Unique and rare bone metastases from occult primary cancer.

Our experience

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Maria Giulia Cristofaro, Amerigo Giudice, Walter Colangeli, Mario Giudice

Unit of Maxillo-Facial Surgery (Chief: Prof. M. Giudice), University "Magna Graecia", Catanzaro, Italy

Unique and rare bone metastases from occult primary cancer. Our experience.

AIM: *The airn of our study is to describe the rare location of metastasis cancers (kidney and prostate) in the jaw bones (maxillary branch and the condyle); this is the first and the only sign of disease.*
MATERIAL OF STUDY: *Two patients referred to us for a swelling in his left preauricolar region with a moderate pain. They underwent a radiologic and bioptic examinations that showed a metastasis which could arise from a primary prostatic and renal adenocarcinoma. The patients underwent surgical treatment (Subtotal-emimandibulectomy and reconstruction with metallic endoprosthesis).*
RESULTS: *The final follow up for the first patient was acceptable and without any motor or sensory deficit. The patient also underwent chemotherapy for his primary tumour and radiotherapy of his mandibular condyle metastasis during the preoperative stage.*
The final follow-up of the second patient was performer two years after the surgery and it did not show any recurrence and after about 18 months from surgery has performed dentistry rehabilitation. The patient had a chemotherapy treatment with the administration of bisphosphonates for the presence of skeletal metastases.
DISCUSSION AND CONCLUSION: *Just 1% of carcinomas metastasizes in jaw bones. The low rate is linked to the low active bone marrow content in jaw bones of adult patients. For the prostatic and breast adenocarcinomas the neoplastic embolis reaches the skeleton directly, passing through the vertebral venous system (Batson's hypothesis). Early diagnosis made the treatment both of the primary tumour and of its recurrence (single metastasis) more effective.*

KEY WORDS: Jaw metastasis, Mandibular condyle metastasis.

Introduction

Metastatic tumours are very common in bones; this site of recurrence ranks third after the liver and the lungs in 12% of malignant neoplasm. However, this figure is understimated since antiblastic tratments, which extend our patients' serviva, further increate the chances for the recurrence of lesions.
The mainly are metastases due to carcinomas, which are defined osteotrope or osteophile due to their specific bone affinity. Among them, the most recurrent are: breast carcinoma (bone metastases in 78% of casa), prostatic adenocarcinoma (bone metastases in 54-73% of casa), lung carcinoma (bone metastases in 30% of cases), thyroid carcinoma (bone metastases in 30-40 % of cases), hypernephroma (bone metastases in 30% of cases), adrenal carcinomas and hepatocellular carcinoma (HCC) in a smaller rate[1].
Cancellous bones are the most affected because of their high red bone marrow content for wich cancer cells have

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Correspondence to: Maria Giulia Cristofaro, Cattedra e U.O. di Chirurgia Maxillo-Facciale, Facoltà di Medicina e Chirurgia, UMG di Catanzaro, Viale Europa, 1, 88100 Germaneto di Catanzaro, Italy (E-mail: Cristofaro@unicz.it)

a special affinity both because vascular spaces have an endothelial hedge that can be easily penetrated and in the bone marrow there are growing factors that foster the development of some metastatic tumors. Vertebral bodies, ribs, sternum, femoral head, pelvic and calvaria bones are the most affected regions.

Materials and methods

Case n. 1

A.S., aged 60, was referred to us in October 2006; he had been suffering, for a month, from a swelling in left parotid-masseterine region coupled with a modest pain that increate any time he chewed. (Fig. 1). He did non report any parestesia, otalgia or any other remarkable symptoms. His familiar and physiological anamnesis did not show any outstandins whereas in his previous one he reported a trauma in the mandibular region for an incidental fall, he suffered to undefined vascular pathologies and he take antihypertensives as pharmacological treatment .

During the extraoral examination we noticed thet his face was asymmetric, due to a 2x3 cm, dense and elastic, egg-shaped neoplasia in his left preauricolar region, which did not suffer from rebound tenderness; the skin had a normal colour and texture. There were not any satellite lymphoadenopathies and/or motor disorders due to the involvment of the 5th and 7th pair of left cranial nerves.

