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CASE REPORT

Bisphosphonate-induced orbital inflammation: more common than once thought?

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Abstract

To report two cases of bisphosphonate-induced orbital inflammation, discuss the clinic-radiological features and management options, and highlight the increasing frequency of an association previously considered extremely rare. A retrospective review of two cases presenting to our department, and review of the literature reporting this association. Two new cases of bisphosphonate-induced orbital inflammation were added to the literature. The first occurred in the context of a risedronate re-challenge, and the second with zoledronic acid. Both cases were managed successfully with topical steroids. Clinicians prescribing bisphosphonates, particularly for the first time, should be aware of the increasingly reported association with orbital inflammation. The presence of suggestive clinical features should prompt urgent referral to an ophthalmologist for appropriate management.

Keywords Bisphosphonate · Orbital inflammation · Risedronate · Zoledronic acid

Introduction

Bisphosphonates are indicated for the management of bone disorders including osteoporosis, Paget's disease, bone metastasis, and multiple myeloma. With an aging population and the recent National Institute of Health and Care Excellence (NICE) guidelines recommending a cost-effectiveness threshold for treatment, this number will only increase [1]. Improved awareness of the association has resulted in an increase in recent reports, aiding our understanding of the clinical presentation of this rare side effect. We add our experience with two cases of bisphosphonate-induced orbital inflammation in an effort to highlight the association.

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Case 1

A 63-year-old female presented with a 24-h history of right-sided periorbital swelling and vertical diplopia. There was no associated trauma or prodromal symptoms. On further questioning, the patient had recently been recommenced on risedronate for osteoporosis 9 days earlier and took two doses, 1 week apart. The patient reported a similar presentation a year earlier when first commenced on risedronate; however, further investigation at the time led to an ipsilateral sphenoid wing meningioma being diagnosed on neuroimaging. This was managed surgically following resolution of the symptoms therefore attributed to this despite improvement after cessation of the drug. Past medical history was otherwise unremarkable.

On this presentation, examination of the right eye revealed a best corrected visual acuity (BCVA) 6/12; there was mild periorbital oedema, marked inferotemporal conjunctival chemosis and injection, 1.5 mm of axial proptosis, mild restriction in upgaze with resultant vertical diplopia, and 1+ cells in the anterior chamber. Examination of the left eye was unremarkable. The patient was afebrile and otherwise systemically well (Fig. 1).

Computed tomography (CT) of the brain and orbits revealed right-sided retro-orbital fat stranding and lateral rectus thickening. Magnetic resonance imaging (MRI) of the brain and orbits with gadolinium revealed a thickened lateral and

