



Case report

Alendronate induced chorioretinitis: The importance of meticulous assessments



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ARTICLE INFO

Keywords:

Uveitis
Drug-induced
Alendronate
Chorioretinitis
Bisphosphonates

ABSTRACT

Purpose: To report a case of presumed bilateral chorioretinitis secondary to alendronate therapy.

Observations: A 71-year-old female presented to the clinic in July 2017 with six months history of difficulty in reading along with floaters in both eyes which were more severe in the right eye. Past medical and surgical history revealed a history of hypertension, gout, hyperthyroidism, osteoporosis, and humerus fracture. She was started on alendronate three months before developing ocular symptoms. On ocular examination, best corrected visual acuity was 20/30 in the right and 20/25 in the left eye. Slit-lamp examination demonstrated normal anterior chamber examination in both eyes. Dilated fundus examination revealed geographic chorioretinal lesions around the optic nerve head in both eyes, more extensively in the right eye; and superior and temporal to the macula in the right eye. Past ocular records in February 2015 did not reveal any such findings. Fundus autofluorescence demonstrated hyper-autofluorescence in the peripapillary lesions in both eyes. The lesion adjacent to the macula in right eye displayed mixed hyper and hypo-autofluorescence. Fluorescein angiography showed combined hyper- and hypo-fluorescence compatible with window defect, staining and blockage. However, no leakage was appreciated in the macula, peripapillary, and peripheral lesions in both eyes. Optical coherence tomography scan showed septate hyporeflective intraretinal spaces in the right eye.

Conclusion and importance: The index report underscore the importance of considering alendronate as an etiologic cause of chorioretinitis, especially in subjects with atypical lesions developing after alendronate therapy. We, therefore, recommend discontinuation of this medication in subjects who develop chorioretinitis after employing this medication.

1. Introduction

Drug-induced uveitis is an important cause of uveitis.¹ Several medications with various modes of administration, including ocular and systemic, have been implicated in causing uveitis. The presumed mechanism of drug-induced uveitis is thought to be a milieu of auto-immune and direct toxic effect of the medication.^{2–4}

One such group of medications is bisphosphonates, which are primarily used for the treatment of osteoporosis and as preventive medications for fracture development in patients with malignant bone disease.^{5,6} Although well tolerated generally, ocular inflammation due to bisphosphonates has been reported as early as 1990s.⁷ The reported side effects that have been associated with bisphosphonates include conjunctivitis, anterior uveitis, episcleritis, scleritis, optic neuritis,

orbital inflammation and most recently age-related macular degeneration (ARMD).^{7–16}

Alendronate is a member of aminobisphosphonate which has potent anti-osteoclastic action and also induces increases in bone mineral density.¹⁷ These properties make it a drug of choice for the treatment of osteoporosis in postmenopausal women. The ocular adverse events of alendronate that have been reported in the literature include conjunctivitis, bilateral anterior uveitis, anterior and posterior scleritis.^{7,9–12} To our knowledge, only two cases of chorioretinitis secondary to alendronate have been reported to FDA and MedsFacts (prevalence: 0.0026%); however, no official report of alendronate associated posterior uveitis has been published in the literature.¹⁸

In this case report, we describe a case of presumed bilateral chorioretinitis secondary to alendronate therapy.

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<https://doi.org/10.1016/j.ajoc.2019.01.007>

Received 7 March 2018; Received in revised form 11 December 2018; Accepted 8 January 2019

