Strontium ranelate improves delayed healing of osteolytic lesions of the jaw in a man with chronic osteomyelitis.

Case report

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Summary

We report the case of a man with osteolytic lesions of the right mandible due to chronic osteomyelitis, with delayed healing after six months of antibiotic therapy. The patient received off-label therapy with strontium ranelate, with significant radiological improvement of his condition after 3 months.

KEY WORDS: osteomyelitis; jaw; strontium ranelate; bone healing.

Introduction

Chronic osteomyelitis of the jaw is classified according to the Zurich Classification in two major categories: chronic primary (aseptic) and chronic secondary osteomyelitis (1). Chronic secondary osteomyelitis is the most common type, usually caused by bacterial invasion from a contagious focus (tooth or pulpal infections, periodontal diseases, extraction wounds, infected fractures) (1). Although mostly described as a sequel of acute osteomyelitis, the clinical presentation of chronic osteomyelitis may show a great variety. Pus, fistula, and sequestration are typical findings of the acute clinical phase, but with chronification of the disease, most symptoms such as pain and swelling are usually less extensive. In cases where the acute phase was clinically silent, chronic osteomyelitis may present with little clinical findings, thus con-

stituting a diagnostic dilemma (1). Radiographically, the main feature of osteomyelitis is osteolysis, starting as early as 10 days after the infection, although forms of sclerosing osteomyelitis have also been described in some occasions (1). Bone biopsy including cultures of tissue samples is the best modality in order to confirm the diagnosis, and antibiotic therapy alone, or in combination with surgical debridement are the basic principles of therapy (1). The outcome of acute or chronic osteomyelitis of the jaw is documented scarcely in the literature. When surgery is performed, systematic or local antibiotic therapy is continued for 1-2 months and early signs of radiological improvement usually present within this time frame (2). Follow-up period according to various authors varies from 6-18 months, and success rates vary according to different cases and treatment regimes (1, 2).

Strontium Ranelate (SrRan) is currently approved for the treatment of severe osteoporosis in postmenopausal women and in men with increased risk of fracture in numerous countries; 2g of SrRan per os daily have been shown to reduce risk of vertebral and non-vertebral fractures in postmenopausal women with osteoporosis, with or without prior fractures (3-6). The effect of SrRan on bone formation and bone resorption has been a matter of longstanding debate; data from preclinical studies, either in cell cultures in vitro or in animals, suggest that SrRan stimulates osteoblastogenesis and osteoblast activity and reduces osteoblast apoptosis, while also decreasing osteoclastogenesis and osteoclast activity and increasing osteoclast apoptosis (7-10). Data from most clinical trials with biochemical markers of bone turnover in the osteoporosis field suggest that SrRan mildly increases bone formation while simultaneously decreasing bone resorption (5, 6, 11). However, recently published data from a study with paired iliac crest biopsies in women with postmenopausal osteoporosis suggest that SrRan has little effect on bone resorption while decreasing bone formation after 6 or 12 months of treatment (12). Nonetheless, data from clinical trials have shown that SrRan is beneficial for the architecture and strength of bone (11, 13, 14). Few case reports in humans with delayed healing of fractures have suggested beneficial effects of SrRan in the process of bone healing (15-17), but to our best of knowledge, no published data are available concerning osteolytic lesions of bone due to osteomyelitis in humans.

We present the case of a man with chronic osteomyelitis of the right mandible, with delayed healing of osteolytic lesions following treatment with antibiotics, who received off-label therapy with SrRan with marked radiological improvement of his condition within 3 months.

