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EPISCLERITIS AND UVEITIS AFTER EXPOSURE TO BISPHOSPHONATES: A CASE STUDY

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ABSTRACT – *Objective:* Available in both oral and intravenous formulations, bisphosphonates are the most frequently prescribed medications for the treatment of osteoporosis. Their side effect profile is well-established, with gastrointestinal involvement being the most common reason for bisphosphonate cessation by patients. Though ocular side effects can occur, episodes of ocular inflammation are rarely reported. However, the current case describes a patient who experienced two episodes of ocular inflammation after separate exposures to bisphosphonates.

Case Presentation: A case of a 64-year-old female with osteoporosis who experienced episcleritis and uveitis after receiving oral and intravenous bisphosphonates is reported. Her initial occurrence of episcleritis was originally thought to be related to viral exposure. However, she then developed uveitis two days after receiving intravenous zoledronate.

Conclusions: This case, therefore, highlights the importance of discussions with patients around less common side effects of oral and intravenous bisphosphonates to allow for earlier identification and treatment of episodes of ocular inflammation.

KEYWORDS: Zoledronate, Bisphosphonate, Uveitis, Episcleritis.

LIST OF ABBREVIATIONS: IV (intravenous), Herpes simplex virus (HSV), Thyroid-stimulating hormone (TSH).

INTRODUCTION

Bisphosphonates are the most frequently used medications for the treatment of osteoporosis[1,2]. They are available in oral and intravenous (IV) formulations. There are two main types of bisphosphonates: non-nitrogen-containing and aminobisphosphonates[3]. The former group includes etidronate, clodronate, and tiludronate, which are rarely used today. Aminobisphosphonates include alendronate, risedronate, ibandronate, pamidronate, and zoledronate. Bisphosphonates bind to hydroxyapatite crystals in bone and are taken up by osteoclasts, resulting in reduced resorption of bone[4]. Their side effect profile has been extensively investigated, with gastrointestinal involvement being the most common reason for bisphosphonate cessation by patients[5]. Though ocular side effects can occur, episodes of ocular inflammation are rarely reported.

The current case describes a 64-year-old female patient with osteoporosis who experienced episcleritis and uveitis after exposure to oral and IV bisphosphonates. Her initial occurrence of episcleritis was originally thought to be related to viral exposure. However, she then developed uveitis two days after receiving intravenous zoledronate. Ocular side effect reversibility has been reported without sequelae within the first month when swift intervention is provided[6]. This case, therefore, highlights the importance of discussions with patients around less common side effects of oral and intravenous bisphosphonates to allow for earlier identification and treatment of episodes of ocular inflammation.

CASE PRESENTATION

A 64-year-old female presented to the clinic with low bone density in the osteoporotic range. She began menstruating at age 11 and went into menopause in her early 50s. Her medical history included osteoporosis, episcleritis, herpes simplex virus (HSV), osteoarthritis, and leukopenia. She also had periods of intermittently abnormal thyroid-stimulating hormone (TSH), with episodes of high and low levels without a clear diagnosis. She experienced a right malleolar fracture in 2024 when she missed one step while moving boxes. She denied kyphotic changes in her posture or historical height loss. There was no parental history of a hip fracture. She quit smoking in her 30s. Her alcohol intake was once per month on average. She consumed one cup of coffee and one herbal or green tea daily. She had no prescribed medications. She supplemented with 3,000 units daily of Vitamin D, 500 mg of calcium, magnesium, and vitamin C. For exercise, she engaged in strength training twice a week, aquasize, walking, and e-biking. Regarding corticosteroid exposure, she had received intra-articular and bursal injections, as well as inhaled corticosteroids. She started alendronate on November 7, 2024. She experienced a severe unilateral headache after starting the medication. She also had an episode of eye pain starting on November 15, 2024. This was determined to be episcleritis (Figure 1). She stopped alendronate after 5 doses due to continued intolerance and concern that her other eye was starting to experience pain. At the time, it had been suggested that her episcleritis was likely due to a viral infection such as HSV. Her eye symptoms improved over the course of 6 weeks, resolving completely after stopping the alendronate.

