed severe conjunctival congestion, moderate conjunctival injection, and tenderness in the left eye, as well as mild corneal stroma edema, with no deposits beneath the cornea. Pupillary examination showed normal, equal, and round pupils with a proper response to light. Further specialized ophthalmic assessment disclosed visual acuity of 0.3 unaided corrected in the right eye and 0.2 unaided corrected in the left eye, bilateral vitreous opacity on ocular ultrasound, and normal intraocular pressure. The revised diagnosis from the ophthalmology team in the second consultation was scleritis, ruling out autoimmune disorders and attributing it to zoledronic acid. The treatment plan included tobramycin eye drops, tobramycin eye ointment, and pranoprofen eye drops for topical use, along with intravenous methylprednisolone at doses of 40 and 80 mg on consecutive days.

On December 16th, there was a notable improvement in the right eye swelling, with a slight reduction in swelling around the left eye. Tenderness in the orbital and lash areas of the left eye decreased, however, there was an exacerbation of pain and no improvement in corneal edema in

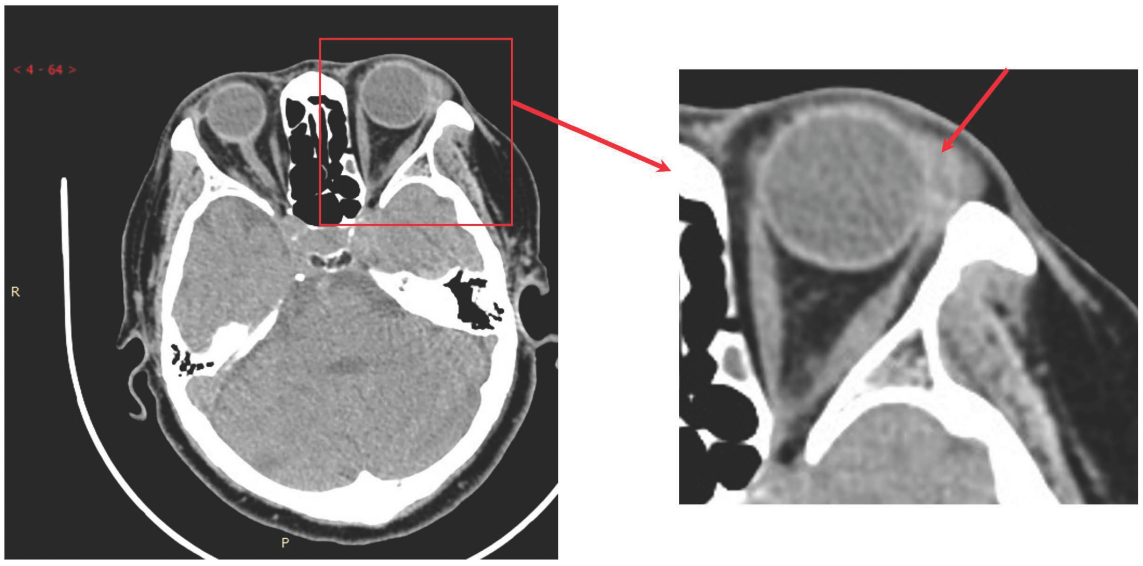

FIGURE 1 The CT scan of the left eye revealed scleral thickening (indicated by the arrow).

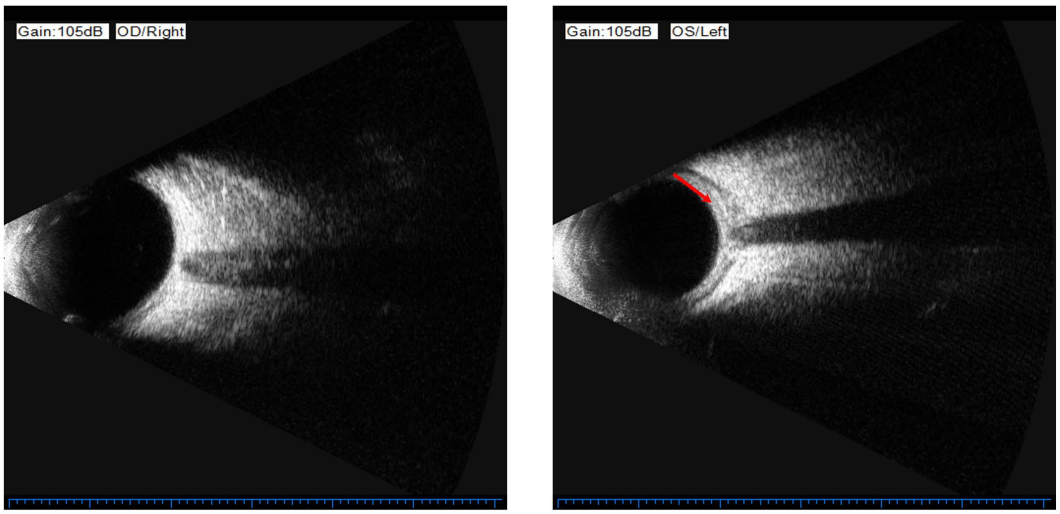

FIGURE 2 The ocular ultrasound revealed normal thickness of the right eye globe wall, while the left eye globe wall appeared thickened with the presence of "T" sign.

