Indian Journal of Pharmacy Practice., 2024; 17(3):298-301.
https://www.ijopp.org

Case Report

Navigating the Uncharted: Alendronate-Related Orbital Inflammation: A Case Report

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ABSTRACT

Alendronate is used to treat cancer-associated bone disease, Paget's disease, post-menopausal osteoporosis, and other bone degenerative conditions. Rare adverse reactions associated with alendronate include ocular effects, such as orbital inflammation, episcleritis, scleritis, and uveitis. These reactions usually occur as an acute-phase response, within a few days of alendronate administration. A 54-year-old woman, diagnosed with post-menopausal breast cancer experienced left eye dryness, swelling, itching, and burning after a month of oral alendronate administration. The patient was effectively managed using topical steroid eye drops with gradual tapering of the dose, which led to the conclusion that alendronate was the cause of the event. To our knowledge, this is the first reported case of an alendronate-induced ocular side effect in India.

Keywords: Alendronate, Adverse Drug Reaction, Anterior Scleritis, Orbital Inflammation, Bisphosphonates, Steroid therapy.

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Received: 13-02-2024;
Revised: 01-04-2024;
Accepted: 04-05-2024.

INTRODUCTION

The prevalence of osteoporosis has a major detrimental effect on one's health. Osteoporosis typically affects one-third of men and half of women in their sixth and seventh decade, respectively. Osteoporosis, characterized by a decrease in bone mass, increases the risk of fracture, mainly in postmenopausal women, possibly due to hormonal changes associated with menopause. Following menopause there is a tendency of decreased bone density as age increases which is caused due to significant decline in levels of estrogen. Studies indicate estrogen, mainly a bioactive form of estrogen called Estradiol (E2) maintains the function of osteoclast and osteoblast in balance however due to decreased Estradiuol there is increased osteoclast activity and decreased osteoblast activity.[1] Due to osteoporosis, there is risk of development of fragile fractures, which are caused due to minimal trauma or stress to the bones which significantly affects the quality of life of the patients. Current available treatment options include anti resorptive medication, like Bisphosphonates, and bone anabolics. Bisphosphonates (BPN) are often prescribed as first-line treatment. Chemically BPN consist of two phosphate group bound together by esterification. Bisphosphonates are classified into two categories non-nitrogen containing (first generation BPN) and nitrogen containing (second and third generation BPN). Alendronate, a second-generation BPN, is the most potent inhibitor of bone resorption used in clinical practice. Oral alendronate has been approved for the treatment of Paget's disease, corticosteroid-induced osteoporosis, postmenopausal osteoporosis, cancerous malignancies of the bone, and hypercalcemia-causing conditions.[2]

Some common Adverse Drug Reactions (ADR) to alendronate include gastrointestinal effects such as esophageal erosions, esophagitis, esophageal ulcers, osteonecrosis of the jaw, hypocalcaemia, severe musculoskeletal pain, and atypical femur fractures. There are also reports of an acute inflammatory response that generally presents as transient pyrexia, myalgia, and headaches.[3] Uncommon ADR of BPN are orbital inflammation, episcleritis, scleritis, and anterior uveitis, with an estimated incidence rate of between 0.046% and 1%.[4]

Here, we report a case of a 54-year-old postmenopausal breast cancer patient with a risk of osteoporosis who experienced symptoms of dryness, swelling, itching, and burning sensation in the left eye after a month of oral alendronate administration at a dose of 70 mg.

DOI: 10.5530/ijopp.17.3.47

CASE REPORT

A 54-year-old postmenopausal woman with a history of Thyroidectomy was diagnosed with early-stage breast cancer positive. No spacing in sentences for Estrogen Receptor (ER) and Progesterone Receptor (PR). The patient underwent modified radical mastectomy, sentinel lymph node biopsy, adjuvant chemotherapy, and hormonal therapy. She completed four cycles of Docetaxel-Cyclophosphamide (TC) chemotherapy and started taking letrozole, an Aromatase Inhibitor (AI), along with oral calcium and 70 mg of alendronate, once a week to prevent AI-related osteoporosis. However, the patient developed symptoms of dryness, swelling, itching, and burning in the left eye accompanied by watery discharge after one month of treatment (Figure 1).