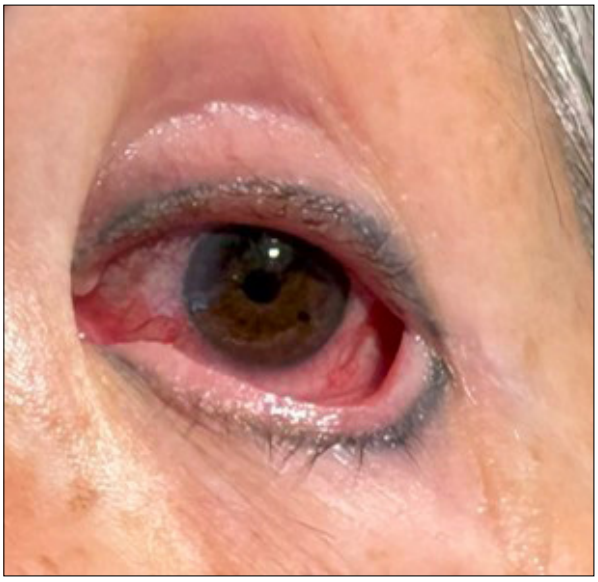

Figure 1. Evidence of left eye episcleritis in November 2024 after exposure to alendronate.

Her investigations indicated normal serum protein electrophoresis, albumin, estimated glomerular filtration rate, creatinine, hemoglobin A1c, TSH, alkaline phosphatase, and phosphate. Her calcium was 2.40 mmol/L, PTH 61 ng/L, and vitamin D 213 nmol/L. She temporarily stopped her vitamin D supplementation due to elevated levels. Her bone mineral density test from October 2024 indicated T-scores of -2.9 at the spine, -1.9 at the femoral neck, and -1.3 at the total hip. There had been a 7.3% loss in her spine density and a 6.5% loss in her total hip density since her last bone mineral density test. Spinal imaging indicated degenerative changes with no compression fractures.

As she was unable to tolerate alendronate, she instead received IV zoledronate. Within 24 hours of receiving the IV zoledronate, she reported flu-like symptoms, including myalgia and arthralgia. She did not get any headache symptoms, unlike her experience with alendronate. Two days after her infusion, she began to feel eye pain similar to her prior episcleritis symptoms. She was assessed by optometry and was diagnosed with uveitis. Her flu-like symptoms resolved within two days. Her eye symptoms resolved after one week with the use of corticosteroid drops.

DISCUSSION

Aminobisphosphonates are the most frequently prescribed medication for osteoporosis treatment. Their side effect profile has been extensively reported, with gastrointestinal involvement being the most common reason for bisphosphonate cessation by patients[5]. Though ocular side effects can occur, episodes of ocular inflammation are rarely reported. The incidence of ocular side effects after bisphosphonate exposure has been noted to be 0.046% to 1%[3,6-8]. Regarding acute anterior uveitis, yearly incidence was noted to be higher in patients receiving zoledronate (1.1%) compared to patients taking alendronate (0.029%)[7,9,10]. The 64-year-old female described in the case study experienced episcleritis after exposure to alendronate, then uveitis within two days of receipt of IV zoledronate. However, in a three-case report of zoledronate-induced acute anterior uveitis by Jin et al[10] (2021), two of the three patients had previously taken alendronate without any ocular sequelae, thus suggesting that prior tolerance of oral bisphosphonates does not exempt patients from ocular side effects when receiving intravenous zoledronate.

Adverse ocular side effects of bisphosphonates include uveitis, scleritis, episcleritis, conjunctivitis, blepharitis, optic neuritis, subconjunctival hemorrhage, ischemic optic neuropathy, and ocular hypertension[6]. The most commonly reported ocular signs and symptoms include conjunctival hyperemia and chemosis, ocular motility deficit, anterior uveitis, anterior scleritis, blurred vision, diplopia, proptosis, and pain[6]. The majority of the reported ocular side effects are unilateral (70-89%)[11]. However, multiple adverse ocular events can arise concurrently. Side effects have been reported to occur with a faster onset in patients receiving intravenous rather than oral bisphosphonates[11]. Ocular side effect reversibility has been reported without sequelae within the first month when prompt treatment was provided[6]. Recurrence of ocular inflammation can occur after re-exposure to bisphosphonates[3]. The majority of the reported cases of bisphosphonate-induced ocular inflammation have occurred in females (60-70%), though this is likely due to the prescribing of bisphosphonates more commonly in women[11].