Available online 09 January 2019

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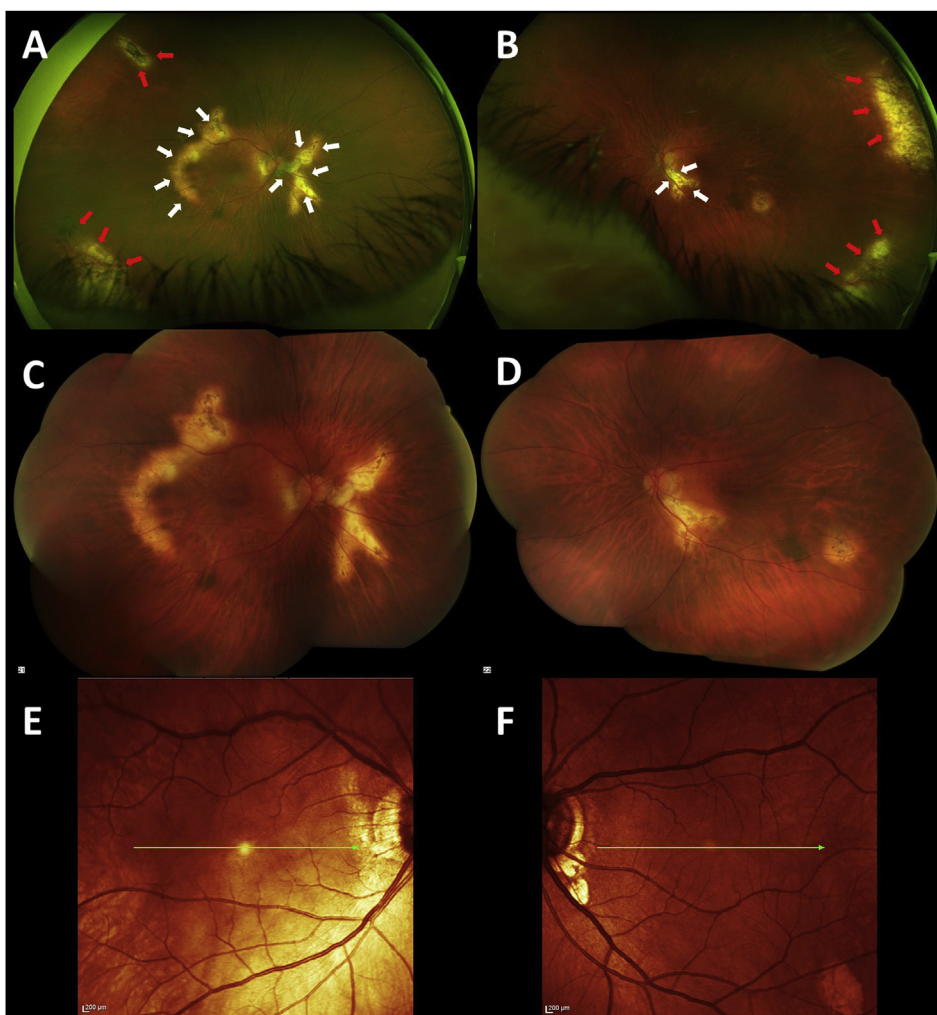


Fig. 1. Color fundus photographs (FP) show geographic chorioretinal lesions around the optic nerve head OU, more extensively OD; and superior and temporal to the macula OD (White arrows) (A and B). These lesions appear stable from those captured in April 2017 (C and D) and cannot be appreciated on photographs from February 2015 (E and F). Multiple patches of chorioretinal atrophy can be seen in the periphery (Red arrows) OU (A and B). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

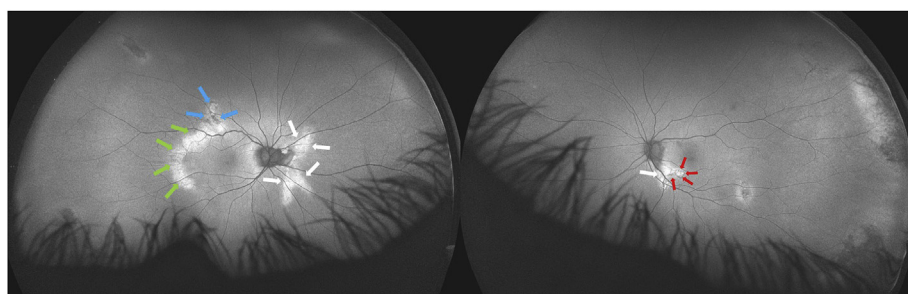


Fig. 2. Fundus autofluorescence (FAF) demonstrates hyper-autofluorescence in the peripapillary lesions OU (White arrows) with a hypo-autofluorescent margin OS (Red arrows). The lesion adjacent to macula displays hyper-autofluorescence (Green arrows) in addition to areas of hypo-autofluorescence (Blue arrows) in the superior part of the lesion OD. The peripheral areas of chorioretinal atrophy show mixed hyper- and hypo-autofluorescent patterns. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2. Case report

A 71-year-old female presented to our clinic in July 21, 2017 for evaluation of her ocular symptoms of difficulty in reading along with floaters in both eyes (OU) which was more severe in the right eye (OD).

Past medical and surgical history revealed history of hypertension, gout, hyperthyroidism, osteoporosis, and humerus fracture. In lieu of these findings, she was started on alendronate in October 2016 which was stopped in May 2017, four months after developing ocular symptoms.

As part of her ocular history, the patient was examined by a retina

specialist in 2015 and was diagnosed with macular schisis in both eyes. The patient reported that she was in her usual ocular state of health until January 2017, when she first experienced floaters and difficulty in seeing in both eyes for which she visited an ophthalmologist in April 2017 and a diagnosis of serpiginous chorioretinitis was established. She was started on mycophenolate mofetil one gram twice a day at that time.