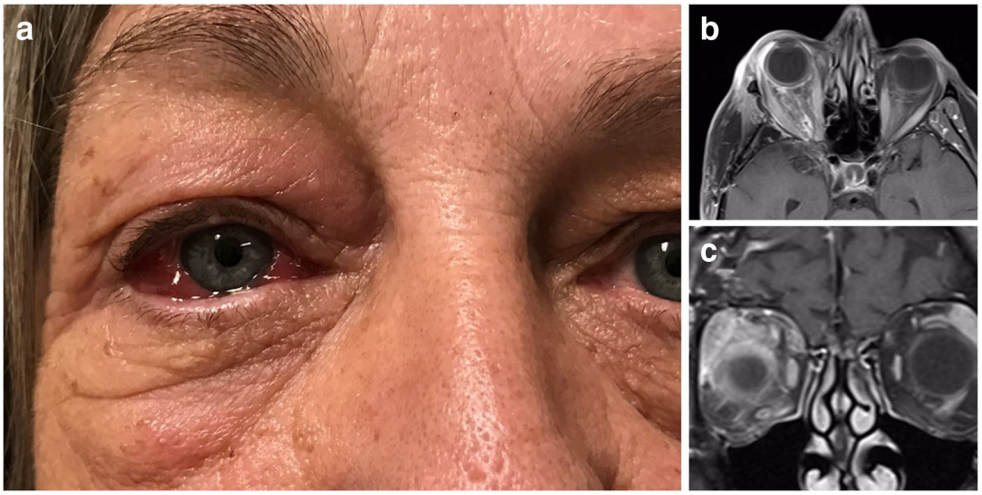

Fig. 1 Case 1. **a** Right-sided conjunctival chemosis and mild periorbital oedema. **b** T1-weighted, fat suppressed MRI, axial view demonstrating enhancement of the thickened lateral rectus and retro-orbital fat following administration of intravenous gadolinium, in addition to mild proptosis. **c** T1-weighted, fat-suppressed MRI, coronal view demonstrating enhancement of the diffusely enlarged right lacrimal gland, and superior rectus, following administration of intravenous gadolinium

superior rectus, lacrimal gland, and retro-orbital fat, favoring inflammation. Serological investigation for specific causes of orbital inflammation was unremarkable.

The patient was commenced on a weekly tapering course of topical prednefrin forte (1%) starting at three times a day for the mild anterior uveitis. After 6 weeks, the patient's orbital signs and uveitis had resolved.

Case 2

A 65-year-old female was referred with a 4-day history of right-sided periorbital swelling and headache. She had received a first dose of intravenous zoledronic acid 8 days prior, for osteoporosis. There was no associated trauma or prodromal symptoms. Her past medical history included lymphoma treated with chemotherapy 13 years previous and breast cancer treated with surgery and adjuvant radiotherapy 20 years previous.

Examination of the right eye revealed BCVA 6/7.5, periorbital oedema, 360-degree conjunctival chemosis and injection, 5 mm of axial proptosis, mild restriction in upgaze with resultant vertical diplopia, and 1+ cells and flare in the anterior chamber with fine inferior keratic precipitates.

An MRI of the brain and orbits revealed right intraorbital fat stranding, with enhancement of the optic nerve sheath, sclera, and periorbital soft tissues following administration of intravenous gadolinium, sparing the extraocular muscles and optic nerve. As with the first case, serological investigation for specific causes of orbital inflammation was unremarkable (Fig. 2).

The patient was commenced on a weekly tapering course of topical prednefrin forte (1%) starting at three times a day for the mild anterior uveitis, in addition to ibuprofen. After 5 weeks, the patient's orbital signs and uveitis had resolved.

Discussion

With the addition of these two cases, we count 38 reports of bisphosphonate-induced orbital inflammation since the association was initially described in 1999 [2–19]. In 28 of these cases, zoledronate was the responsible agent. Therefore, the purpose of this small case series is not to describe a unique disease, but rather to raise awareness of the association of orbital inflammation, particularly amongst clinicians who might prescribe bisphosphonates as part of their clinical practice. It is an association which is likely under-estimated and may become more prevalent as increasing numbers of patients are prescribed bisphosphonates for an increasing variety of indications.

Orbital inflammation, which may present with any number of variations in tissue involvement, has a wide range of differential diagnoses and should always be appropriately investigated. Overwhelmingly, the three most common etiology are thyroid eye disease (TED), idiopathic orbital inflammatory disease (IOID), and infection. In our academic department, each patient undergoes contrast-enhanced MRI of the orbits, and laboratory investigations for complete blood count, electrolytes, inflammatory markers, thyroid function, viral serology, blood cultures, angiotensin-converting enzyme, and autoimmune screen.

Of the two classes of bisphosphonates, it is only the newer aminobisphosphonates, with a nitrogen side chain, that have been linked with cases of orbital inflammation [20]. At a molecular level, they are associated with gamma-delta T cell–stimulating effects, which the nonaminobisphosphonates do not exhibit [21]. The most recent estimates reported a mean age of presentation with bisphosphonate-induced orbital inflammation of 66.6, with a slight female predominance, and our two cases are in keeping with this [5]. The mean time to symptom onset is 2.9 days, with the most common signs including periocular oedema and erythema, conjunctival

