

High-grade chondroblastic and fibroblastic osteosarcoma of the upper jaw

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ABSTRACT

Osteosarcomas (OS) are extremely uncommon in maxillofacial region (6%-10% of all sarcomas). Jaw lesions are diagnosed on average two decades later than sarcomas of long bone, with a peak incidence between 20 and 40 years. Head and neck OS (HNOS) are associated with a lower metastatic rate than long bone OS, and they have a better 5-year survival rate, ranging between 27% and 84%. Approximately 80% of HNOS originate from soft tissues, while 20% arise from bone. The majority of OS were classified as osteoblastic HNOS (77.0%), followed by chondroblastic (15.8%) and fibroblastic (3.4%). Patients older than 60 years were more likely to be diagnosed with other histologic types compared with patients 60 years or younger. The authors describe a rare case of Stage II high-grade mixed chondroblastic and fibroblastic osteosarcoma of the upper jaw diagnosed in a subject older than 60 years. CT i.e., total body scintigraphy, radiograph of chest, and epatic ultrasonography have been executed to staging (T3N0M0). The size of the tumor >6 cm, histopathological findings, and patient older than 60 years, made necessary a multimodality therapy. Surgery (right subtotal maxillectomy with closure of surgical area by local sliding and advanced cheek flap) and adjuvant radiotherapy (for overall 6500 Gy) were the definitive treatment. Follow-up at 2 years shows no local recurrence and the patient is disease free.

Keywords: Maxilla, osteosarcoma, surgery

INTRODUCTION

Osteosarcoma (OS) is the most common primary malignancy of bone, with a reported incidence of 1:100,000.^[1] On the contrary, it is rare in maxillofacial region. Fernandez *et al*, report 16 patients with OS of the jaw observed from 1993 to 2003 in the Department of Oral and Maxillofacial Surgery, University of Maryland, Baltimore.^[2] Luna-Ortiz *et al*, describe 21 cases of osteogenic sarcoma of the maxillary region in a Mexican mestizo population observed during a 20-year period.^[3]

Lecornu *et al*, report in 2011 a retrospective cohort study of 47 patients with jaw osteosarcoma (JOS) treated at Massachusetts General Hospital from 1967 through 2007.^[4]

In well-known analysis of National Cancer Data Base (NCDB),

Smith *et al*,^[5] reported that only 496 cases of head and neck OS (HNOS) were registered in the last 11 years. This corresponds to HNOS that were diagnosed or treated at the reporting hospital between 1985 and 1996. Because the NCDB does not capture all cases of malignancy that occur each year, they estimated that at least 70% of all malignancies are reported and that fewer than 70 cases of HNOS occur each year in the United States. So approximately from 6% to 10% of all sarcomas occur in HNOS and the mandible and maxilla are the predominate locations, although extragnathic bone and soft tissues sites may be affected.^[6-8] Jaw lesions are diagnosed on average two decades later than sarcomas of long bone, which have a peak incidence between 10 and 14 years. HNOS are associated with a lower metastatic rate than long bone OS, and they have a better 5-year survival rate, ranging between 27% and 84%.^[2]

The majority of HNOS were osteoblastic (77.0%), followed by chondroblastic (15.8%) and fibroblastic (3.4%). Patients older than 60 years were more likely to be diagnosed with other histologic types compared with patients 60 years or younger.^{19,10}

We describe an uncommon case of high-grade mixed chondroblastic and fibroblastic osteosarcoma of the maxilla in a subject older than 60 years.

CASE REPORT

A 62-year-old man was admitted to Maxillofacial Surgery Institute, Health Sciences Department, University of L'Aquila Italy, on May 16, 2008. Extraoral clinical examination revealed a significant swelling of the right cheek, appeared in April 2008. Patient suffered from paresthesia in the right facial side. Intraoral examination revealed a large ulcerated mass in the toothless superior right arch, vestibular fornix, and palate [Figure 1a]. The lesion bled easily and was hard in consistency. [Figure 1a]. Panoramic radiograph [Figure 1b] revealed a mixed radiolucent and radiopaque area in the right maxilla with irregular and undefined borders. Computed tomography [Figure 2a] showed a round tumor-like mass involving the upper right alveolar process, palatal structure, and the inferior third of the maxillary sinus, with vestibular expansion accompanied by