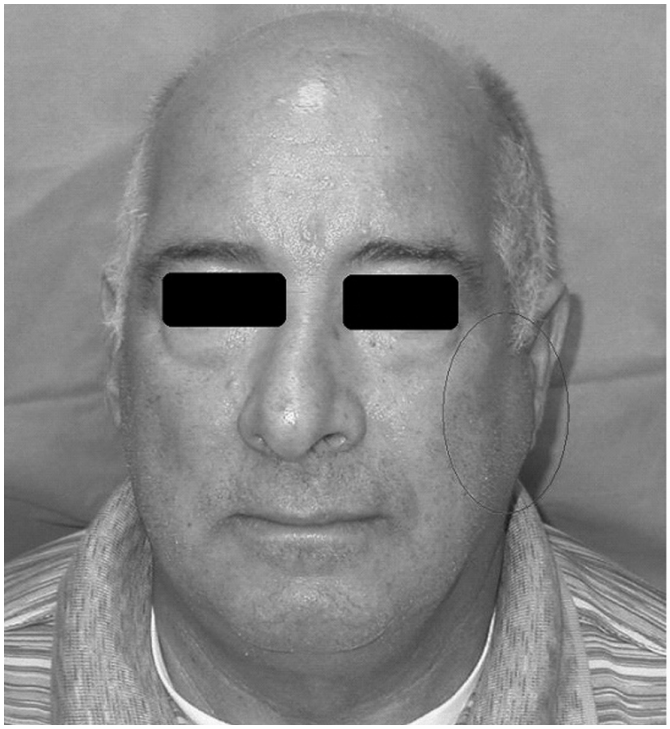

Fig. 1: Left preacuricolar swelling.

Examining the oral cavity we noticed its poor dental hygiene, rampant caries in tooth 3.4, the presence of some composite fillings, a metal –porcelain bridge composed by 5 elements (Teeth 1.3 – 1.7) and another one consisting of 3 elements (Teeth 2.2 – 2.4); when our patient opened his mouth his left TMJ clicked and we also observer a modest side deviation of the medial line homolateral to the lesion.

The other structures of the oral cavity were intact. He underwent an Orthopantomography (OPT) and a Computerized Tomography(CT) that showed an osteolytic lesion in the left mandibular condyle and its pathological fracture (Fig. 2). The functional assessment of TMJ joints proved a slight increase in the traslation of the right condyle as against the controlateral one.

Neck ultrasonography highlighted just a few reactive intrparotid lymphonodes on the left and one of them was about 16mm large.

Routine analysis, urine and blood, did not show any problem; the same was for the clinical and instrumental assessment of his cardiopulmunary system. Doppler ultrasound proved the prensence o fan obstructive peripheral vascular disease in the lower limbs.

The bioptic examination discosed that is was the site of a metastasis having a cribriform and micropappillary pattern due to an adenocarcinoma; it was coupled with reactive bone formation, which could issue from a primary prostate tumour (Fig. 3). The patient thus was esamine by an urologist. The histological examination was performer by means of a prostate needle aspiration biopsy underultrasound guidance on a poorly vascularised extra- capsular1.1 cm-mass. It was hypoechogenic, and showed a conventional acinar adenocarcinomaof the prostate, whose overall Gleason scores were 7 with Gleason pattern 5 (Gleason score modified according to IUSP 2005) as well a perineural invasion. The patient

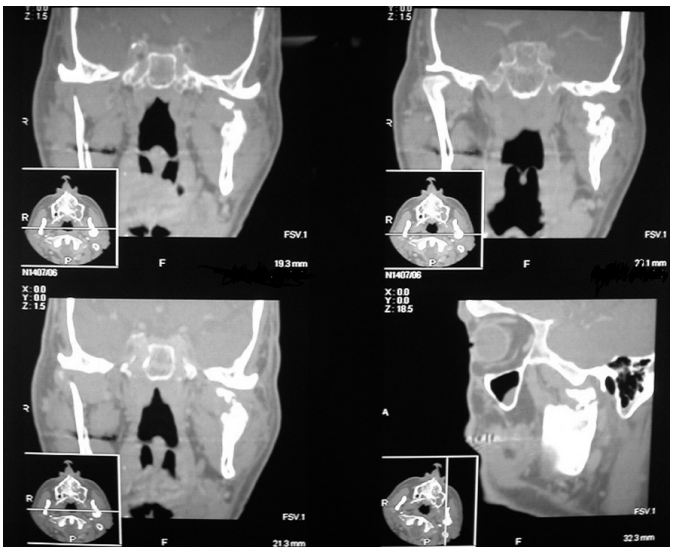

Fig. 2: Preoperative CT revealing an osteolytic lesion with mandibular-condyle pathologic fracture.

