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Metastatic prostate adeno-carcinoma and Paget's bone disease of the mandible

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Summary

Prostate cancer is the most common non-cutaneous malignant lesion in males over 70 years of age. Diagnosis in advanced stages of the disease is not exceptional, through metastatic lesions as debut. The most characteristic of these lesions are osseous with osteoblastic behavior, uncommon in maxillary bones. On the other hand, Paget's disease is a chronic metabolic disorder attributed to osteoclast dysfunction. At the craniofacial level, the characteristic affectionation is an increase in size, a "cotton flakes" pattern or circumscribed osteoporosis. The fact that this is only located in the mandible is exceptional. A case of Paget's disease of the right hemi-mandible bone is presented in which a metastasis is developed due to prostatic adenocarcinoma.

Key words: *Paget's bone disease, osteitis deformans, prostate cancer, metastasis, oral neoplasms.*

Introduction

Prostate cancer (PC) is the most common non-cutaneous malignant lesion in men over 70 years. There is genetic predisposition and several exogenous factors have been proposed, but without sufficient evidence to recommend lifestyle changes that might prevent PC. Screening programs are controversial, by digital rectal examination and prostate-specific antigen (PSA) levels, with individualized strategies suggested based on the risk profile. The eco-guided biopsy is standard for diagnosis, corresponding in more than 95% of cases to acinar cell adenocarcinoma¹.

On the other hand, Paget's disease of bone (PDB) is a chronic condition of unknown cause due to osteoclast dysfunction, with increased bone remodeling that triggers bone growth and disfigurement. It presents genetic susceptibility, is more predominant in Caucasians, slightly more frequent in males and exceptional in individuals under 40 years. No cure has been found, although bisphosphonates are usually prescribed depending on metabolic activity and symptomatology²⁻⁵.

Clinical Case Report

A 77-year-old man, ex-smoker of 20 packs per year, ex-drinker of 7 units of standard drink/day until 2 years previous, and with a history of high blood pressure, ischemic stroke and intervening left carotid stenosis. His treatment was standard with atorvastatin, valsartan, hydrochlorothiazide and clopidogrel reported. He was diagnosed with stage IV prostate adenocarcinoma Gleason 3+4, with PSA values of 110.47 ng/mL and alkaline phosphatase (FA) of 142 U/L initially, and bone metastases in vertebrae C7 and D1. The serum levels of calcium, phosphorus and parathyroid hormone were within normal limits and treatment began with complete androgen blockade. After 19 months, he presented right hemifacial swelling, with bulging of both cortical of the ipsilateral mandible branch (Figure 1) and without ulceration of the oral mucosa upon examination. The pathological anatomy provides a new diagnosis of PDB in mixed phase, without data suggestive of malignancy (Figure 2). There is no suspicion of involvement in other skeletal regions.

He did not receive treatment for symptomatic stability until 11 months later, when the maxillofacial clinic is accentuated. Radiologically, sclerotic intensification with mandibular bone growth, soft tissue increases in masticatory space, as well as lymphadenopathies in right cervical Ia and Ib levels (Figure 3). A new submucosa biopsy of soft tissues and bone showed fibrous tissue with changes of sclerosis and intense artifact, with infiltration by malignant cells of epithelial aspect positive for CK, AE1/AE3 and PSA. In addition, he is diagnosed with a new bone metastasis at the level of the left iliac blade. Chemotherapy is ruled out, and two doses of 20 Gy of radiotherapy are applied with an antalgic intention in the jaw and pelvis.

After 9 months, in a control bone scan, new metastatic foci are seen in right orbit, ribs on both sides, sacral column, left humerus, both scapulae and right femoral diaphysis. He underwent surgery with intramedullary rod for femoral neck fracture. The patient died 46 months after the initial oncological diagnosis, following prolonged bed rest at home.

Figure 1. Orthopantomography. Irregular sclerosis of right hemimandible. Widening of adjacent periodontal spaces

