

Distinct Acute Unilateral Fibrinous Anterior Uveitis After Zoledronic Acid Infusion: A Case Report

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Abstract

Purpose: To report a case of a distinct acute unilateral fibrinous anterior uveitis after zoledronic acid infusion.

Methods: Case Report.

Results: A 68-year-old woman presented with a burning, itching and reddened right eye with visual deterioration for about five days. She had received her first intravenous infusion of zoledronic acid the day before the onset of the symptoms. Her best-corrected visual acuity was 6/24. She was mainly treated with topical corticosteroids (prednisolone 1% eye drops and subconjunctival dexamethasone) and scopolamine 0.25 %. This treatment resulted in a significant improvement of the findings and symptoms within a few days.

Conclusions: It is crucial that patients receiving bisphosphonates are accurately informed about the possibility of ocular inflammation, other inflammatory side effects and their symptoms to ensure early treatment.

Introduction

Zoledronic acid is a drug of the amino- or nitrogen containing bisphosphonate (NBP) group, which is used to inhibit bone resorption in patients with postmenopausal osteoporosis and for the management of hypercalcemia associated with osteolytic bone cancer, metastases, multiple myeloma, and Paget's disease of the bone.¹ In general, bisphosphonates are well tolerated with a predictable and manageable side-effect profile.² Most frequent adverse events are reported to be bone pain, nausea, fatigue, fever, vomiting, anemia, and myalgia.³ However, intravenous NBPs are known to be associated with an incidence of up to 40% of mild to severe acute phase reactions (APR).^{2,4} It has been shown that NBPs can activate T-cells and lead to a release of several cytokines, which may, amongst others, evoke ocular and orbital side effects such as conjunctivitis, anterior uveitis, scleritis, and orbital inflammation.⁵ This is the basis for our Case report of a severe acute unilateral anterior uveitis in a 68-year-old female patient, after a single infusion of zoledronic acid.

Clinical Case

A 68-year-old female patient was referred to our ophthalmic outpatient department complaining of a burning, itching, and reddened right eye with sticky eyelids in the morning, associated with a visual deterioration for approximately five days. She stated that she had no other symptoms aside from the eye. The day before the onset of the symptoms, she had received her first intravenous infusion of zoledronic acid for the treatment of osteoporosis. The patient had annual ophthalmic follow-ups but had no notable ophthalmic history and had never had these symptoms before. She also reported that there was no inflammation, headache, fever, or surgery in the past and did not suffer from any rheumatologic

conditions. She denied taking any further concomitant drugs, except for a supplement of Calcium and Cholecalciferol. She had ovarian cancer one year ago, which was treated with neoadjuvant chemotherapy and surgery.

At her initial consultation (day-0), her best-corrected visual acuity (BCVA) was 6/24 and 6/6 (Snellen) to her right and left eye, respectively. Intraocular pressure was 11 mmHg in the right and 17 mmHg in the left eye. Slit-lamp examination of her right eye revealed hyperemia of the conjunctiva and chemosis (Fig. 1A). The cornea showed Descemet's folds (Fig. 1B, yellow arrow) and fine corneal precipitates inferiorly. The anterior chamber was deep and showed fibrinous strands with coagulated blood (Fig. 1A), a positive Tyndall effect, and cell grade of 2+ (according to the SUN working group anatomic classification of uveitis⁶). The pupil was distorted due to an onset of circular posterior synechiae (Fig. 1A and 1B) and circular hyperemic iris vessels were noticeable (Fig. 1D, white arrow). As expected, taking the age of the patient into account, the lens had a slight opacification. Due to the severity of the anterior chamber findings, detailed funduscopy was not possible. Ultrasonographic examination (A-scan and B-scan) of the eye revealed no involvement of the vitreous body (Fig. 1C and 1E). No relative afferent pupillary defect (RAPD) was seen. Spectral-domain optic coherence tomography (SD-OCT) examination of the right eye excluded intra- and subretinal fluid. The examination of the left eye showed no pathologic changes, especially no signs of uveitis.

We immediately suspected acute zoledronic acid associated unilateral anterior uveitis and local therapy to the right eye was started with prednisolone 1.0 % (Pred Forte® gtt opht 1 % 5 ml, Allergan AG) eye drops hourly, prednisolone eye ointment (Ultracortenol® eye ointment. AGEPHA PHARMA s.r.o.) at night, and scopolamine 0.25 % (SCOPOLAMINE Dispersa® Gtt Opht 0.25 %, Omnivision AG) eye drops twice daily. A complete synechiolysis with tropicamide 0.5 % (Mydriaticum Dispersa Gtt Oph 0.5 %, OmniVision AG, Puchheim, Germany) and phenylephrine 5.0 % (Neosynephrin-POS 5.0 % Gtt Oph, Ursapharm GmbH, Saarbrücken, Germany) was not possible.

