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SHORT COMMUNICATION

Spontaneous bisphosphonate–related osteonecrosis of the left hemi-mandible: Similarities with phossy jaw

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ABSTRACT

Intravenous bisphosphonates (BP) play a key role in the treatment of bone metastases. As a long-term side effects BP, a form of avascular osteonecrosis of the jaw has been reported. Although, invasive oral local procedures are often present in clinical history of patients suffering from bisphosphonates-related osteonecrosis of the jaws (BRONJ), about up to 50% of BRONJ are spontaneous. We report a case of a 68-year-old female with a spontaneous wide bone sequestration of the left mandibular body onset after infusion of zoledronic acid for 18 cycles for osseous metastasis due to metastatic anaplastic thyroidal carcinoma. Surprisingly the clinical aspects of the patient initially reminded us of the famous pathology described in 1899 called *phossy jaw*. This case is remarkable not only for the spontaneity of the osteonecrosis, but, above all, for the clinical similarity with cases of *phossy jaw*, described for the first time in the literature, thereby suggesting a potential common pathogenesis.

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CASE REPORT

A 68-year-old Caucasian female was referred from the Oncology Department to the Maxillo-Facial Surgery Department in January 2009 for the evaluation and treatment of mandibular osteonecrosis. She had been diagnosed with metastatic anaplastic thyroidal carcinoma with multiple lung and osseous metastasis without any involvement of the jaw; comorbidity included only arterial hypertension. The patient had undergone a total thyroidectomy and received chemotherapy with combination of cisplatin (CDDP) 60 mg/m2 and epirubicin (EPI) 75 mg/m2 every 3-4 weeks. She had also undergone a monthly 4-mg infusion of zoledronic acid for 18 cycles and an antalgic therapy had also been performed.

The patient was referred for us for observation due to the intense pain experienced during chewing and swallowing following laceration of the left side of the tongue by the sharp edges of the left, exposed mandibular bone. During anamnesis, the patient referred that the pain in the left mandibular region appeared in July 2007, but no medical consultation was asked by the patient; it was apparently spontaneous and the patient had no dental treatment during the period of the infusion of zoledronic acid. The painful symptoms and the alleged osteonecrosis were never subjected to any medical treatment until January 2009. While being physical examined, the patient appeared partially obnubilated, with an asymmetrical face with moderate swelling of the tissues in the left emi-mandibular region. *Foetor ex ore* was also observed. The clinical aspects of the patient initially reminded us of the famous pathology described in 1899 in workers exposed to white phosphorus and called *phossy jaw* [Figures 1a and 2]. An intraoral examination revealed a wide exposure of the left emi-mandibular body, which was freely mobile protruding from the mouth [Figure 1b].[1]

The patient underwent various radiological tests and a chest X-ray revealed macro- and micro-nodular opacities in both lung fields, which were subsequently reported as metastatic lesions. Maxillofacial computerized axial tomography with tridimensional reconstruction revealed a wide bone sequestration of the left mandibular body with, extending from the neck of mandibular condyle to the symphysis, to include the coronoid process and a lacunar area with a well-defined margin in the upper left

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parietal region [Figure 3]. After an intravenous antibiotic prophylaxis and under local anesthesia, thought a buccal approach a sequestrectomy followed by a curettage of the residual cavity with the removal of the other small bone fragments of size <1 cm were performed [Figure 2]. The histopathological examination of the specimen demonstrated bone necrosis with no evidence of metastatic disease. Due to the probable release of bacterial toxins, the patient showed a worsening state of obnubilation, leading to torpor and lethargy for about 4 hours after surgery, followed by a spontaneous resolution with an improvement in the clinical conditions. After two days the patient was discharged and after a 2-month period of follow-up, no further regions of necrosis were detected.