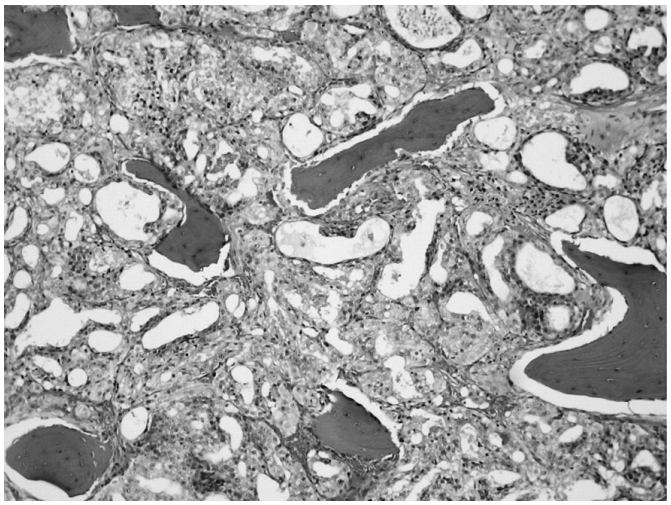

Fig. 3: Microscopic appearance of prostatie carcinoma. Adenocarcinoma composed of small glands, the individual glands having a irregular round configuration and cribriform pattem.

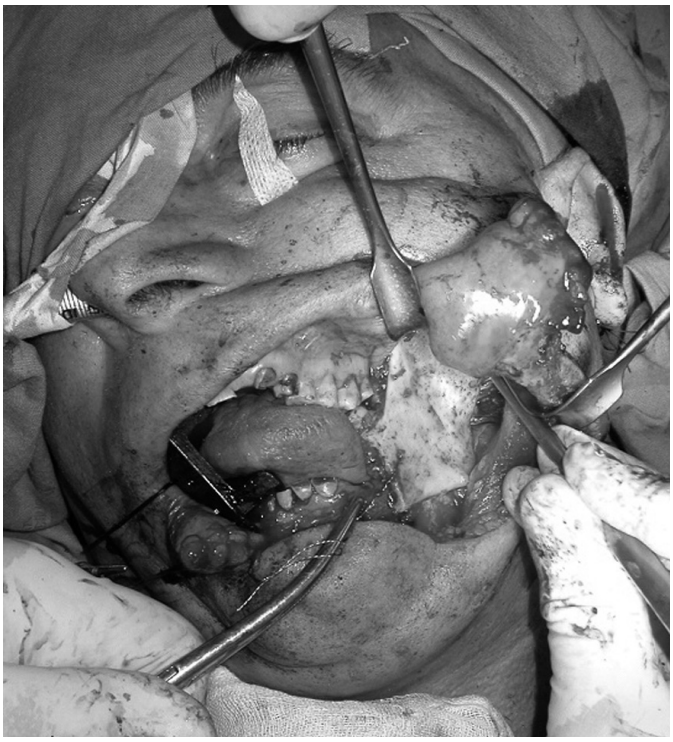

Fig. 4: Intraoperative view of the subtotal hemimandibulectomy.

A

B

Fig. 5 (A, B): Reconstruction time images with titanium replacement piate.

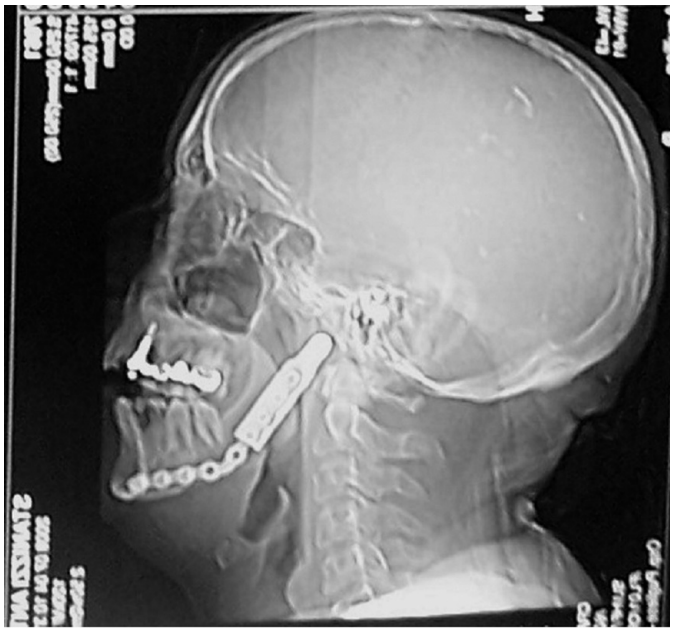

Fig. 6: XR control: CT after 12 months since surgery.