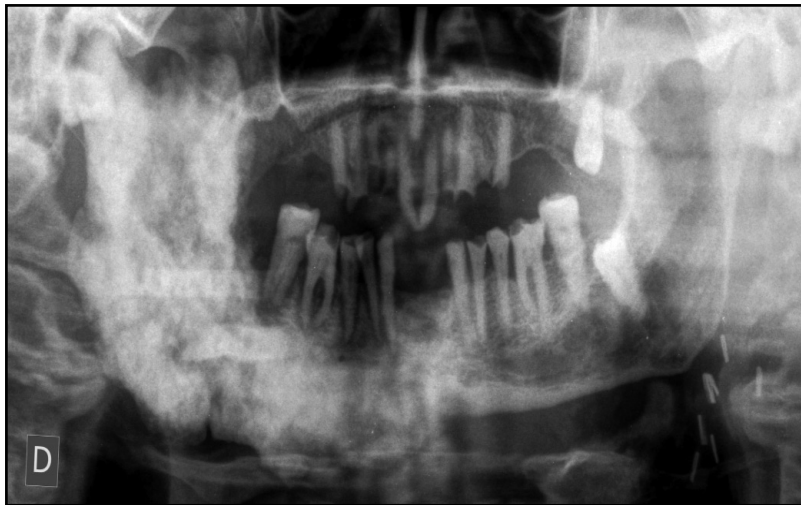
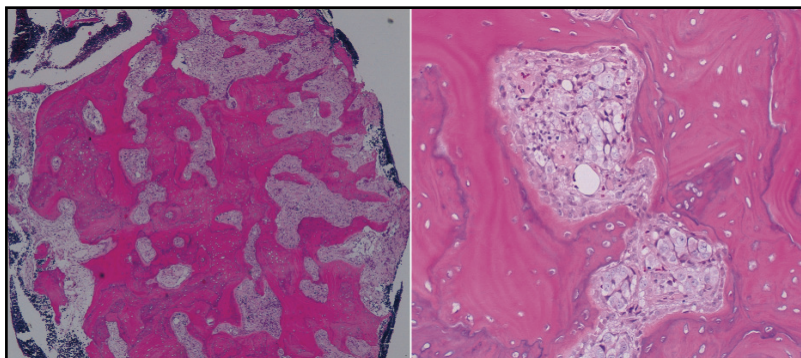


Figure 2. Hematoxylin & Eosin 10x, 200x. Loss of demarcation between cancellous and cortical bone. Hyperostosis with mosaic pattern, increased bony trabeculae and prominent basophilic lines. Multinucleated osteoclasts and isolated eosinophilic intranuclear inclusions. Bone marrow with fibrous stroma



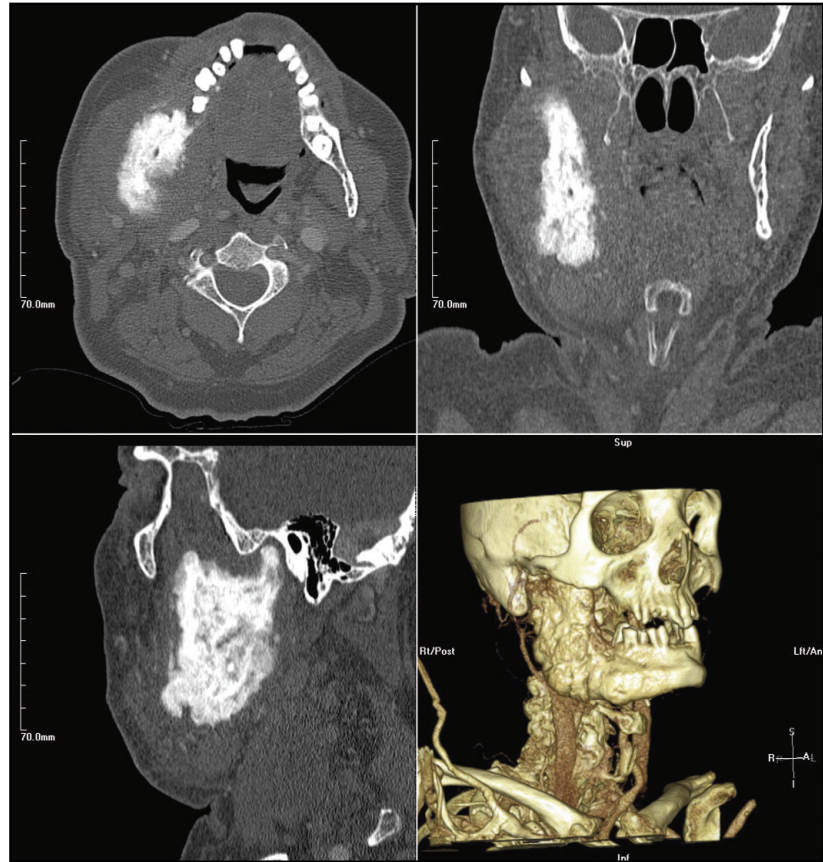
Discussion

According to the literature, 3% of intraoral malignant lesions correspond to metastasis. The most frequent regions affected are the mandible in the molar area, with its rich vascular supply and a remnant of bone marrow in adults and the gum adhered to soft tissues. In many cases, these are late complications of advanced malignant disease with multiple visceral metastases, although up to 25% of cases are the first manifestation. Globally, the most common primary cancers in the maxillary bones are those of the breast, while in soft tissues they are those of the lung. In males, maxillary metastases of prostatic origin correspond to 11%, versus 1.5% in soft tissues. Inflammation, pain, sensitive alterations of relatively rapid evolution, or a bleeding exophytic hyperplastic lesion are usually the usual symptoms, which can easily be misinterpreted as benign pathology. The histology may simulate primary intraoral neoplasms, especially those poorly differentiated originating in salivary glands, requiring additional immune-histochemical and molecular techniques^{6,7}.

