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Bisphosphonate-associated osteonecrosis of the jaw: A key role of inflammation? ☆

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ABSTRACT

Osteonecrosis of the jaw (ONJ) can be associated with nitrogen-containing bisphosphonates (NBPs) therapy. Various mechanisms of NBP-associated ONJ have been proposed and there is currently no consensus of the underlying pathogenesis. The detailed medical and dental histories of 30 ONJ patients treated with NBPs for malignant diseases (24) or osteoporosis (6) were analyzed. The necrotic bone was resected and analyzed histologically after demineralization. In 10 patients the perinecrotic bone was also resected and processed without demineralization. Alveolar bone samples from 5 healthy patients were used as controls. In 14 ONJ patients, serial technetium-99m-methylene diphosphonate scintigraphic scans were also available and confronted to the other data. Strong radionuclide uptake was detected in some patients several months before clinical diagnosis of ONJ. The medullary spaces of the necrotic bone were filled with bacterial aggregates. In the perinecrotic bone, the bacteria-free bone marrow characteristically showed an inflammatory reaction. The number of medullary inflammatory cells taken as an index of inflammation allowed us to discriminate two inflammation grades in the ONJ samples. Low-grade inflammation, characterized by marrow fibrosis and low inflammatory cells infiltration, increased numbers of $TRAP^+$ mono- and multineacleated cells was seen in patients with bone exposure <2 cm^2. High-grade inflammation, associated with larger lesions, showed amounts of tartrate-resistant acid $phosphatase^+$/$calcitonin\ receptor^-$ mono- and multinucleated cells, osteocyte apoptosis, hypervascularization and high inflammatory cell infiltration. The clinical extent of ONJ was statistically linked to the numbers of inflammatory cell. Taken together these data suggest that bone necrosis precedes clinical onset and is an inflammation-associated process. We hypothesize that from an initial focus, bone damage spreads centrifugally, both deeper into the jaw and towards the mucosa before the oral bone exposure and the clinical diagnosis of ONJ.

Introduction

Postmenopausal osteoporosis, Paget's disease, and metastatic bone diseases are characterized by high bone turnover. One of the most efficient ways to treat these affections is the use of bisphosphonates. Among them nitrogen-containing bisphosphonates (NBPs) are the most potent in inhibiting bone resorption [1]. Osteonecrosis of the jaw (ONJ) associated with NBPs therapy is a recently described detrimental effect first reported in 2003 [2]. ONJ is characterized by an area of exposed bone in the maxillofacial region that does not heal within 8 weeks, in a patient who has no metastasis or radiation therapy in the craniofacial region [3]. High repeated doses of NBPs administered intravenously to cancer patients, are most frequently associated with ONJ [4–6]. In contrast, patients receiving oral NBPs for osteoporosis are less prone to ONJ [7].

Various mechanisms of NBP-associated ONJ have been proposed. It is generally admitted that this adverse effect targets the jaws because they concentrate NBPs owing to their high bone turnover compared with other anatomical sites [8], and bisphosphonate toxicity on osteoclasts [9]. It has also been proposed that NBPs may have an antiangiogenic effect, reducing blood flow and thus inducing bone cell necrosis and apoptosis [10,11]. One alternative explanation is an "outside-in" process in which mucosal damage provides oral bacteria with access to the underlying bone, leading to bone infection and necrosis [12]. NBP soft tissue toxicity would thus be the trigger leading to necrosis of the mucosa and bone [13–15]. Genetic variations may also constitute a risk factor; it was recently shown that ONJ is associated with gene polymorphisms in multiple myeloma patients [16,17]. Moreover, the primary disease is probably a predisposing factor as frequency of ONJ is 2 fold higher in multiple myeloma than in breast

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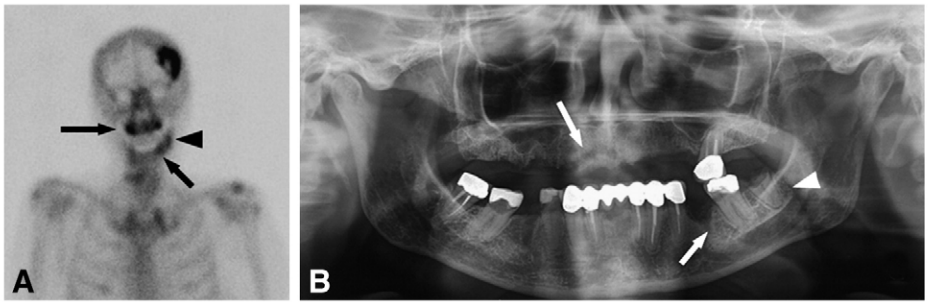
Patient 1



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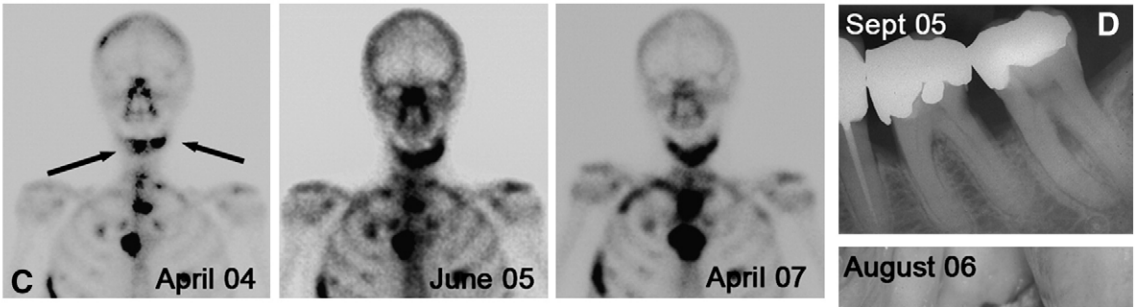

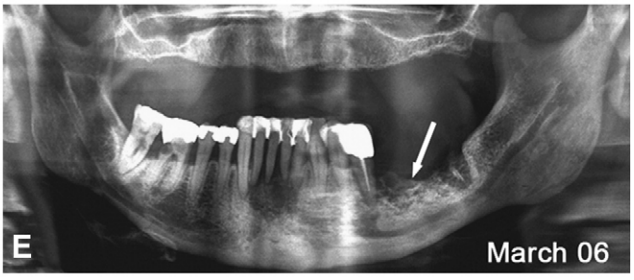

Patient 3