Bisphosphonate-associated osteonecrosis of the jaw in a Chinese rheumatoid arthritis patient

ML Yip FHKCP, FHKAM (Medicine), WN Lao FHKCP, FHKAM (Medicine), AKM Wong FRCP (London), FHKAM (Medicine), MH Chan FRCP (Edin), FHKAM (Medicine)

ABSTRACT
Osteonecrosis of the jaw is a rare complication of bisphosphonate therapy. For patients receiving bisphosphonates for the prevention of glucocorticoid-induced osteoporosis, this complication has not been reported. We report one such case in a rheumatoid arthritis patient taking risedronate for prevention of steroid-induced osteoporosis.

Key words: Arthritis, rheumatoid; Diphosphonates; Jaw; Osteonecrosis; Osteoporosis; Steroids

INTRODUCTION
Bisphosphonate therapy is recommended for patients on long-term glucocorticoids as a means of minimising osteoporosis and reducing fracture risks.1,2 In patients with rheumatoid arthritis, osteoporosis is even more common due to the disease itself as well as its treatment.3,4 Bisphosphonate-associated osteonecrosis of the jaw is an uncommon but serious complication, which mostly occurs in patients undergoing oncological treatment, but rarely in those with osteoporosis only.5-8 It has not been reported in patients taking bisphosphonates for prevention of steroid-induced osteoporosis. We present one such case in a Chinese rheumatoid arthritis patient using bisphosphonate for the prevention of steroid-induced osteoporosis.

CASE REPORT
A 65-year-old man was diagnosed to have seropositive rheumatoid arthritis since 1996. He had persistent active disease with high levels of inflammatory markers and was treated with non-steroidal anti-inflammatory drugs on a regular basis. Multiple disease-modifying agents including methotrexate, sulphasalazine, hydroxychloroquine, azathioprine, and cyclosporin A had been used to treat him, but were stopped owing to major side effects or lack of response. He was also prescribed prednisolone (10–20 mg daily) for control of his arthritis.

Since 2005, his condition appeared under control on treatment with leflunomide 20 mg daily and prednisolone 7.5 mg daily. As his fourth lumbar vertebra was collapsed and his spine was osteoporotic, risedronate (35 mg weekly) was prescribed with a view to prevent further glucocorticoid-induced osteoporosis.

12 months after bisphosphonate therapy, he complained of fatigue and very poor appetite, despite a relatively static rheumatoid arthritis activity. His haemoglobin level decreased progressively from 12.6 to 9.5 g/dl, his serum albumin fell from 34 to 27 g/l (over 4 months), and he was noted to have a slightly increased body temperature. Leflunomide therapy was terminated. Septic workup yielded nothing. The results of upper endoscopy, colonoscopy and a small bowel enema were all negative except for a small internal haemorrhoid.

He was then noted to have painless swelling of the left lower jaw, which had been present for a few months. A periodontal abscess was revealed, and dental extraction and drainage was performed. The patient continued to have jaw swelling and tenderness after the procedure and developed persistent slightly increased temperature, despite
treatment with amoxicillin for 2 weeks. He also had difficulty in chewing large pieces of food and had to reply on soft diet. A non-healing tooth socket was noted (Figure 1). Magnetic resonance imaging of the mandible showed necrotic bone and micro-abscesses in the non-healing tooth socket. Bone biopsy of the exposed area showed necrotic bone dentritus (Figure 2) and markedly inflamed and granulating marrow tissue and mucosal fragments. Culture from the wound grew Streptococcus milleri and Bacteroides fragillis.

The patient was diagnosed as having bisphosphonate-associated osteonecrosis of the jaw with acute osteomyelitis. Risedronate was discontinued, and an 8-week course of ceftriaxone and metronidazole was given. A dental surgeon performed gentle debridement of the non-healing tooth socket and applied protective covering to the site. The base of the tooth socket was clean, and patient’s haemoglobin and albumin level gradually increased, while appetite and functional status also improved. Leflunomide was resumed for control of his arthritis 1 month later. Despite clinical and biochemical improvement, the tooth socket remained exposed and unhealed after 3 months.
Six months later, granulation began to appear and healing ensued.