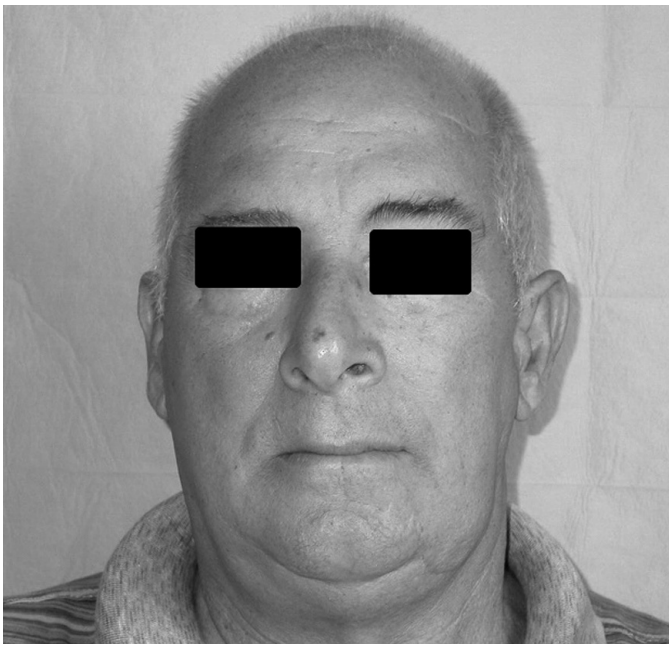

Fig. 7: Clinical control after 1 year since surgery.

underwent also to a Technetium99-skeletal scintigraphy which highlighted a strong pathological increase in the uptake of the radioactive tracer by the mandibular condyle and part of his left ascending ramus of mandible, whereas all other skeletal segments did not show any problem. Thus our patient was hospitalized again in our department to undergo a left subtotal hemimandibulectomy (Fig. 4) follone by a reconstruction by means of a titanium replacement plate (Fig. 5 a,b). His peripheral vascular disease led us not to use free microvascularized flaps. The postoperative course was satisfactory and without any motor or sensory deficit. Again, the istological examination confirmed the metastatic site of a prostate adenocarcinoma with intact resection margins. Clinical follow-ups were carried out after 1, 3, 6 and 12 months; 6 months later the patient underwent a skull CT (Fig. 6) and 12 months later a skeletal scintigraphy; the final follow –up was performer two years after the surgery and it did not show any recurrence (Fig. 7). The patient also underwent chemotherapy immediately in order to treat his primary tumour and radiotherapy of his mandibular condyle metastasis during the preoperative stage.

Case n. 2

E.R., aged 60, was referred to us in December 2008; he had been suffering, for a month, from a swelling in his left preauricolar region coupled with functional mouth opening limitation (Fig. 8).
The OPT made after two days of onset of pain showed the presence of a gap left mandible bone interesting. On extraoral physical examination was noted a facial asymmetry for the presence ,in left preauricular region, of a swelling about 2.5 x 2 cm, above intact skin, hard-elastic consistency, with undefined margins and fixed to the floors below, painful on palpation; absence of satellites lymphadenopathy and / or functional deficits as noted hypoesthesia while dependent on the territory of innervation of the third branch of the fifth pair of the left cranial nerves. Intraoral examination we noted marked tenderness to digital pressure of the branch, reduced mouth opening (maximum 2.5 cm), with moderate left side deviation. the other structures of the oral cavity appeared intact in the exploration. The Tc scan of the patient facial bones showed a large area of osteolysis in left ascending branch of the mandible with the facture line in the condylar (Figg. 9, 10). The lesion was subjected to needle biopsy, with histological report as "poor-

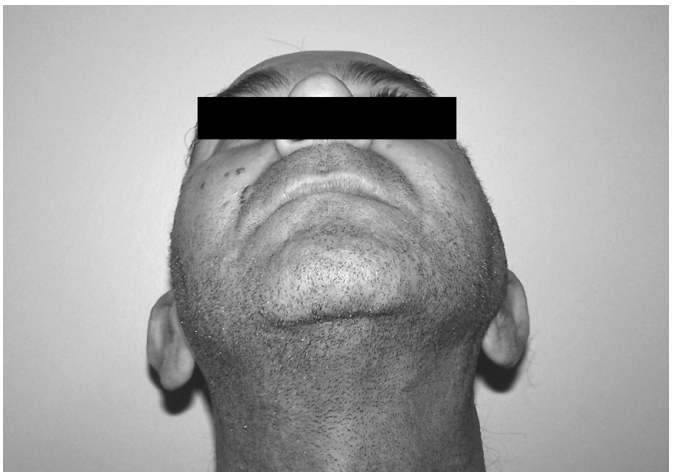

Fig. 8: Left preauricolar swelling.