peripheral bone destruction. The lesion showed irregular high and low density areas. Regional pathological lymph nodes were not detected. Incisional biopsy was performed on May 18, 2008, with diagnosis of mixed sarcoma. Total body scintigraphy [Figure 2b] showed pathological tracer only in the right maxilla. Chest X-ray and hepatic ultrasonography were negative. Blood tests including serum alkaline phosphatase were normal except for leukocytosis and elevated ESR. On May 25, 2008, right subtotal maxillectomy was performed under general anesthesia with closure of the surgical area by local sliding and advanced cheek flap, using standard procedures [Figure 3].

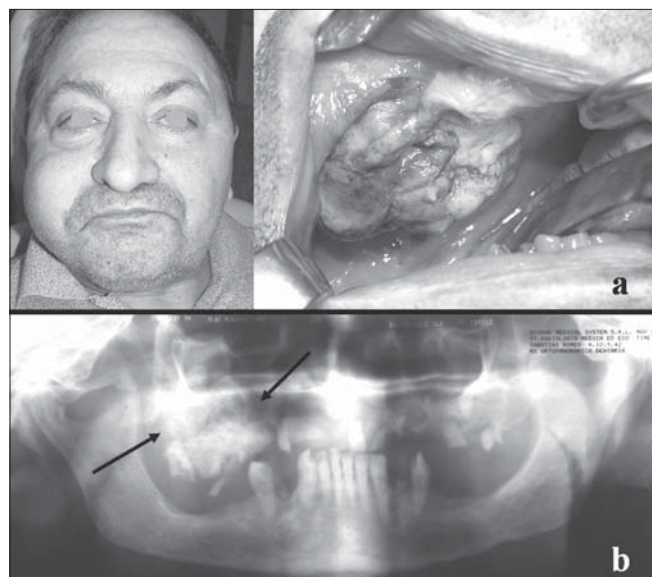


Figure 1: (a, b) Clinical and radiographic aspect of the tumor

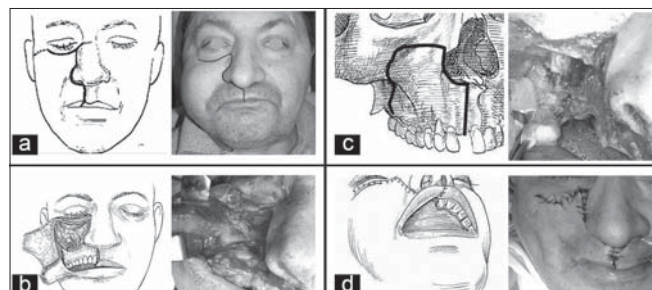


Figure 3: (a) Weber-Fergusson approach. Intraoperative aspects show the tumoral mass (b) and subtotal maxillectomy (c). (d) Final view

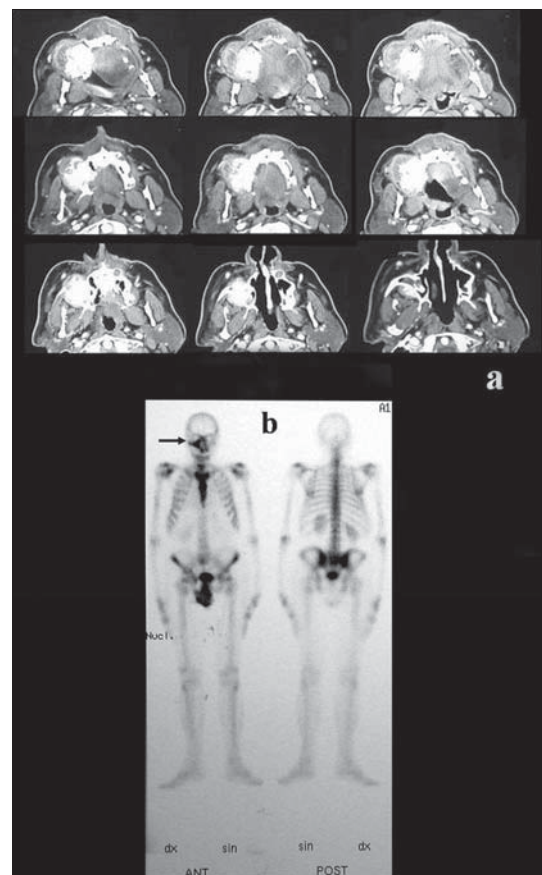


Figure 2: (a) CT axial scan for loco-regional staging of the tumor. A lymph-node is present in 1b level (white arrow) (b) Total body scintigraphy shows a pathological tracer in the right maxilla (black arrow)