DISCUSSION

Bisphosphonates are synthetic analogues of naturally occurring pyrophosphates that have high affinity for hydroxyapatite crystals in the matrix of bone. They are strong inhibitors of osteoclastic activity; most have a long elimination half life and are usually retained in body for years.8

Indications for bisphosphonate use include treatment of osteoporosis, hypercalcaemia of malignant and non-malignant conditions, and less commonly, paget’s disease of bone, and osteogenesis imperfecta in childhood.8 In patients with osteoporosis, bisphosphonates are known to reduce the risk of hip and vertebral fractures.4 Moreover, they are recommended for the prevention of glucocorticoid-induced osteoporosis.1,2

Bisphosphonate-associated osteonecrosis of the jaw was first reported in 2003.9 Before then, dental surgeons often treated the condition as chronic osteomyelitis of the jaw. Since the first description, many more cases have been reported,6,9-12 mostly in association with intravenous use of nitrogen-containing bisphosphonate (pamidronate or zoledronic acid) for patients with myeloma or metastatic bone disease.5,9,10,13 In 2 prospective trials involving more than 500 patients with multiple myeloma treated with either pamidronate or zoledronic acid, 7 to 11% of patients developed osteonecrosis of the jaw after a median interval of 39 months.10,11 In a systematic review, 65% of such cases involved the mandible, 26% the maxilla, and in 9% it involved both the mandible and maxilla.5 The underlying mechanism remains unclear, but could include a complex interplay of bone metabolism, local trauma, increased demand of bone repair, infection and hypovascularity.5,6,13

Additional risk factors for osteonecrosis of the jaw include intravenous, high potency bisphosphonate use, long duration of therapy, old age, and underlying comorbidities, particularly haematological or solid malignancies.5,13,14 Dental disease, dental surgery, oral trauma, periodontitis and poor dental hygiene all predispose to the risk.5,13,14 Chemotherapy and treatment with immunosuppressive agents or corticosteroids are also common risk factors.13,14

Pain is not very common, only two thirds of affected patients experience pain during the course of the disease.5 Our patient did not complain of pain, and the jaw swelling went unnoticed for a few months. Although lack of pain may be a feature, in our patient the use of non-steroidal anti-inflammatory drugs and steroids might also have masked the pain. All these factors could have contributed to a delay in diagnosis. Severe pain can occur when necrotic bone becomes infected after it is exposed. Cultures of the exposed bones may grow Actinomyces, or other oral commensals responsible for the inflammation or osteomyelitis.5,13 In advanced disease, fistula and sequestration may develop, and result in pathological fractures of the jaw and loss of function of the mandible or maxilla. Initial dental radiographs are usually normal.5 Computed tomography, magnetic resonance imaging and bone scans may be useful in early detection and to define the extent of involvement.15

No effective curative therapy is available. The aim of treatment is to control any pain and infection once they develop. Surgical treatment is not indicated in the early stages. In advanced disease, debridement of the necrotic bone and resection may become necessary.6,13

Bisphosphonate-related osteonecrosis of the jaw is rare in non-cancer patients. In an Australian study, its estimated prevalence was 0.01 to 0.04% in those taking weekly doses of oral alendronate.12 It has not been extensively studied in Chinese populations or in Hong Kong, because screening for osteoporosis and prescription of bisphosphonate is not common, and physicians lack awareness of this complication.

In our patient, weekly oral risedronate was started for the prevention of further vertebral collapse while taking long-term steroids. He fulfilled all the criteria of bisphosphonate-related osteonecrosis of the jaw, namely: exposure to bisphosphonates, exposed bones for longer than 8 weeks, and no history of radiation therapy to the maxilla or mandible.13 Our patient had a history of multiple courses of immunosuppressant therapy and disease-modifying anti-rheumatic agents to control rheumatoid arthritis and was taking leflunomide and prednisolone when the disease developed. These agents may all be
associated with the disease, although this has not yet been determined. At the very least, these agents certainly predisposed our patient to subsequent osteomyelitis.

No clinical trials are available to support or refute when bisphosphonate treatment should be discontinued. Nonetheless, because of their anti-angiogenic properties, we decided to cease the treatment in order to promote better healing of the exposed bone. If the main indication for bisphosphonate use is osteoporosis prevention, discontinuation is also recommended. As occurs commonly, our patient had delayed wound healing, and his tooth socket remained exposed and unhealed for a long period, even though he appeared biochemically and clinically clear of infection.

Prevention and regular surveillance is of paramount importance, as there is no specific therapy for osteonecrosis of the jaw. Although the risk is small, physicians should be aware of this complication of bisphosphonate therapy, particularly in patients with rheumatic diseases, in whom glucocorticoids and immunosuppressives may be an integral part of the management. Dental health screening is advised when bisphosphonate therapy is to be started, and regular dental check ups are essential.

References