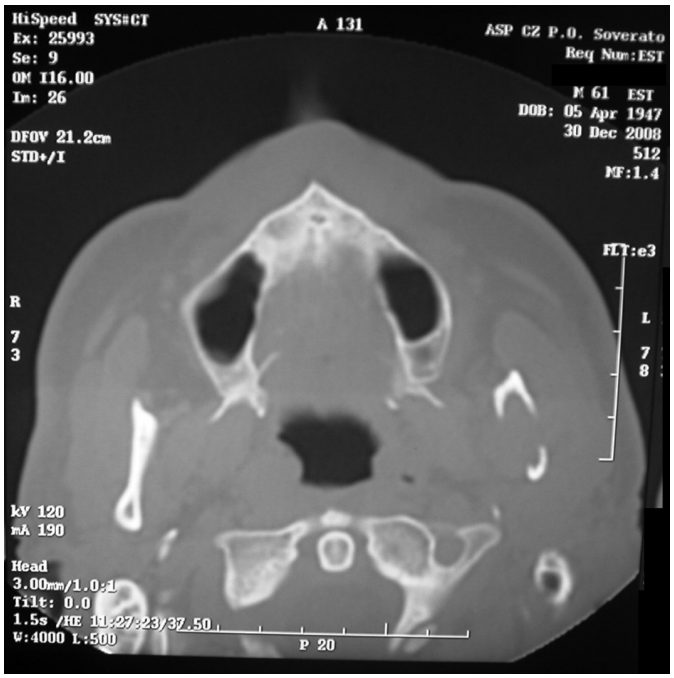

Fig. 9: Preoperative CT revealing an osteolytic lesion of ascending branch of the left hemimandible.

Fig. 10: Preoperative 3D CT revealing a osteolitic minus with left condylar mandibolar fracture.

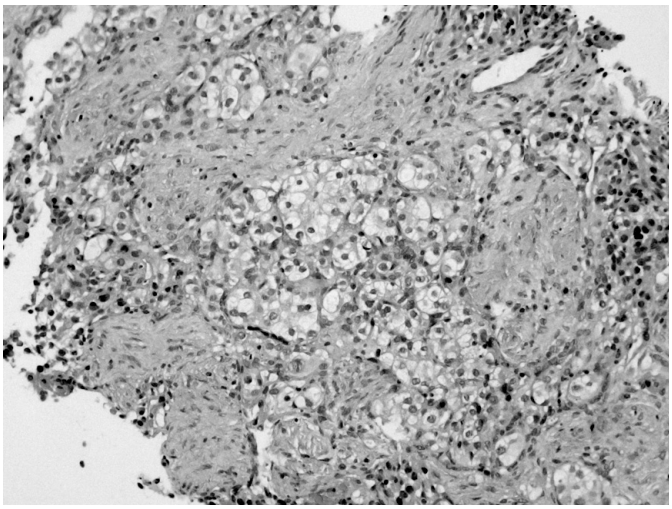

Fig. 11: Localization of carcinomas show evidence of glandular differentiafion, the pattern of growth is predominanfly solid, with formation of large nests of tumor separated by a stroma that is characteristically endowed with prominent vessels.

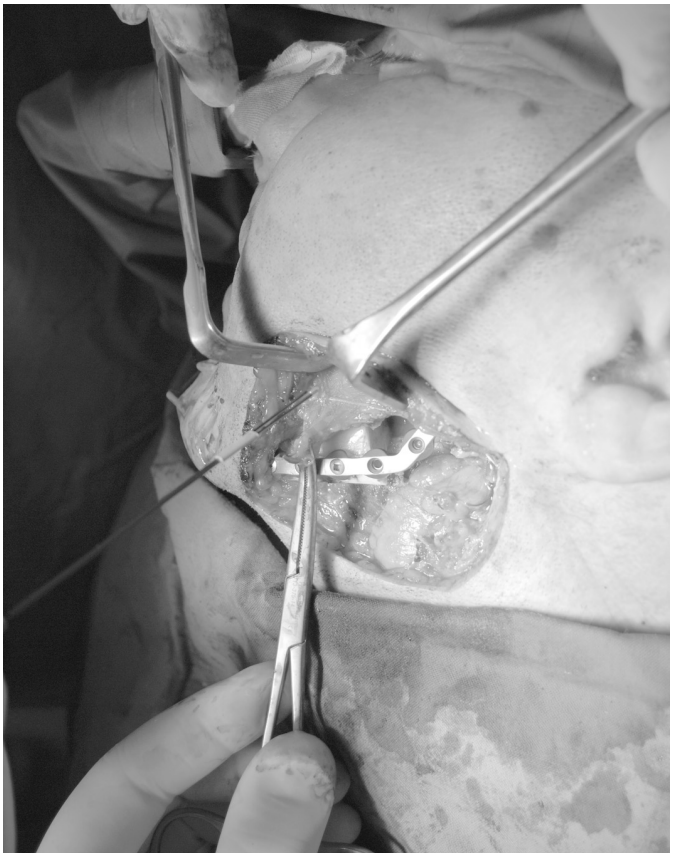

Fig. 12: Reconstruction time images with titanium replacement.