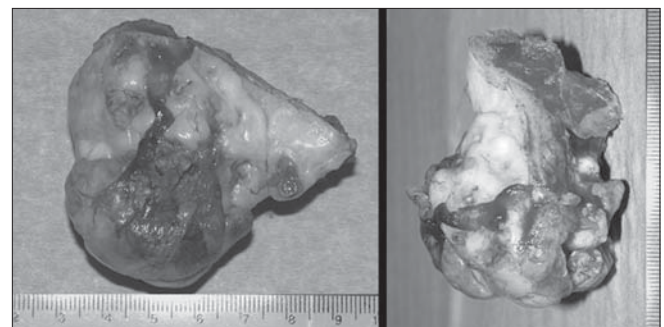


Figure 4: Tumor size is greater than 6 cm

Macroscopic and Microscopic findings

Macroscopically tumor measured 6.5 x 5 x 4 cm. It involved alveolar and palatal structure of right maxilla [Figure 4]. Histologically [Figure 5], the tumor showed diffuse osteoid production, chondroid, and fibroblastic proliferation. Under high-power magnification, the cells had generally round and oval hyperchromatic nuclei with inconspicuous nucleoli. The nuclear chromatin was dispersed finely, and the cytoplasmic boundaries appeared indistinct. Immunohistochemical studies revealed positive reactions for S-100 protein. Surgical margins were free, and they had no residual disease. Surgical margins were clear. Tumor was diagnosed as Stage II mixed, chondroblastic, and fibroblastic osteosarcoma (high-grade tumor without metastases). Postoperative course has been regular and uneventful. On June 10, 2009, the patient was discharged from the hospital with acceptable clinical conditions, except for numbness of the right cheek and aesthetic alteration. In view of the tumor size being greater than 6 cm, histopathological findings and the patient being older than 60 years, multimodality therapy was planned. On June 25, 2009, radiotherapy treatment was started for overall 6500 Gy. The follow-up at 2 years reveals no recurrence and the patient appears disease free [Figure 6].

DISCUSSION

OS involves the head and neck region in approximately 10% of all sarcomas. The mandible and maxilla are the most frequently affected sites, followed by the paranasal sinuses^[11] and skull. HNOS occurs in a population older than the one in which

sarcoma of the long bones occur, with a peak of incidence from 20 to 40 years. Males are affected slightly more often than females.^[6,7,12]

Approximately 80% of HNOS originate from soft tissues, while 20% arise from bone.^[8,13] Soft tissue sarcomas arise from the mesenchyme, including muscle, endothelial cells, cartilage, and supporting elements.^[14] Also, the periodontal ligament may be a mesenchymal site of tumoral degeneration.^[8] In these cases, the widened periodontal space and sunburst appearance at radiological examination are classically described.

Unlike the development of squamous cell carcinoma, the sarcoma is unrelated to smoking and alcohol use. Certain sarcomas are related to genetic syndromes (e.g., Li Fraumeni syndrome-osteosarcoma),^[15] environmental exposures^[16] (e.g., radiation-multiple sarcoma types), and medical conditions (e.g., lymphedema - angiosarcoma - malignant fibrous histiocytoma^[14] - retinoblastoma, related to alterations in chromosome 13-Paget disease). In the head and neck, the most common sarcoma in children is rhabdomyosarcoma; in adults, osteosarcoma, fibrosarcoma, and chondrosarcoma. Metastatic osteosarcoma of the jaws is extremely rare.^[17,18]

Sarcomas are classified according to the histologic tissue from which they are derived, and more than 30 histologic subtypes have been described. Most head and neck sarcomas appear at