At the follow-up visit the next day (day-1), the patient already reported an improvement of the pain and redness and she confirmed she had used the therapy as prescribed. Clinical examination showed no significant changes in the findings at this time and the BCVA remained 6/24 in the right eye, therefore Dexamethasone (MEPHAMESON® injection solution 4 mg/ml, Mepha Pharma AG) was injected subconjunctivally. The existing topical therapy was continued. Tropicamide (0.5 %) and phenylephrine (5.0 %) eye drops were applied at 10-minute intervals for a total of 30 minutes to initiate resolution of the posterior synechiae.

The following day (day-2) showed further subjective improvement. The patient reported no more pain. The BCVA improved to 6/19 in the affected eye. Clinically, there was a mild decrease of the fibrinous structure and coagulated blood, and the posterior synechiae had greatly improved. Dexamethasone was again injected subconjunctivally.

On day-5, BCVA was already 6/12 in the right eye. The fibrin in the anterior chamber had completely regressed (Fig. 2B) and the cell grade had decreased to 1+. We also noted a decrease in conjunctival hyperemia (Fig. 2A). Based on the significant improvement of the findings, Scopolamine (0.25 %) was stopped and Prednisolone (1.0 %) was reduced to five times daily.

At the follow-up on day-16, the patient reported significant subjective improvement in visual acuity. The BCVA was 6/7.5 in her right eye. The anterior chamber no longer showed signs of irritation with +0.5 pigmented cells. The fibrinous strands and coagulated blood were no longer present. At this time, topical therapy consisted of prednisolone (1.0%) three times daily and continued to be tapered weekly according to the regimen.

No retinal or vitreous involvement was identified at any time point.

Discussion

Zoledronic acid is an intravenous, highly potent NBP and is an established therapy in osteoporosis, Paget's disease, and the prevention of skeletal-related events in cancer and metastases.¹ Due to its high affinity to hydroxyapatite and high half-life in mineralized bone, it is administered once yearly. The mechanism of action of this antiresorptive agent is thought to inhibit bone resorption by inhibiting farnesyl pyrophosphate synthase and preventing protein prenylation after internalizing during bone resorption of osteoclasts.⁷ This action may also lead to the development of the APR because of the accumulation of isopentenyl diphosphate and dimethylallyl diphosphate in monocytes, which may result in the activation of adjacent $\gamma\delta$ -T-cells with the release of interferon- γ and TNF.⁸ Inflammatory changes in the eyes, mainly of the anterior segment (conjunctivitis, episcleritis, anterior uveitis), but also panophthalmitis and orbital inflammation have been associated with the intravenous infusion of NBPs⁵. Their occurrence within the time frame of three days after injection suggests, that eye symptoms may be part of the APR.⁵ Due to our suspicion that the inflammatory reaction was caused by the zoledronate infusion, and at the patient's explicit request, we did not perform any further diagnostics with regard to the clarification of other causes of acute uveitis anterior.

Within this case report we aim to present an acute unilateral fibrinous anterior uveitis, which seems to be associated with the APR of a zoledronic acid infusion. The incidence of acute anterior uveitis is estimated to be 0.8% after zoledronic acid⁹. We included images to provide an illustration of the dramatic clinical findings, but also underline the good therapeutic response to corticosteroids. Due to the lack of objective amelioration after initial treatment with eyedrops only, we also used subconjunctival steroids. A few reports indicate the need of systemic corticosteroids¹⁰⁻¹². However, in most cases local therapy will be sufficient to treat anterior uveitis⁹.

As for making the diagnosis, there are case reports indicating the need of further work-up to exclude other reasons for anterior uveitis. In our case the patient had declined further diagnostic work-up so we used the Naranjo Adverse Drug Reaction Probability Scale¹³ to evaluate whether the zoledronic acid may be

the potential cause for the ocular adverse reactions. Our patient's final score was 5, which indicates the trigger was probably the infusion of zoledronic acid. Nevertheless, we believe that the time frame of 48 hours between NBP infusion and the onset of symptoms afterwards was crucial for making the diagnosis¹⁴.

It could be brought into question whether repeated treatment of the same medication will lead to another episode of inflammation, or whether it is only associated with the initial dose.¹⁵ Evidence suggests, however, that repeated treatments of the same or other bisphosphonates can lead to relapses.¹⁶

There was a delay of five days after the onset of symptoms before the patient sought ophthalmological help. Seeking an earlier consultation through a better understanding of her symptoms may have led to a less dramatic episode of the uveitis. Therefore, patients receiving bisphosphonates must be accurately informed about potential ocular and other inflammatory side effects and their related symptoms. In the event that patients experience ophthalmologic symptoms, they should immediately consult an ophthalmologist.