Ophthalmologist-directed diagnostic tests revealed high levels of C-Reactive Protein (CRP). The patient was prescribed empirical antibiotics and prednisolone eye drops to alleviate the symptoms, and alendronate was discontinued with a working diagnosis of anterior scleritis and preseptal cellulitis. Contrast MRI of the brain and orbits was normal, and other causes of ocular inflammation were ruled out. The relationship between the drug and ocular reaction was evaluated using the Naranjo Adverse Drug Reaction Probability Scale (Figure 2), and the severity was assessed using Hartwig's severity assessment scale (Figure 3).

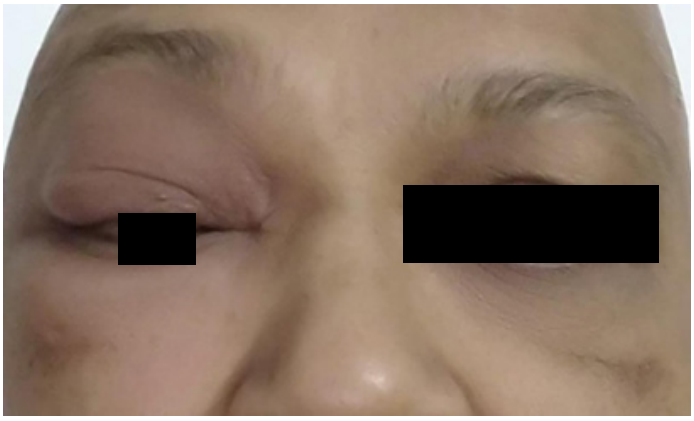

Figure 1: Ocular inflammation post alendronate administration.

Once alendronate was discontinued, the symptoms improved after a positive de-challenge with topical steroids, which gradually decreased accordingly. After the reaction, calcium and vitamin D supplements were administered as an alternative to alendronate. The patient was diagnosed with bisphosphonate-induced orbital inflammation.

DISCUSSION

BPN are a class of drugs that inhibits bone resorption. Alendronate belongs to the 2nd generation BPN which is a member of the amino BPN family. The drug has been associated with orbital inflammation, manifested as uveitis, scleritis, conjunctivitis, and, in some cases, pain in one or both eyes. Activation of gamma-delta (γδ) T cells was found to be the cause of these effects, resulting in the induction of pro-inflammatory markers such as Interleukin (IL)- 1, IL 6, and tumor necrosis factor-alpha.[5]

To date, approximately 101 reports of orbital inflammation linked to BPN have been documented, making this an uncommon side effect.[4] Our patient presented with itching, swelling, and burning sensation, which were symptoms of alendronate-induced ocular inflammation. Acute phase reactions can be caused by several factors, including Including changes in the bone levels of bone turn over markers, immune system dysregulation, and other hypotheses published in recent articles.[5]

Questions	Yes	No	Don't know	Score (in our case)
1. Are there previous conclusive reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	+1	+2	0	+2
6. Did the reaction reappear when the placebo was given?	+1	+1	0	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have similar reaction to the same or similar drugs in any previous reaction?	+1	0	0	0
10.Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
			TOTAL	7

Figure 2: The adverse drug reaction is assigned to a probability category from the total score as follows: Definite >8, Probable 5 to 8, Possible 1 to 4, Doubtful <1. The ADR caused by alendronate in our case is thus a probable one. (Score =7).