the left eye. A CT scan of the orbit revealed thickening of the sclera in the left eye (Figure 1). Subsequent ultrasound examination of the eye showed thickening of the left eye globe wall with the presence of "T" sign (Figure 2), and an OCT examination follow-up indicated mild choroidal wave changes (Figure 3). The progression was suspected to be posterior scleritis, prompting an immediate increase in the dosage of methylprednisolone to 80 mg twice daily via intravenous drip for 3 days, resulting in a significant improvement in symptoms. On December 19th, the dosage of methylprednisolone was reduced to 40 mg twice daily via intravenous drip for 3 days before transitioning to oral prednisone 30 mg twice daily.

4 | OUTCOME AND FOLLOW-UP

Following discharge, the patient attended regular ophthalmology follow-up appointments where the prednisone dosage was gradually decreased. During this period, the patient independently discontinued the medication twice, resulting in ocular discomfort. Upon resuming the

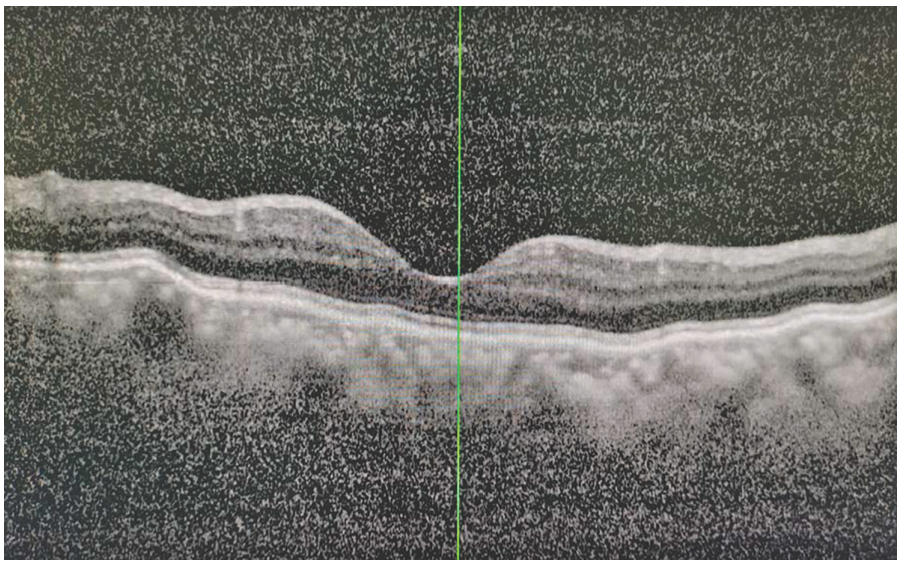

FIGURE 3 OCT examination revealed choroidal folds in the left eye.

medication, the symptoms improved, leading to complete recovery.

5 | DISCUSSION

Bisphosphonates are inorganic derivatives of pyrophosphate, composed of a central carbon atom bonded to two phosphonate groups and two substituent side chains (R side chains). The R side chain of zoledronic acid contains a bisphosphonate ring with two nitrogen atoms, which inhibits farnesyl pyrophosphate synthase in the mevalonate pathway, leading to a significantly higher inhibition of bone resorption mediated by osteoclasts compared to similar drugs.[2] However, due to the inhibition of this enzyme, upstream substances such as isopentenyl diphosphate and dimethylallyl diphosphate accumulate, leading to the activation of γδT cells.[3,4] Additionally, studies have shown that zoledronic acid promotes M1 macrophage polarization mediated by TLR-4.[5] These mechanisms contribute to the most common adverse reaction of intravenous zoledronic acid being flu-like acute phase reactions.[1,3]

In comparison, severe ocular adverse reactions caused by bisphosphonates include periorbital inflammation, uveitis, and scleritis, with a low incidence rate that has not attracted widespread attention among clinicians, leading to delays in treatment. Foreign literature estimates the incidence rates of periorbital inflammation and uveitis to be between 0.046% and 1.1%,[6,7] with scleritis having a significantly lower incidence compared to uveitis.[8,9] Only three cases of zoledronic acid-related anterior uveitis and one case of periorbital inflammation have been reported domestically, with no literature reporting scleritis. The exact pathogenesis of these adverse reactions, especially scleritis, remains unclear; some studies suggest that the drug may be secreted by the lacrimal gland into tears, causing transient irritation to the mucosa, leading to the release of intraocular cytokines and other acute-phase proteins, or activation of γδT cells within the eye socket.[10]