ly differentiated carcinoma. Investigating molecular morphology we found: Cytokeratin 7-, Cytokeratin 20-, PSA -, TTF1-, RCC focally and low positive, CD 10+,highly suggestive of a primitive renal" (Fig. 11). Therefore, the patient underwent a total body CT scan that highlighted against the middle third of the right kidney, a nodular contour to regular size of 3.5 cm. In view of this report, he was sent to the urologist, in the light of histological examination and CT scan, surgical treatment should be recommended for the renal lesion. After in

January 2009 underwent for a right radical nephrectomy. Histological examination showed: "Double renal cancer: 1)Renal oncocytoma, maximum diameter 2.5 cm, 2) renal adenocarcinoma of usual type (clear cell carcinoma), Furhman grade 2, expansive margins, the maximum diameter was 4 cm. No evidence of vascular invasion of the perirenal adipose tissue. Margin of the ureter and renal vessels free of neoplastic infiltration. Associated lesions: simple renal cysts". After a short recovery period, was admitted to our department and underwent surgery for " Left subtotal emimandibulectomy and reconstruction with metallic endoprosthesis " for mandibular condyle metastasis from left renal cancer (Figg. 12, 13). As in the first case we describe we did not use of microvasculature fibula flaps for different reasons :general and severe peripheral arterial vascular insufficiency.

Histological examination confirmed the localization of metastatic clear cell carcinoma. The postoperative course was normal, clinical checks were conducted periodically at 3, 6, 12 and 24 months; post-operative OPT gave a good stability tank to metallic endoprosthesis (Fig. 14). After about 18 months from surgery the patient has performed rehabilitation dentistry (removable prosthesis) (Fig. 15). In the oncologic follow up ,the presence of cancer metastases to skeletal (right clavicle, proximal femur, distal third of right femur, right II right coast) detected with scintygraphy in December, the patient had a chemotherapy treatment with the administration of bisphosphonates.

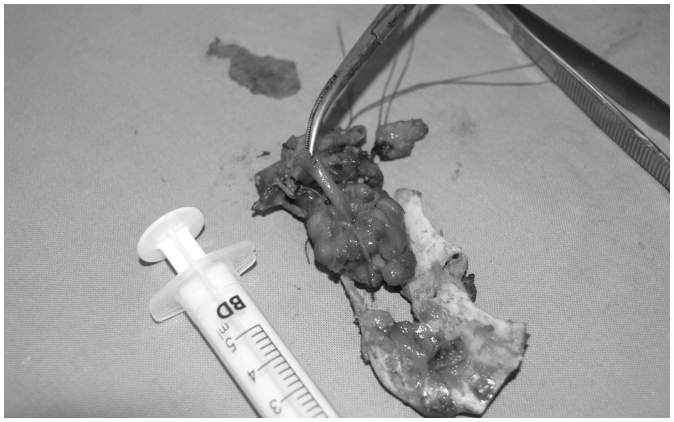

Fig. 13: Specimen.

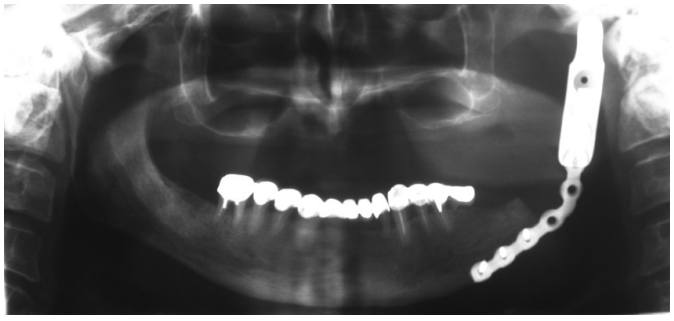

Fig. 14: OPT investigation two years after surgery.

Fig. 15: Surgical wound two years after surgery: mandibular profile retained.