Declarations

Conflict of Interest Statement:

No potential competing interest was reported by the authors.

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Statement of Ethics

To publish this case report and any accompanying images, we received the written informed consent from the patient. This study was conducted in accordance with the Declaration of Helsinki. No vote of the Ethics Committee is required for this Case Report.

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Author Contributions

Klemens Paul Kaiser co-wrote the main text and designed the case report.

Ferhat Turgut performed the clinical examination and reviewed the manuscript.

Matthias Dieter Becker reviewed the manuscript and provided critical feedback.

Vita Louisa Sophie Dingerkus co-wrote the main text and provided critical feedback.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Figures

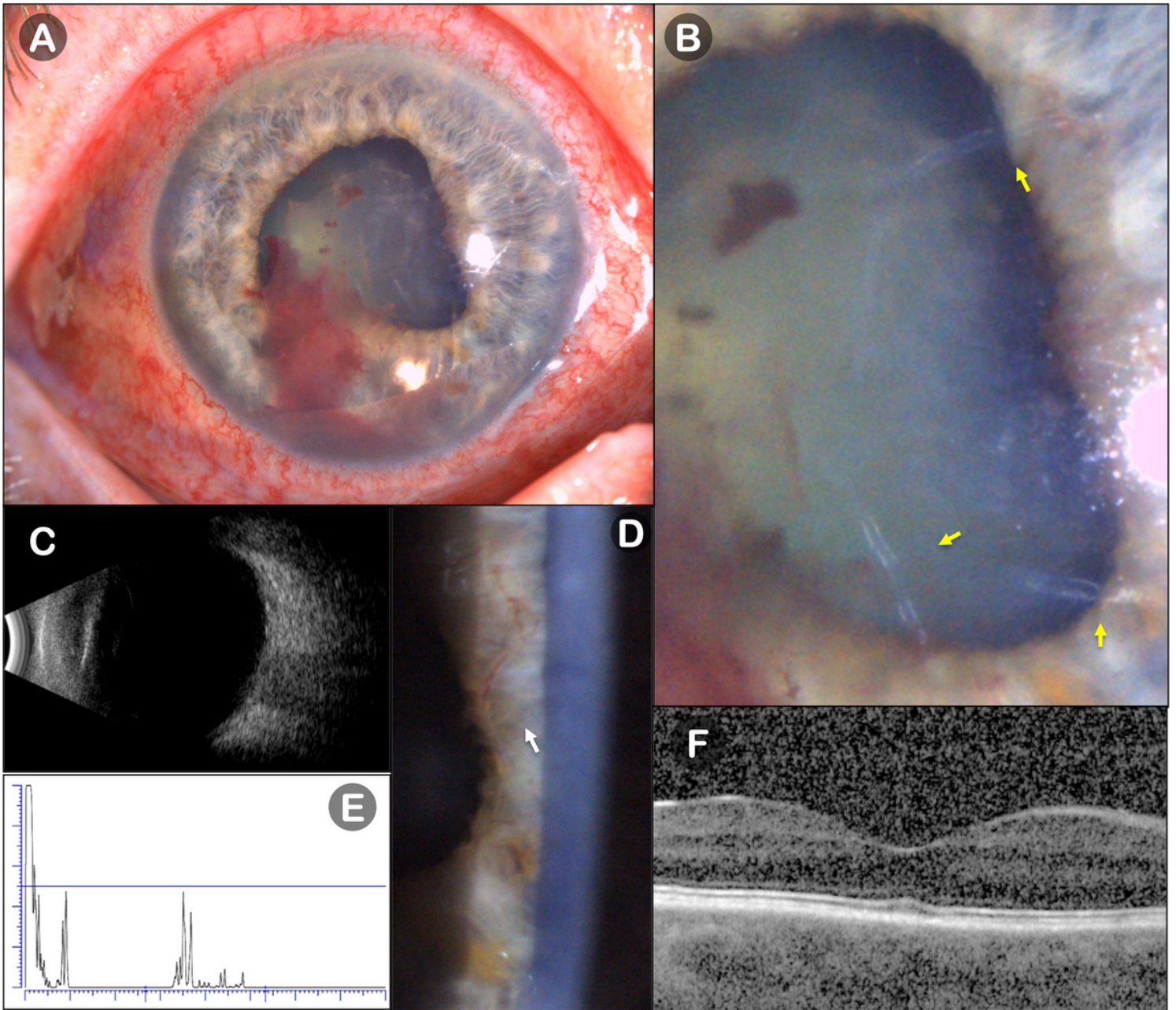


Figure 1

shows conjunctival hyperemia, distorted pupil due to posterior synechiae, fibrinous strands with blood clots (A), Descemet's folds (B, yellow arrows), hyperemia of the iris vessels (D, white arrows), ultrasonography of the affected eye with no signs of vitreous involvement in A-scan (E) and B-scan (C) and SD-OCT examination with no sign of intraretinal or subretinal fluid (F) at her second consultation (Day-1) in our outpatient department.