Case report

A man, 46 years old, Caucasian and of Greek origin was referred for consultation after having been conservatively treated for secondary chronic osteomyelitis of the right mandible

for 6 months. The patient reported onset of symptoms 5 years prior to referral, following a simple dental procedure (root canal aponeurosis) with pain and oedema over the jaw (right mandible) and pus that lasted only 3-4 days after the procedure. He was initially treated by his dentist with oral antibiotics (cefaclor + clindamycine hydrochloride) and non-steroid anti-inflammatory drugs (NSAID's) for 10 days. Initial improvement of symptoms was soon followed by recurrent episodes of pain and swelling without pus, or fistula or exposed bone in the oral cavity, treated symptomatically with NSAIDS. Panoramic dental X-ray at that time was reported to be normal, as were laboratory findings including white blood cells count (WBC), Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP). The patient had no previous history of systematic serious infections and had never been hospitalised for any reason. Previous history consisted only of skin lesions of the palms and soles at the age of 40 that were regarded as "psoriasis-like" by a dermatologist, and were treated with topical solutions with complete remission. He reported no joint pain or diagnosis of arthritis in the past, had no history of fractures or known bone metabolic disorders and was a smoker for 25 years (20 cigarettes per day). Upon presentation at the 4th Internal Medicine Department of our hospital he had pain, tenderness and swelling over the right mandible but without pus, fistula or exposed bone. His laboratory findings presented evidence of inflammation: White Blood Cells (WBC)= 12,400 (normal range 4,000-10,000), Erythrocyte Sedimentation Rate

(ESR)= 45mm/1st hour (normal range<20), C-Reactive Protein (CRP)= 2.05 (normal range<0.5), Alkaline Phosphatase (ALP)=76 U/L (range 40-129). The panoramic x-ray revealed osteolytic lesions of the right jaw and bone scanning with Tc 99m revealed increased uptake of the right mandible and sternoclavicular joints (Figure 1). Although the patient had no clinical evidence of synovitis or arthritis of the sternoclavicular or any other joints, and presented with distinct radiological appearance of lytic lesions without sclerosis, due to his previous history of skin lesions of palms and soles, SAPHO syndrome (Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis) was considered for differential diagnosis, as it often also affects the mandible (1). A bone biopsy was thus performed in order to obtain cultures from the lesions of the right mandible, and *Streptococcus Salivarius* was identified as the pathogen. Due to the extent of the osteolytic lesions and the complexity and possible complications of the surgical procedure that would be needed to address the problem, conservative therapy was proposed. The patient received levofloxacin per os for 6 months, with improvement of the clinical symptoms and remission of laboratory findings. After having completed 6 months of therapy with antibiotics, a CT scan of the jaw was performed, and delayed healing of the osteolytic lesions of the right mandible was diagnosed (Figure 2). The patient was then referred to the Bone Metabolic Unit for consultation in order to exclude the co-existence of a bone metabolic disorder, as well as with the question of locally compromised bone strength and possible susceptibility

Figure 1 - A. Panoramic x-ray of the patient upon presentation at the Internal Medicine Department of our hospital. B. Bone scanning with Tc 99m at the time of diagnosis.

Figure 2 - CT scan of the right mandible after 6 months of treatment with antibiotics.

to low energy fracture of the right mandible. Laboratory findings at the time of consultation consisted of: Osteocalcin=14.8 ng/ml (range 11-46), ALP=67 U/L (40-129), serum beta Cross Laps= 0.196ng/ml (<0.580), Parathyroid Hormone = 17.4 pg/ml (15-65), serum Calcium=9.4mg (8.2-10.2), serum Phosphorus= 4.6mg (2.5-5.0), 25 (OH) vitamin D= 18.7 ng/ml, WBC= 10,000, CRP=negative, ESR=25mm. Dual Energy X-Ray Absorptiometry (DXA) of the Lumbar Spine revealed normal Bone Mineral Density with T- score=-0.6 (Z-score=-0.8). To optimize levels of vitamin D, although clearly they were not indicative of osteomalacia, the patient was prescribed cholecalciferol 800 IU per day along with 1000 mg of Calcium. A bone agent used in the osteoporosis field was then considered in order to promote bone healing; clinical relevant data at the time were not existent with the exception of few case-reports of bisphosphonate-related osteonecrosis of the jaw treated with teriparatide (18, 19). Since off-label therapy with teriparatide was expensive and would not be re-embursed by the patient's social security, we proposed off-label therapy with Strontium Ranelate, with the hypothesis that SrRan would decrease osteoclastic activity at the site of the lesions as well as possibly enhance osteoblastogenesis locally. The patient provided informed consent and commenced therapy with SrRan 2g per os daily, was re-evaluated clinically on a monthly basis and then given a new prescription. Since his first monthly visit, he reported even more pronounced improvement of his condition and no side-effects from SrRan. After 3 months of therapy with SrRan, we proposed a new CT- scan of the jaw, that showed marked improvement of the osteolytic lesions (Figure 3). The patient returned for monthly evaluations for another 4 months, and then decided to discontinue therapy, as he considered his medical condition to be resolved.