Discussion

From a review of literature just 1-8% of carcinomas metastasizes in jaw bone [2,3]; this recurrence is observed in 42% of breast carcinomas in women against other tumours, in 22% of lung carcinomas and in 12% of prostatic adenocarcinoma, and in 16% of kidney cancers [4]. The low rate is linked to the low active bone marrow content in jaw bones of adult patients, in which the higher content can be found in the rear part of the mandible (molar7premolar region). This explains why metastases are more recurrent there [3,5,6]; they rarely affect the upper jaw (maxilla/mandible ratio is 2:1) its recurrence in mandibular condyle is even exceptional, just 40 cases had benn reported in itenaltiona letterature up to 2008 [7]. Some epidemiological studies proved that the six sex distribution of metastatic jaw tumours is quite quivalent and they affect above all patients 40-70 years old. The spread of metastases may occur throught the blood or the lymphatics as well as owing to contiguity, although less frequently. It is important to notice that bone metastases do not always occur in tumour primary site; e.g. a prostatic adenocarcinoma or a breast and kidney cancer can develop just bone metastases, neglecting other regions such as the lungs. This paradoxal mode of metastatic dispersal can be explained by hypothesizing that neoplastic emboli reach the skeleton directly and not seed through the portal vein in the liver or in the lungs carried by the caval system [8]. In these cases (as in breast ,prostate and kidney cancer) neoplastic cells travel in a vertebral venous system passing through the vertebral canal and anastomosing sacral, lumbar, mesenteric and thoracic veins as well those which penetrate vertebral bodies and the cranial bones. Baston proved that

prostatic venous plexus connects itself to the inferior vena cava and to the internal vertebral venous plexus, which has no valves and runs paravertebrally from pelvic veins up into the dural venous sinuses [9]; thus, neoplastic embolis can reach the system of vertebral veins and metastasize directly in bones, avoiding the the sistemic circulation. (The passage of cancer cells in these regions can be caused by an increase in intrapleural and intr-abdominal pressure that favours the inversion of venous flow).
In the maxilla, cancer cells alter the balance between osteoclast/osteoblast activity; in most cases osteoclast activity prevails, it can be observed by x-ray studies, showing the presence of an osteolytic area. More rarely we can notice an increase in osteoblast activity leading to a marked new bone formation; but these areas are common in prostate, lung and bladder cancer. The gardening of the bone, which looks dense or slightly porous, could be consistent with a simple osteosclerosis. Their fast development causes some pathologic fractures, as in our reports.
In most cases jaw bones metastases occur after the patient has been diagnosed a primary tumour; in a smaller rate their diagnoses concide with the primary tumour one. Exceptionally bone metastasis is the first clinical sign of a latent or early cancer, as for prostate and kidney cancer [10].
As a matter of fact, in these clinical cases descrived by the Authors, the first clinical sign was tha appearance of a swelling in the preauricolar area that suggested either TMJ dysplasy/dystrophy or a TMJ inflammatory response.
Actually, it is rather difficult to diagnose metastases in jaw bones and namely in the mandible:and indeed, they often are diagnosed late [11]. This difficulty is above all due to the lack of specific symptoms, which are sometimes silent for a long time, characterized by pain and parestesia in the area innerved by the trigeminal nerve. The presence of a swelling that alters the vestibular profile is less frequent. They are rarely found in parotid-masseterine area, as in the cases described by the Authors; all this suggested that the patient had suffered a trauma, a parotitis or any other TMJ disorders [12,13]. Therefore we must consider all dysplastic and inflammatory pathologies as well as malignat primary and metastatic tumors when we make a differential diagnosis. This occurence must be kept in mind when we deal with patients reporting in their anamneses any carcinoma that often originates bone metastases.
Strumental researches are decisive for diagnosis: OPT is the first examination that a patient had to do; it can reveal the presence of one or more radiopaque or mixed areas in jaw bones, or lower rate of radiolucent areas. CT scan shows bone better team and pathological fracture as in our cases; MRI of jaw bones gave further details on the extent and infiltration of soft tissues ; skeletal scintigraphy is fundamental test to asses the possible presence of metastases in other parts of the skeleton; biopsy of the lesion provided us the diagnosis.
The critical element to make diagnosis is provided by biopsy of specimens taken from a lesion in our cases, it was decisive beacause we dealt with a bone metastasis deriving from an occult primary carcinoma and the site of its recurrence was almost rare. The histological examination of the bioptic specimens from the suspected lesion made us link this metastasis with the primary prostate and knidney cancer from the beginning; it suggested us to examine these organs.
Treating these metastases is not easy since they are often diagnosed late and frequently we deal with patients suffering from any advanced – stage cancer, in which surgery would not improve the quality of their lives.
Radical surgery is indicated in single metastasis; it must be coupled with chemio-radiotherapy. The survival for early prostate cancer in over four years is about 10% only in those cases where the diagnosis was early.
About 10% of precociously diagnosed cases shows a 4-year survival rate; for the renal cancer, the survival rate drops dramatically.

Conclusion

Data reported in literature highlight a low incidence of jaw bones metastases; they are even less recurrent in mandibular condyles owing to their low red bone marrow (hematopoietic active) content in adulthood. All this makes their diagnosis diffucult and late owing to the lack of precocious clinical signs (poor involvement of soft tissues in the oral cavity).
Moreever, in our cases jaw bone metastasis, and namely mandibular condyle metastasis, is endorsed by the hypothesis suggested by Batson, who identified a direct way of neoplastic cells from prostatic veins to the internal vertebral venous plexus, which has no valves, and reach the cranial bones, avoiding the sistemic circulation. This hypothesis can be made also for lung and bladder cancers. Our cases are exceptional because the mandibular condyle metastasis was the first clinical sign of an occult primary prostate and renal carcinoma, whose early diagnosis made the treatment both of primary tumour and of its recurrence (single metastasis) more effective.