DISCUSSION

Bone metastases are one of the major causes of morbidity in patients with breast, prostate, lung, renal and thyroidal cancer. From their first introduction in 1995,[2] intravenous bisphosphonates (BP) have played a key role in the standard treatment for metastatic disease spread to the bone from solid cancers, in treatment of multiple myeloma and management of malignant hypercalcemia. For BP it has been demonstrated they have a favorable impact both on the natural history of the disease and the quality of life, decreasing pain and skeletal-related events. In addition to well-known side effects (such as a flu-like syndrome, alterations in creatinine and hypocalcemia), the use of BP has also been linked to the development of a particular form of avascular osteonecrosis of the jaw as a long-term complication and called bisphosphonate-related osteonecrosis of the jaws (BRONJ).[2,3]

Although the first description of BRONJ was ascribable to Marx and Stern in 2002,[4] BRONJ may be considered an analogous to the historically-documented, occupational industrial disease recognized more than 100 years earlier and called phossy jaw.[5] This term was referred to a nonhealing bone exposures, localized only in the mouth, which had been caused by exposure to white phosphorus during the manufacture of matches.[1,5] The first case series was reported in Vienna in 1845 and, of the 22 cases analyzed, approximately 11% of those exposed to white phosphorus developed the disease. In that pre-antibiotic era, phossy jaw was fatal in about 20% of cases, usually due to septicaemia or meningitis. In 1910, in the United States, John Andrews published a report of 150 cases of phossy jaw from 15 of 16 match factories then in operation.[1,5] Thereafter, the substitution of white phosphorus with an amorphous red phosphorus, which did not possess the toxic properties of white phosphorus, reduced the incidence of jaw osteonecrosis.[1,5]

After many years, the use of BP in medicine coincided with the onset of a disease, which was clinically similar to phossy jaw, and termed BRONJ. Likely, in order to emphasize the common etiology and the clinical similarity between the two historically distinct clinical entities, for the new entity the terms osteochemonecrosis or bis-phossy jaw were also used. As regards phossy jaw chronic daily exposure to airborne phosphates in miners was probably able to cause an accumulation of phosphorus compounds in the

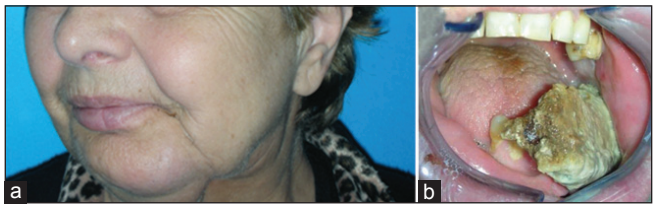

Figure 1: (a) The patient appeared with an asymmetrical face with moderate swelling of the tissues in the left emi-mandibular region. The clinical aspect of our patient was similar to the necrosis of the jaws observed in workers exposed to white phosphorus and so called phossy jaw[1]; (b) the intraoral examination revealed a wide exposure of the left emi-mandibular body, which was freely mobile protruding from the mouth

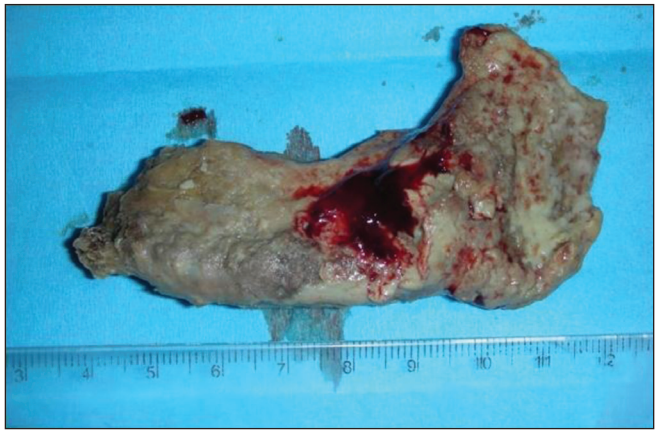

Figure 2: The wide bone sequestration of the left mandibular body obtained after sequestrectomy remembering the phosphorus necrosis of entire lower jaw excised by Mr McCarthy in 1884 (London Hospital Medical College Museum)[1]