Discussion

In the present case report, therapy with SrRan 2g per os daily improved delayed healing of osteolytic lesions in a man with chronic osteomyelitis of the jaw within 3 months.

Chronic mandibular osteomyelitis represents a diagnostic and therapeutic challenge, and healing of bone lesions is under-reported. In cases due to bacterial infection, antibiotics alone or in combination with various surgical procedures are considered the treatment of choice (1). When SAPHO syndrome is suspected, notably in cases of sclerosing osteomyelitis, bisphosphonates as well as corticosteroids have been rarely reported as additional therapy (20). It is also well known that teriparatide has been used in several cases of bisphosphonate-related osteonecrosis of the jaw with positive results (18, 19). In the case of our patient, while SAPHO syndrome was also suspected, the precipitating event of a dental procedure that was complicated with infection seemed to provide the most plausible explanation for his condition. Indeed, bone biopsy revealed a low-grade infection from *Streptococcus Salivarius* and the prevailing radiological appearance was one of extensive osteolysis, that was still present after 6 months of antibiotic therapy. When considering a bone agent in order to promote bone healing, we hypothesised that a drug that would decrease bone resorption locally while maintaining or promoting adequate bone formation at the site of the lesions could be beneficial. Teriparatide, that would promote bone formation by promoting osteoblastogenesis, was ruled out of the question mainly on the basis of cost as it would not be reimbursed by the patient's social security. SrRan seemed to represent a plausible solution in the setting of bone healing for our patient, since it could be speculated, based mainly on preclinical models (7-10), that it would decrease further bone resorption locally by affecting the osteoclasts and possibly promote differentiation of prodromal cells of the osteoblastic lineage that would populate the bone lesions to osteoblasts. Indeed, in the setting of fracture healing, which is quite different than that of postmenopausal osteoporosis, data in animals suggest that SrRan may be beneficial as it is associated with improved bone microstructure, callus volume and biomechanical properties (21-23). Few case-reports in humans have also shown a positive effect of SrRan on fracture-healing either on atypical subtrochanteric fractures or fractures of the wrist or femur (15-17). Finally, published data from paired iliac crest biop-

Figure 3 - New CT-scan after 3 months of therapy with SrRan showed considerable improvement of the lesions.

sies suggest no deleterious effects from the incorporation of strontium in newly formed bone, and no effect on bone mineralisation either (24, 25).

The main limitation of our study is that we have practically no way of knowing how soon would the osteolytic lesions begin to heal in our patient had we not attempted therapy with Strontium Ranelate, or whether he would have experienced a fragility fracture of the right mandible during that time. However, the osteolytic lesions as proven by the computed tomography scans were poorly improved after 6 months of therapy with antibiotics, and marked improvement was noted after only 3 months of treatment with SrRan. It must also be noted, that the patient reported perfect clinical condition during therapy with SrRan, and that he decided on his own to discontinue therapy after a total of 7 months, because he regarded his medical condition to be resolved. He has been free of symptoms and in excellent overall health for more than a year ever since.

We conclude that, following antibiotics, off-label therapy with SrRan was helpful in improving delayed healing of osteolytic lesions of the jaw in this male patient with chronic osteomyelitis

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