In cases of PC, the Gleason scale allows, together with the TNM staging, to establish risk groups. To assess the locoregional extension, magnetic resonance is generally employed, while for remote extension, computed tomography and bone scintigraphy are used, where the most characteristic metastases are located¹. PC cells frequently secrete factors that promote bone formation, such as bone morphogenic proteins (BMPs), and RANK-L inhibitors, attenuating osteoclastic action⁶. Therefore, most metastases will be osteoblastic although they have also been reported in a mixed, osteolytic form, even without radiological evidence. As with other mandibular neoplasms, diagnosis is not unusual after pain or paresthesia-hypoesthesia of the inferior dental nerve that does not improve after dental treatments⁸⁻¹¹. They have not only been reported at mandibular level, but also in branches¹², condyles¹³ and parotid glands with bone infiltration¹⁴.

The number and location of bone metastases in PC are among the most commonly used but not validated prognostic factors, in addition to visceral metastases, the Gleason score, PSA and AF. The usual management is androgen blockade combined or not with chemotherapy. The prescription of

Figure 3. Computerized tomography. Axial, coronal, sagittal and 3D. Cortico-medullary sclerosis with soft tissue enlargement surrounding the right hemimandibular branch.



bisphosphonates, radiotherapy, even cytoreductive surgeries or metastasectomies to improve quality of life is recognized for palliative purposes¹.

As for PDB, the location is segmental, monostotic or polyostotic, most common in the pelvis, femur, spine, skull and tibia, although it can affect any bone and may present with pain, arthralgias and compression syndromes. There is an increased risk of fracture and malignancy. It is asymptomatic in many cases, carrying out the diagnosis when complications appear or characteristic radiological images. The Paget-affected bone presents vascular alterations, with regional vasodilatation, which could increase cardiovascular risk. The bone scan allows us to assess the extension. In the active phase of the disease, though not a specific datum, serum FA increases along with other replacement markers. Histology usually shows a mosaic pattern, with areas of osteoclastic and osteoblastic activity. Multinucleated osteoclasts and cytoplasmic or intranuclear inclusions are more typical of the initial rest phase. In addition, it presents with bone marrow fibrosis and arteriovenous shunts³⁻⁵.

Increased cranial size, a "cotton flakes" pattern or circumscribed osteoporosis, are the most characteristic findings at the head level of the PDB, with singular mandibular involvement considered exceptional. The teeth erupt mispositioned and migrate with bone growth, showing in radio-

graphs both radiolucent areas as of hypercemen-tosis or ankylosis of roots. In these cases, the extractions are complex, alveolar healing is slow with localized osteitis, and there is an increased risk of secondary osteomyelitis. Loco-regional sur-gical remodeling has its role, and additional pre-cautions should be taken to control haemostasis and infections with optional oral surgery^{5,15,16}.

Bisphosphonates slow the differentiation of common precursor cells, promote apoptosis and suppress bone resorption by osteoclasts, hence their indication in active PDB and in symptomatic bone metastases. They also have anti-angiogenic properties and a half-life of up to 11 years after bone incorporation. Before starting treatment, whatever the disease and route of administration, a dental examination and extraction of periodon-tal teeth on or adjacent to the lesion, in order to prevent osteonecrosis are recommended^{2,17-19}.

The main differential diagnoses of craniofacial PDB are fibrous dysplasia and fibro-osteomas⁵. In the present case, as there was a recent change in the lesion with a soft-tissue component, sarcoma-toid malignancy would also be included, with osteonecrosis being less likely due to the lack of a history of bisphosphonates, anti-angiogenesis and radiotherapy. However, due to the vascular altera-tions and the compromised scarring of the Pagetic bone, spontaneous osteonecrosis could be trigge-red²⁰. Although the patient developed unfavorably, it has been shown that PC and PBD association delays metastatic progression and increases ove-rall survival²¹.

Conclusions

Metastatic PC is not uncommon in our setting, with a high survival rate. The mandibular location of this oncological or other lineage is a challenge for both clinicians and pathologists. Occasionally, the overlap of bone disease can hinder diagnosis even more, highlighting metabolic disorders, both training and recovery, and the side effects of the-rapies, such as osteonecrosis.

Conflict of interests: The authors declare no con-flicts of interest.

The precepts of the Helsinki declaration on clinical studies have been observed throughout this rese-arch work.

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