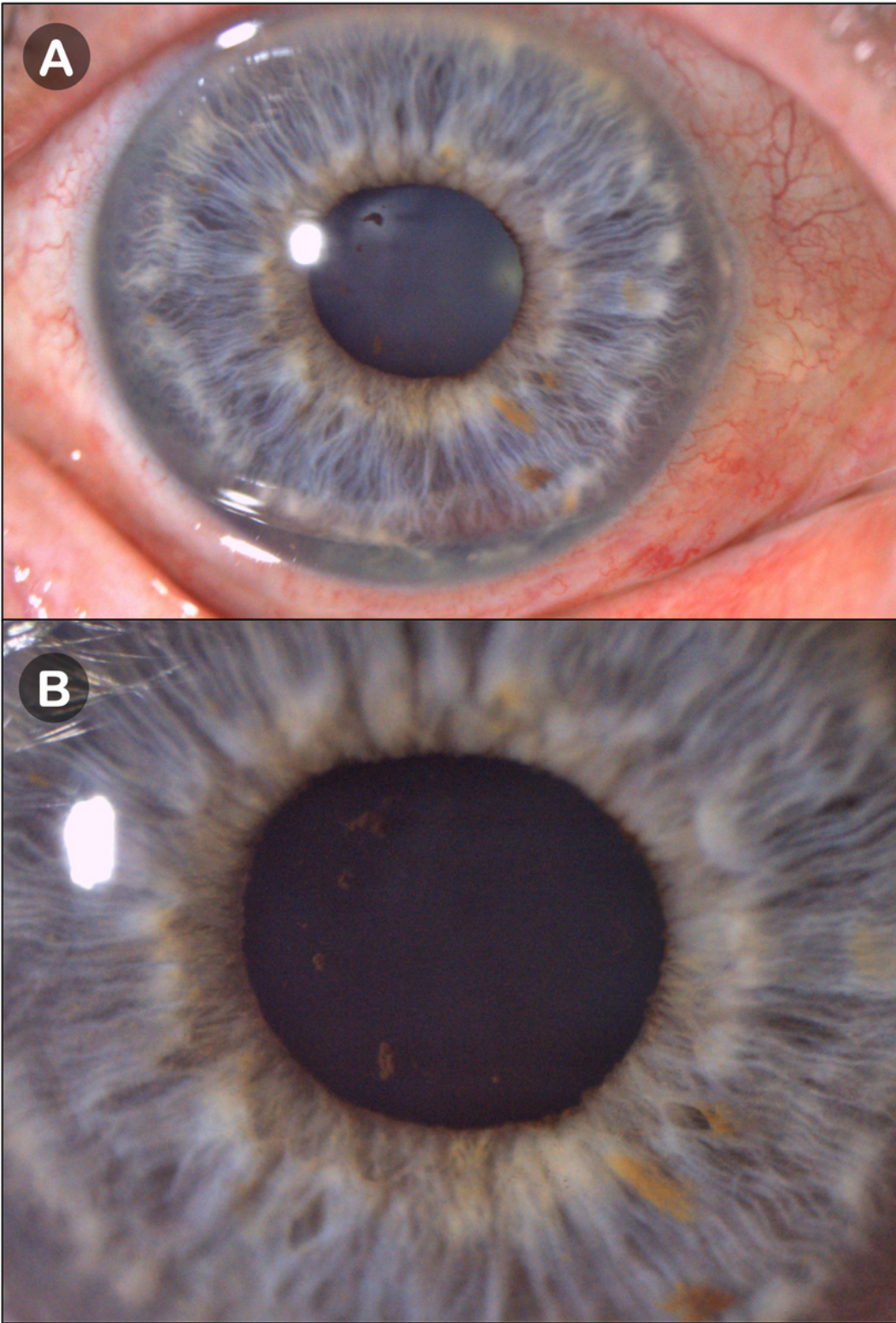


Figure 2

depicts the findings on day-5 with significantly less conjunctival hyperemia (A) and regression of the fibrinous strands and blood clots and resolution of the posterior synechiae (B).