DESCRIPTION	YES/NO	LEVELS	SEVERITY
An ADR occurred but required no change in treatment with the suspected drug	NO	LEVEL 1	MILD
The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay.	NO	LEVEL 2	
The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. AND/OR An Antidote or other treatment was required. No increase in length of stay	YES	LEVEL 3	**MODERATE**
Any Level 3 ADR which increases length of stay by at least 1 day. OR The ADR was the reason for the admission	YES	LEVEL 4	
Any Level 4 ADR which requires intensive medical care	NO	LEVEL 5	SEVERE
The adverse reaction caused permanent harm to the patient	NO	LEVEL 6	
The adverse reaction either directly or indirectly led to the death of the patient	NO	LEVEL 7	

Figure 3: Hartwig's severity assessment scale was used to identify reaction as of moderate severity.

Our patient was postmenopausal and diagnosed with breast cancer. Estrogen deficiency in postmenopausal women makes them more susceptible to osteoporosis.[6] Breast cancer treatment includes hormone therapy using AI. The patient was taking letrozole (2.5 mg), which has osteoporosis as a prominent adverse effect due to the decrease in circulating estrogen levels, contributing to a decrease in bone mineral density.[7] These factors justified the use of alendronate in this patient. Following the alendronate therapy, the patient developed signs and symptoms of ocular inflammation. In general, the time to development of alendronate-related ocular symptoms ranges from 10 to 28 days.[8] In this case, the patient developed ocular symptoms within one month of alendronate administration. Interestingly, according to the literature review in a study conducted by Shay Keren *et al.* (2022, Argentina), pamidronate and zoledronate had a shorter mean time (around 11-17 days), for the development of ocular side effects than alendronate.[9]

Laboratory investigations revealed that the patient had CRP of 6.65, an Erythrocyte Sedimentation Rate (ESR) of 37 mm/h lymphocyte count of 43.7%, and neutrophil count of 46.8%. A study evaluating peripheral blood counts of alendronate patients, revealed high neutrophil levels.[10] The patient presented with a mild elevation in CRP level and ESR. There are multiple reports of alendronate-induced inflammation accompanied by high CRP and ESR levels.[9,11,12]

The appropriate treatment for BPN-induced ocular side effects is determined by patient evaluation and prompt diagnosis. To determine the best course of action, thorough ophthalmologic evaluation is necessary. Our patient was treated with amoxicillin and prednisolone eye drops, and the symptoms subsided. Existing data suggest that systemic steroids, steroidal eye drops, and cycloplegics are the preferred treatment options.[13] According to this study, discontinuation of amino-BPN alone was effective in managing ocular effects and did not require steroidal therapy.[9] This led to an improvement of symptoms without the need to use other drugs for the treatment of symptoms.

CONCLUSION

The scarcity of challenging data makes it difficult to determine the exact cause and effect relationship between treatment and outcomes. In mild cases of BPN-induced orbital inflammation, medication may be continued; however, in severe cases, it should be permanently discontinued. There is a strong correlation between the temporal association of symptoms of ocular inflammation and the possible etiology of these reactions. Complete recovery is expected with an accurate diagnosis and appropriate care. Typically, resolution without significant complications is the norm; however, it is essential to exercise caution to prevent the occurrence of this problem.

ACKNOWLEDGEMENT

The authors extend their gratitude to the patient and family for providing valuable information for the purpose of the case report.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

PATIENT CONSENT

Informed consent for publication of this case report and the accompanying image was obtained in writing from the patient. All personal identifiers have been removed or altered to protect patient privacy. The procedure followed was in accordance with the ethical standards of our institution.

ABBREVIATIONS

BPN: Bisphosphonates; **ADR:** Adverse Drug Reactions; **ER:** Estrogen Receptor; **PR:** Progesterone Receptor; **TC:** Docetaxel-Cyclophosphamide; **AI:** Aromatase Inhibitor; **CRP:** C - Reactive Protein; **MRI:** Magnetic Resonance Imaging; **IL:** Interleukin; **γδ:** Gamma-Delta; **ESR:** Erythrocyte Sedimentation Rate.

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Cite this article: Johnson J, Sajan R, Rakesh MP, Chandra P, Sujithra H, Unnikrishnan MK. Navigating the Uncharted: Alendronate-Related Orbital Inflammation-A Case Report. Indian J Pharmacy Practice. 2024;17(3):298-301.