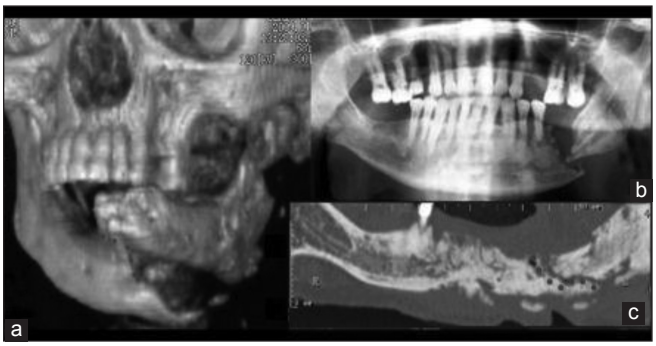

Figure 3: (a) Maxillo-facial computerized axial tomography with tridimensional reconstruction. Wide bone sequestration of the left mandibular body with, extending from the neck of mandibular condyle to the symphysis, to include the coronoid process. (b) Panoramic X-ray of the jaws and (c) Computed tomography of the mandible revealed bone sequestration and the fracture line (see red point) of the left hemi-mandible

bone, inducing the same clinical picture as today related to the medical use of BP. In particular, the explanation for the similarity between the two conditions can be found in the chemical features, because white and yellow phosphorus molecules [P4O10] react with [H2O] and [CO2] (continuously produced, introduced and expelled during respiration), and with common amino acids (i.e., lysine) in humans to produce a powerful amino-BF, which is comparable to modern pamidronate or alendronate.

Today, the etiology of BRONJ remains still unknown and the multi-factorial pathogenesis is related to many local or general factors, including the impairment of local immunity of the jaw bone, the suppression of bone turnover, the inhibition of angiogenesis, the BP toxicity to soft tissues, the direct BF toxicity to bone, and fungal or bacterial infections.[4,6]

It is a clear evidence that the most reported risk factors for the development of BRONJ are the assumption of BP, and in particular the potency and the route of administration of BP (0.01-0.04% for oral BP vs 0.8-12% for intravenous BP)[4] associated with an history of tooth extractions or other dento-alveolar surgical procedures; but in the last 3 years there has been an increasing observation that over 40% of BRONJ are spontaneous or at least non-surgery triggered.

In many of these latter cases, it is impossible to consider the connection with dental diseases (periodontal and/or endodontic infections), local trauma (i.e., poor-fitted dentures), poor oral hygiene or anatomical abnormalities which act on a jaw bone made susceptible by BP.[4,6]

The anti-angiogenic activity and the excessive reduction bone turnover induced by BP remain the two main mechanisms which may predispose jaw bones to osteonecrosis. The alteration of the angiogenesis in newly formed hard and soft tissues may have important effects on the quality and quantity of bone perfusion, resulting in an impaired response of osseous tissue to surgical intervention, local trauma and infections.[3] Any wound connected to endodontic or periodontal infection or denture trauma may expose the edentulous ridge of the mandibular and maxillary bones, made more susceptible by the assumption of BP, to a micro-organism infection with higher risk to develop a BRONJ, which may clinically mimic and so be misdiagnosed, at least in its initial phases, with a dental disease and eventually later treated with a tooth extraction.[4] The result appears as a non-healing postextractive site diagnosed as BRONJ.[4]

Hence, on the basis of these considerations and according to the experts' opinion, it is possible that the first changes in the jaw bones induced by BP may have already developed before surgical procedures are performed, being these latter a possible consequence of a pre-existing BRONJ and not a precipitating factor.[6]

Although BRONJ usually may manifest itself with exposed necrotic bone, associated or not with suppuration and pain, more recently there have been reported cases of BRONJ without bone exposure, at least in their early stages. This variant of BRONJ may be characterized by pain, sinus tract, tissue swelling which could precede of weeks or months the onset of frank bone exposure.[7] The case reported is remarkable not only for the spontaneity of the osteonecrosis, unrelated to any invasive local procedure, but, above all, for the clinical similarity with cases of phossy jaw [Figures 1a-b and 2],[1] thereby evocating a potential common pathogenesis.

Despite the fundamental role of BP in the management of serious diseases and their complications, it is extremely important to consider the existence of this long-term complication which can be often difficult to manage. Furthermore, due to the BP antineoplastic properties, their use will probably increase in the future, and thus the education and collaboration among the specialists involved (e.g., dentists, maxillofacial surgeons and oncologists) is crucial to preventing and eventually treating this devastating condition.

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