On ocular examination, best corrected visual acuity (BCVA) was 20/30 and 20/25 in OD and OS, respectively. Pupillary reactions were normal. Slit-lamp examination demonstrated normal anterior chamber examination OU. Dilated fundus examination revealed geographic

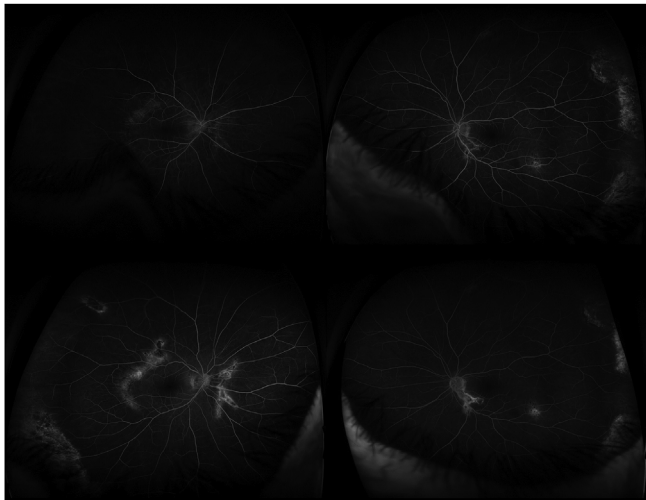


Fig. 3. Fluorescein angiography (FA) shows combined hyper- and hypo-fluorescence compatible with window defect, staining and blockage. However, no leakage is appreciated in macula, peripapillary, and peripheral lesions OU.

chorioretinal lesions around the optic nerve head OU, more extensively OD; and superior and temporal to the macula OD. These changes were not present in the medical records and photographs taken in February 2015 and were stable compared to photographs taken in April 2017. There was also a small atrophic lesion in the inferior arcade OS. On peripheral examination, there were multiple patches of chorioretinal atrophy OU (Fig. 1).

Fundus autofluorescence (FAF) demonstrated hyper-auto-fluorescence in the peripapillary lesions OU with a hypo-auto-fluorescent inferior margin in OS. The lesion adjacent to right macula displayed hyper-autofluorescence in addition to areas of hypo-auto-fluorescence in the superior part of the lesion. The peripheral areas of atrophy showed nonspecific mixed hyper- and hypo-auto-fluorescent patterns (Fig. 2). Fluorescein angiography (FA) showed combined hyper- and hypo-fluorescence compatible with window defect, staining and blockage. However, no leakage was appreciated in macula and peripheral lesions OU (Fig. 3). An optical coherence tomography (OCT) scan showed septate hyporeflective intraretinal spaces OD with progression compared to OCT done in February 2015 (Fig. 4). Full-field electroretinography (ff-ERG) and multifocal ERG were also performed and did not reveal diffuse retinal dysfunction, although there was some reduction in full-field amplitudes and patchy depression in central macula OD in multifocal ERG compatible with the cystic changes.

Various laboratory tests were including complete blood counts, peripheral blood smears, electrolytes, and liver function tests, calcium, phosphorus and phosphate, interferon gamma release assay (IGRA), syphilis antibody, and toxoplasmosis IgG/IgM antibodies, among others, were performed, and all were within normal limits.

Based on these findings and a temporal relationship to alendronate, possible diagnosis of presumed alendronate induced chorioretinitis was considered. Mycophenolate was discontinued, and no additional therapy was started due to highly likelihood of drug induced etiology. The patient was instructed not to restart alendronate therapy. The lesions have remained stable without any treatment at the follow-up visit five months after her initial visit in July 2017 (Fig. 5).