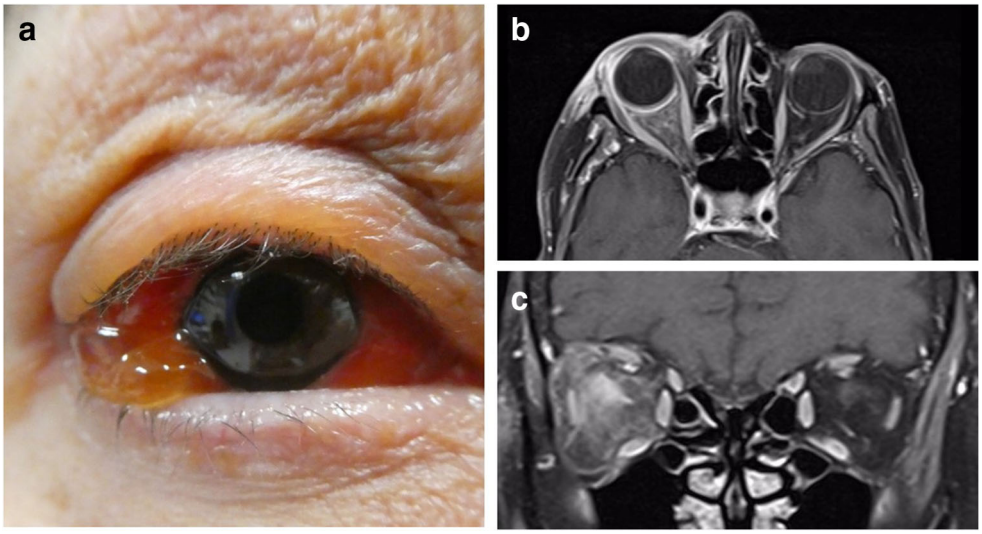

Fig. 2 Case 2. **a** Right-sided conjunctival chemosis with periorbital oedema. **b** T1-weighted, fat-suppressed MRI, axial view demonstrating enhancement of the posterior sclera, retro-orbital fat and optic nerve sheath following administration of intravenous gadolinium, in addition to mild proptosis. **c** T1-weighted, fat-suppressed MRI, coronal view demonstrating enhancement of the right retro-orbital fat following administration of intravenous gadolinium, with sparing of the extraocular muscles

injection and chemosis, and restricted or painful eye movements [5]. In the four cases of oral bisphosphonate use, the mean time to symptom onset is much slower, approximately 19.7 days, reflecting the differing pharmacodynamics and slower onset of drug action [4, 5, 22]. One case has been reported in which a patient was successfully treated with high-dose oral prednisolone for orbital inflammation with myositis 1 day following infusion with zoledronic acid; however, they had no recurrence of inflammation 1 month later when re-challenged with zoledronic acid. Another patient received six doses of intravenous ibandronate without complication, before developing orbital inflammation several hours after switching to zoledronic acid. This suggests that it may be possible to re-trial bisphosphonates if necessary, preferably using a different class [5].

While in both our patients the indication for bisphosphonate therapy was osteoporosis, this association is by no means exclusive to this patient group with a previous review noting 13 out of 29 cases of bisphosphonate-induced orbital inflammation reported in patients without osteoporosis [5]. The alternative indications in these reports included bony metastases, Paget's disease, osteonecrosis of the knee, and Charcot arthropathy [5]. As mentioned above, a thorough laboratory investigation for other causes of orbital inflammation should be performed prior to attributing the diagnosis to bisphosphonate therapy, and an MRI is essential due to the possibility of inflammation eluding detection on CT scan [13]. While not required in our cases, the prompt administration of high-dose corticosteroids appears to be an effective treatment option and should be at least considered depending on severity [2, 5, 20].

The addition of our two cases highlights the importance of recognizing bisphosphonates as a cause of orbital inflammation. The diagnosis is made clinico-radiologically in the presence of orbital inflammation in close temporal association to bisphosphonate administration. With the number of patients prescribed bisphosphonates increasing, it is important for clinicians to be aware of the association and promptly refer patients with suggestive clinical features urgently to an ophthalmologist for appropriate management.

Compliance with ethical standards

Conflict of interest None.

Declaration The content of this submission has not been published or submitted for publication elsewhere.

Declaration of Helsinki The report adhered to the ethical principles outlined in the 2013 amended Declaration of Helsinki.

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