Riassunto

Le metastasi rappresentano la forma tumorale più frequente delle ossa, sede di processi ripetitivi in circa il 12% delle neoplasie maligne, collocandosi al 3° posto dopo il fegato e i polmoni.
Le ossa spugnose sono quelle più colpite per la maggior presenza di midollo rosso ematopoietico attivo verso il quale le cellule tumorali hanno una particolare affinità sia perché gli spazi vascolari hanno una barriera endoteliale facilmente penetrabile, sia perché nel midollo sono

presenti fattori di crescita che favoriscono lo sviluppo di alcuni tumori metastatici. I corpi vertebrali, le coste, lo sterno, l'estremità superiore del femore, le ossa del bacino e la calotta cranica sono, in ordine di frequenza, le sedi più interessate.
Le metastasi ossee però non sempre si localizzano in quegli organi che invece anatomicamente ne dovrebbero essere interessati. Per esempio può accadere che un carcinoma della mammella, della prostata e del rene, come nei due casi clinici riportati dagli Autori, può dare solo metastasi ossee, lasciando libere altre sedi come il polmone, il fegato, etc.. Questa paradossale distribuzione delle vie di diffusione metastatica può spiegarsi ipotizzando che gli emboli neoplastici raggiungono lo scheletro attraverso altre vie non seguendo i filtri obbligati come quello epatico (attraverso la vena porta) e polmonare (attraverso il sistema cavale). In questi casi le cellule neoplastiche attraversano un sistema venoso vertebrale che passa lungo il canale vertebrale e si anastomizza sia con le vene sacrali, lombari, addominali, toraciche e sia con le vene che penetrano nei corpi vertebrali e nelle ossa craniche. In particolare Batson ha dimostrato che il plesso venoso prostatico drena oltre che nel sistema della vena cava inferiore anche nel plesso venoso vertebrale, privo di valvole e che si distribuisce lungo la colonna vertebrale a partire dalle vene pelviche fino ai grandi seni venosi del cranio. Pertanto, emboli neoplastici possono raggiungere il sistema delle vene vertebrali e metastatizzare direttamente nelle ossa, evitando la circolazione sistemica.
Nella maggior parte dei casi le metastasi ossee a carico dei mascellari si manifestano successivamente alla comparsa del tumore primitivo. Eccezionalmente la metastasi mascellare rappresenta la prima espressione clinica di un cancro iniziale o latente di altra sede, come si verifica per il cancro della prostata e del rene.
Nei casi riportati dagli Autori la prima manifestazione clinica della lesione metastatica è stata la comparsa di una tumefazione in corrispondenza della regione preauricolare, suggestiva di una patologia distrofico-displastica dell'ATM o di un processo infiammatorio a carico della stessa.
È bene quindi considerare nella diagnosi differenziale clinica non solo le patologie displastiche, infiammatorie e traumatiche, ma anche quelle neoplastiche, primitive o secondarie.
Le indagini strumentali sono dirimenti nella diagnosi: l'ortopantomografia, la TAC dei mascellari evidenzia meglio la compagine ossea, la Risonanza Magnetica i tessuti molli e la scintigrafia ossea total-body per valutare l'eventuale presenza di metastasi in altre parti dello scheletro; la biopsia della lesione sospetta, infine, fornisce l'elemento decisivo nella diagnosi.
Nei casi da noi descritti, la biopsia è stata addirittura determinante in quanto trattatasi di metastasi ossea piuttosto rara da primario "occulto" di altra sede.
L'approccio terapeutico non è semplice se consideriamo che la diagnosi è più delle volte tardiva e che più delle volte si tratta di pazienti con cancro in fase avanzata, nei quali l'aggressione chirurgica non porterebbe a un miglioramento della qualità della vita.
In entrambi i casi descritti dagli Autori l'intervento chirurgico è stato radicale ed è consistito in una "emimandibulectomia e ricostruzione immediata con l'utilizzo di placca sostitutiva in titanio".
Un intervento chirurgico radicale è indicato nella metastasi unica associato a radio-chemioterapia. La sopravvivenza per il cancro primitivo prostatico, a oltre i quattro anni, è di circa il 10% solo in quei casi in cui la diagnosi è stata precoce; per quello renale la percentuale si abbassa drasticamente.

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