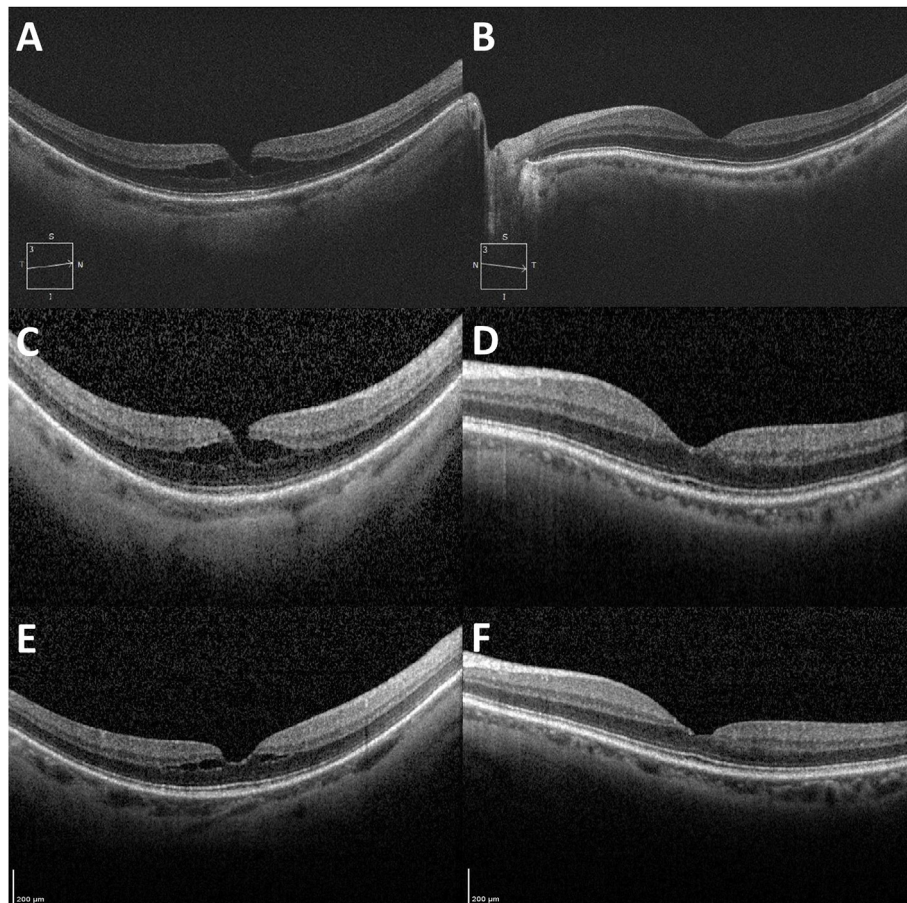


Fig. 4. An optical coherence tomography (OCT) scan shows septate hypo-reflective intraretinal spaces in OD (A) similar to scan performed in April 2017 (C) and with progression compared to OCT done in February 2015 (E). The OCT OS does not reveal significant structural and contour changes over time (B, D and F).

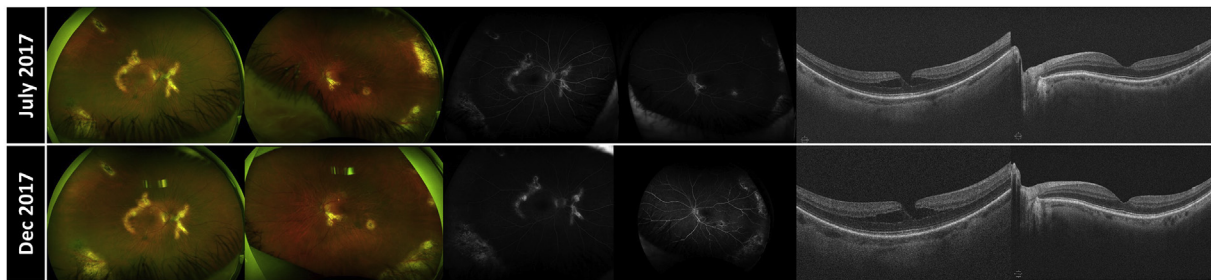


Fig. 5. Color fundus photographs (FP), fluorescein angiography (FA) and optical coherence tomography (OCT) images of the patient at the time of presentation in July 2017 and 6 months after stopping alendronate and 5 months after stopping all the medications in Dec 2017. There has been no progression of the lesion on FP, FA and OCT despite receiving no treatment. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3. Discussion

Much of our clinical knowledge in regard to ocular side effects of systemic medications is based on post marketing surveillance.^{16,19} The temporal relationship, specific pattern of involvement, de-challenging, and re-challenging of the medication play an important role in determining whether or not a specific ocular manifestation is a side effect of systemic medication.²⁰

Ocular side-effects of bisphosphonates are rare with an incidence between 0.046% and 1%.²¹ Nitrobisphosphonates have been implicated in causing ocular inflammation with positive re-challenge testing in cases of pamidronate.^{20,21} The mechanism of these ocular adverse events has not been completely established; however, nitrobisphosphonates have been shown to induce levels of pro-inflammatory cytokines including, interleukin 1 (IL-1), IL-6, IL-8, and tumor necrosis factor alpha (TNF- α) by activation of a specific subset of T-cells (gamma delta T cell).^{22–24} In contrast, the non-nitrobisphosphonates have been shown not to increase the levels of TNF- α and IL-6 and can be considered in subjects who experience ocular inflammation secondary to nitrobisphosphonates. However, recent reports have reported cases of uveitis with non-nitrobisphosphonates as well.²⁴