No clear mechanism of action to explain the cause of ocular inflammation from bisphosphonate exposure has been elucidated. However, it has been proposed that ocular inflammation occurs through activation of gamma delta T cells and subsequent inflammatory cytokine release[6,11,12]. Some studies have also noted trace bisphosphonates secreted by the lacrimal gland into tears, which may lead to ocular inflammation[8,10]. The risk of ocular inflammation has been reported to be increased in patients with underlying inflammatory/autoimmune diseases[6]. Interestingly, the 64-year-old case study patient had a history of abnormal TSH levels and leukopenia, though no clear autoimmune diagnosis was determined. It has also been suggested that patients with lower levels of vitamin D may have a higher risk of ocular inflammation[8,10,13]. However, the female presented in the case study had elevated levels of vitamin D, rather than a deficiency.

CONCLUSIONS

In summary, the current case study describes a female patient who experienced a rare side effect of ocular inflammation after exposure to oral and IV bisphosphonates. She was still able to perform all her activities of daily living and did not require hospitalization. It has been suggested that patients with autoimmune comorbidities may be more likely to develop ocular inflammation after bisphosphonate exposure[6]. Interestingly, the case study patient had a history of abnormal TSH levels and leukopenia. Though the case study patient experienced ocular side effects with both oral and IV bisphosphonates, tolerance of an oral bisphosphonate does not guarantee exemption from ocular side effects upon exposure to zoledronate[10]. Ocular side effect reversibility has been reported without sequelae within the first month when timely intervention is provided[6]. This case therefore highlights the importance of discussions with patients around less common side effects of oral and intravenous bisphosphonates to allow for earlier identification and treatment of episodes of ocular inflammation.

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Ethics Statement:
The article has been written by following Helsinki Declaration and its latest amendments.

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REFERENCES

1. Amin U, McPartland A, O'Sullivan M, Silke C. An overview of the management of osteoporosis in the aging female population. Womens Health 2023; 19: 17455057231176655.
2. Campbell T. Polyarthritis following infusion of zoledronic acid: a case study. Beyond Rheumatol 2023; 5: e481.
3. Keren S, Leibovitch I, Ben Cnaan R, Neudorfer M, Fogel O, Greenman Y, Shulman S, Zur D, Habot-Wilner Z. Aminobisphosphonate-associated orbital and ocular inflammatory disease. Acta Ophthalmol 2019; 97: e792-e799.
4. White S, Jacob A, Gregson C, Bhalla A. Severe polyarthritis secondary to zoledronic acid: a case report and literature review. Clin Cases Miner Bone Metab 2015; 12: 69-74.
5. Kennel KA, Drake MT. Adverse effects of bisphosphonates: implications for osteoporosis management. Mayo Clin Proc 2009; 84: 632-638.
6. Nouraeinejad A. Osteoporosis, bisphosphonates, and ocular inflammation. Eur J Ophthalmol 2022; 33: 637-642.
7. Patel DV, Bolland M, Nisa Z, Al-Abuwsi F, Singh M, Horne A, Reid IR, McGhee CN. Incidence of ocular side effects with intravenous zoledronate: secondary analysis of a randomized controlled trial. Osteoporos Int 2015; 26: 499-503.
8. Ma D, Xiao C, Zhao D, Li G, Cheng W, Deng X, He D, Liu K. Posterior scleritis following a single infusion of zoledronate for osteoporosis: a case report and literature review. Clin Case Rep 2024; 12: e9068.
9. Etminan M, Forooghian F, Maberley D. Inflammatory ocular adverse events with the use of oral bisphosphonates: a retrospective cohort study. CMAJ 2012; 184: E431-E434.
10. Jin X, Shou Z, Shao Y, Bian P. Zoledronate-induced acute anterior uveitis: a three-case report and brief review of literature. Arch Osteoporos 2021; 16: 104.
11. Kanda P, Guerrero-Cordova I, Dhillon J, Tsang A. Case report: a severe case of zoledronate-associated diffuse orbital inflammation and uveitis in a patient with metastatic breast cancer. Front Ophthalmol 2024; 4: 1372429.
12. Roelofs AJ, Jauhiainen M, Monkkonen H, Rogers MJ, Monkkonen J, Thompson K. Peripheral blood monocytes are responsible for gammadelta T cell activation induced by zoledronic acid through accumulation of IPP/DMAPP. Br J Haematol 2009; 144: 245-250.
13. Crotti C, Watts NB, De Santis M, Ceribelli A, Fabbriciani G, Cavaciocchi F, Marasini B, Selmi C, Massarotti M. Acute phase reactions after zoledronic acid infusion: protective role of 25-hydroxyvitamin D and previous oral bisphosphonate therapy. Endocr Pract 2018; 24: 405-410.