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Zolendronate-associated inflammatory orbital disease

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Abstract

Bisphosphonate infusions are associated with adverse events in approximately a third of patients. Ocular complications are rare and even more so, inflammatory orbital disease. Bisphosphonate-induced orbital inflammation is not a well recognised complication and there have been only a few published case reports of this. We present a case of orbital inflammatory disease associated with zolendronate infusion.

Case report

Our patient is a 62-year-old man with longstanding Type 1 diabetes. He had developed Charcot arthropathy of the right foot as a complication of his diabetes. As part of his treatment, the patient received an infusion of zolendronate. There were no immediate complications.

The following day he developed nausea and bilateral periorbital swelling. Symptoms progressed over the next 48 hours; he experienced blurring of vision and discomfort of his eyes. The patient presented to hospital 4 days after having had zolendronate. On admission he was afebrile. His blood results revealed a normal white cell count, a mildly elevated neutrophil count of 8.2, a normal ESR and a CRP of 95. Thyroid function tests were normal. Examination findings were notable for bilateral periorbital oedema with associated erythema and conjunctival injection. Findings were worse on the left eye.

He denied any preceding head and neck infections. He had no known thyroid disorders or connective tissue disorders. Initial concerns given his comorbidity of Type 1 diabetes were of an underlying infection. Intravenous antibiotics were started prophylactically. Despite antibiotics, there was an alarming progression of the periorbital oedema resulting in complete ptosis of the left eyelid and partial ptosis on the right. There was significant chemosis involving both eyes (worse on the left) with subsequent impairment of extraocular movements. Visual acuity was unchanged from his pre-morbid state; 6/6 on the right and limited to hand movements on the left. Confrontational visual field assessment was normal.

An enhanced contrast CT scan did not show evidence of orbital cellulitis, however it was inconclusive for cavernous sinus thrombosis. The patient was commenced on anticoagulation treatment with intravenous heparin as empirical therapy for the latter condition until it could be fully excluded with further imaging.

An ophthalmology consult was organised. Fundoscopy revealed normal optic discs and no retinal venous congestion. An MRI scan showed normal enhancement of the cavernous sinus. There was evidence of supraorbital soft tissue swelling but no orbital collection. Anticoagulation therapy and intravenous antibiotics were stopped. The

patient made a gradual recovery during the remainder of his hospital stay and was well enough to be discharged home on Day 10.

A clinical diagnosis of an orbital inflammation secondary to zolendronate infusion was made. Inflammation was predominantly pre-septal in this case. Our patient made a full recovery.

Discussion

Bisphosphonates are inhibitors of osteoclast-mediated bone resorption. They now constitute the standard treatment for osteoporosis, Paget's disease of the bone, hypercalcemia of malignancy and skeletal complications of malignancy. There has also been evidence for its use in diabetic neurogenic arthropathy.

The most common adverse effect of intravenous infusions of bisphosphonates is a flu-like syndrome in about 9% of patients.[1] Ocular complications occur less frequently; conjunctivitis is reported to occur in approximately 1%.[1] Uveitis and episcleritis have been reported to occur rarely, in less than 0.01%.[1]

Inflammatory orbital disease resulting from bisphosphonates, occur even more rarely.

There have been a handful of case reports in the literature describing the development of orbital inflammation following both intravenous pamidronate and zolendronate. As of the end of 2009, a literature search we conducted identified 5 reported cases; 3 cases were secondary to pamidronate and 2 cases were secondary to zolendronate.[2,3,4,5]

In all cases, a presumptive diagnosis of orbital inflammatory disease secondary to the bisphosphonate infusion was made based on the close temporal relationship between the infusion and the onset of orbital symptoms. Among the reported cases, the onset of symptoms was within 72 hours of the bisphosphonate infusion and there was a rapid clinical resolution of symptoms with institution of steroids.

The extent of inflammation varies. In this case report, inflammation was restricted to the pre-septal region of the orbit, however both pre-septal and post-septal regions can be involved leading to a greater severity of clinical findings. Asymmetric eye involvement is often the case. Clinical findings include upper and lower eyelid oedema, conjunctival injection, chemosis and impaired extra-ocular movements. Patients frequently experience orbital pain.. There may be deterioration of visual acuity and a relative afferent pupillary defect may be present. Proptosis can also occur. Findings on CT or MR imaging vary across a wide spectrum; from no gross abnormalities to oedema of the soft tissues of the eye, enlarged rectus muscles and extensive pre- and post-septal fat stranding.

The mechanisms underlying this uncommon complication are uncertain. In one study, bisphosphonate stimulated release of cytokines through activated T cells has been demonstrated following a first dose of pamidronate which appeared to correlate with the development of an acute phase reaction.[6] From this observation, it has been postulated that the same mechanism may underlie the development of bisphosphonate-induced inflammatory orbital disease.[2]

Through its proven efficacy, the use of intravenous bisphosphonates is increasing. This case highlights the importance of recognition of this very rare adverse reaction

associated with bisphosphonate infusions. Awareness of this possible complication will lead to improved patient care by minimising unnecessary delay in the diagnosis and through early institution of corticosteroids for symptomatic relief.

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