Alendronate is a nitrobisphosphonates, with a potent anti-osteoclastic activity and is one of the mainstays for treatment of post-menopausal osteoporosis. The most common side effects of alendronate include gastrointestinal problems. In 1999, three cases developed scleritis with and without anterior uveitis secondary to alendronate therapy and this was the first reported instance of ocular inflammation secondary to alendronate.⁷ Discontinuation of alendronate and concomitant topical and systemic steroid management resulted in resolution of the inflammation without recurrence. Bilateral acute anterior uveitis is another commonly reported side effect of alendronate with a severe case leading to corneal graft rejection.^{10–12} McKague et al. reported a case of chronic conjunctivitis secondary to alendronate, which persisted even after switching to other bisphosphonates and resolved only after complete abstinence from bisphosphonate treatment.⁹ Only two cases of chorioretinitis secondary to alendronate have been reported to FDA and MedsFacts (prevalence: 0.0026%) - available on MedsFacts website (<http://factmed.com/report-FOSAMAX-causing-CHORIORETINITIS.php>); however, no report and photographs have been published in the literature.¹⁸ The exact mechanism by which alendronate causes chorioretinal inflammation is not known. However, in addition to having the pro-inflammatory properties of the nitrobisphosphonates, alendronate, at higher concentrations, has been shown to induce expression of inflammatory cytokines such as IL-8 in cultured human retinal pigment epithelial (RPE) cells which can be a potential pathway by which it can induce retinal inflammation.

The temporal relationship between the use of alendronate and chorioretinal lesions in our patient highly suggests possible drug-induced etiology in this case. Additionally, the pattern of involvement and pattern of fundus autofluorescence, which is not compatible with

what typically is seen in serpiginous and ampiginous chorioretinitis, angioid streaks, Paget's disease or myopic degeneration, also guided us towards considering a possible diagnosis of drug-induced chorioretinitis. Furthermore, stability of the lesions after discontinuing of the medication is generally not seen in serpiginous choroiditis which is characterized by centrifugally spreading lesions over time from the peripapillary region with a leading edge of active lesions and resolving lesions with atrophy of the retinal pigment epithelium and choriocapillaris. Even though the index patient had a history of foveal schisis in OD possibly secondary to myopia, there was no history of change in refraction of both eyes since her visit to ophthalmologist in 2015 which could suggest progressive myopic denegation to be the cause of the lesions. Based on these findings as well as temporal relationship with alendronate, we presume that our patient likely has bilateral chorioretinitis secondary to alendronate therapy. Considering the possibility of drug induced etiology, no therapy was started, and the patient was informed not to restart alendronate therapy. She was instructed to follow up closely at regular intervals.

4. Conclusion

Although ocular side effects are rare in subjects treated with alendronate, with chorioretinitis being even a rarer presentation, the index report outlines a case of chorioretinitis with a likely drug induced etiology secondary to alendronate. This report underscores the importance of considering medications such alendronate as a possible etiologic cause of chorioretinitis especially in subjects who develop atypical lesions following the therapy. However, caution must be exercised before labelling a drug as an underlying cause of chorioretinitis as it is important and imperative to consider and rule out other infectious and non-infectious causes, establish a strong temporal relationship, and make sure the presentation does not fit into other known categories along with evidence from the literature of inflammatory properties of the compound. Based on our report, we recommend discontinuation of alendronate in subjects where its role is suspected in causing chorioretinitis.

Acknowledgments and Disclosures

QDN is a recipient of a Physician Scientist Award from Research to Prevent Blindness, New York, NY. QDN is a consultant for Santen, and has received research support from Genentech, Santen, and Regeneron. QDN has institutional consulting agreement with AbbVie, and honorarium from Bayer and XOMA. QDN also chaired the Steering Committee for the RISE and RIDE Study and was on the Steering Committee for the VISTA Study, and other studies sponsored by Genentech and Regeneron.

YJS has received research support from Astellas, Genentech, and Optovue. YJS serves as a consultant for Genentech, Inotek, and Optos.

DVD is a consultant for Allergan, Genentech, Regeneron, and Santen

and has received research support from Genentech, Regeneron, and Santen. DD also chaired the Steering Committee for the VISTA Study.

MH, AM, QY, NN, MSH have no financial disclosures.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ajoc.2019.01.007>.

Abbreviations

ARMD	Age-related macular degeneration
BCVA	Best corrected visual acuity
FA	Fluorescein angiography
FAF	Fundus autofluorescence
ff-ERG	Full field electroretinography
IGRA	Interferon gamma release assay
IL	Interleukin
OCT	Optical coherence tomography
TNF- α	Tumor necrosis factor alpha

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