The patient in this case was diagnosed with primary osteoporosis, with a clear history of zoledronic acid use. Within 48 h of medication administration, the patient presented with bilateral eye redness and severe eye pain, exacerbated at night and radiating to the head. These are typical symptoms of scleritis, with involvement of the cornea and choroid. Imaging studies revealed thickening of the sclera on eye CT and a "T" sign, indicative of scleral inflammation with fluid accumulation below the Tenon's capsule and around the optic nerve. These findings serve as reliable evidence of scleritis. There was no history of eye trauma, surgery, infection, or autoimmune disease, as confirmed by supplementary tests. Treatment with corticosteroids effectively controlled the inflammation, leading to resolution within a few weeks, in line with the characteristics of medication-induced scleritis.

Currently, it is believed that antiviral or antibacterial drug therapy has no significant effect on ocular inflammation caused by zoledronic acid. In most cases of ocular inflammation, timely administration of systemic or topical corticosteroids is required to expedite recovery; however, there is no standardized dosing regimen. Faryal et al. reported a case where bisphosphonate therapy was used to treat severe ocular inflammation caused by multiple myeloma, with the patient showing a significant reduction in eye swelling and pain 3 days after intravenous administration of methylprednisolone 500 mg once daily.[10] Upon discharge, the patient was prescribed oral prednisolone 60 mg, gradually tapering every 3 days until symptoms subsided. Additionally, studies have found that judicious use of topical eye drops can help prevent posterior synechiae, alleviate ciliary muscle paralysis and spasms, decrease

exudation, and reduce intraocular pressure.[11] Anvitha et al. reported a case of an elderly female patient who experienced headaches, bilateral redness, and eye pain after the first use of zoledronic acid for osteoporosis.[12] It is noteworthy that the patient had a history of vitamin D deficiency several months prior, and low levels of vitamin D are associated with an increased incidence of anterior uveitis due to proinflammatory responses.[12] Furthermore, some evidence suggests that patients with lower vitamin D levels have a higher incidence of acute ocular inflammatory reactions, emphasizing that optimizing vitamin D levels before treatment may help prevent such adverse reactions.[13] Consistent with previous literature, the patient in this case had low levels of 25-hydroxyvitamin D, although further research is needed to investigate the correlation between vitamin D levels and ocular inflammatory reactions caused by zoledronic acid.

In summary, considering scleritis as one of the most severe ocular side effects of zoledronic acid, capable of leading to severe and permanent visual impairment, and in most studies, patients who undergo re-administration of the same or other bisphosphonate drugs often experience a recurrence of ocular inflammation. In this case, an elderly woman with osteoporosis did not receive further treatment with such medications. However, Benderson et al. reported a case of an elderly male patient with multiple myeloma who developed scleritis after using zoledronic acid, and subsequent ocular ultrasound confirmed the regression of scleral thickening after restarting with the less potent pamidronate salt after 1 month.[14] Before medication administration, the patient received 100 mg of methylprednisolone via intravenous injection and experienced only mild conjunctivitis 3 days after infusion. Following this, monthly pamidronate therapy was continued, with oral corticosteroids taken before each infusion, and no further ocular discomfort was reported.[14] Taking into account the benign outcome of timely diagnosis and treatment of zoledronic acid-related scleritis and the apparent decrease in inflammatory response upon re-administration of such drugs, especially in cases of malignant bone metastases, hypercalcemia, and similar special circumstances, it may not be an absolute contraindication for patients with zoledronic acid-related ocular adverse effects, particularly scleritis, to undergo bisphosphonate therapy again. Further accumulation of clinical evidence is essential, and a careful assessment of the risks and benefits for each individual patient is crucial before making a decision.

AUTHOR CONTRIBUTIONS

Dingling Ma: Conceptualization; writing – original draft. **Can Xiao:** Data curation; resources. **Deshui Zhao:** Data curation; resources. **Guohua Li:** Supervision. **Wei Cheng:** Validation; visualization. **Xin Deng:** Validation; visualization. **Dan He:** Funding acquisition; writing – review and editing. **Kai Liu:** Supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

All the data used and analyzed during this study are available from the corresponding author upon reasonable request.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study received approval from the Ethics Committee of Xiangtan Central Hospital (approval number: 2021–12-011).

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