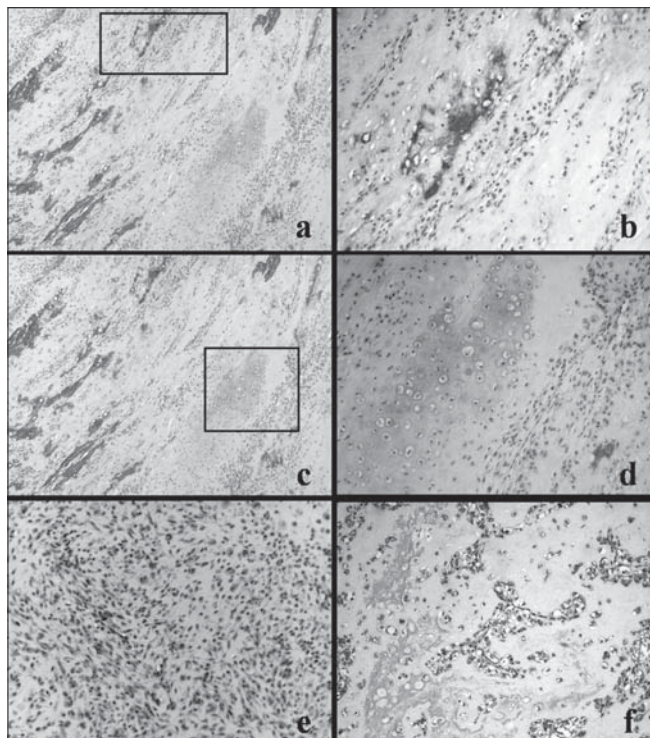


Figure 5: Histopathological pattern of the tumor: (a) osteoblastic proliferation (H & E, x4); (b) High-power magnification (H & E, x10). (c) Chondroblastic proliferation H & E, x4; (d) High-power magnification (H & E, x10); (e) Fibroblastic proliferation (H & E, x4); (f) Immunohistochemical pattern (positivity for S-100 protein)

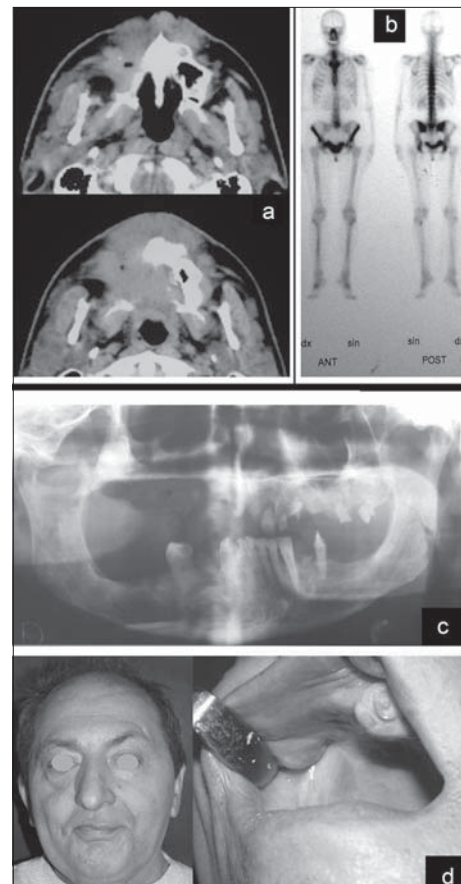


Figure 6: Follow-up at 2 years [(a) CT scan, (b) total body scintigraphy, (c) panoramic radiograph, and (d) clinical finding]

presentation as localized disease. Regional metastases occur in 10-15% of overall HNOS; most of these arise from high-grade primary lesions. At presentation, distant metastases are rare in absence of regional metastases; the presence of nodal metastases should prompt a search for distant metastases. Most common site of distant metastases is the lung, followed by the liver and bone. Local recurrence is common in high-grade tumors often in the first year.^[19] The AJCC staging systems for osteosarcoma of the bony sites and soft tissues were used to classify the extent of disease for patients with these types of lesions.^[20,21] The staging system for bony sites (up to and including the 4th edition) takes into account extracortical extension and tumor grade. The three categories are Stage I (low-grade tumors without metastases), Stage II (high-grade tumors without metastases), and Stage IV (all tumors with regional or distant metastases); Stage III does not exist.^[5] *Histopathologic grade:* Gx, grade cannot be assessed; G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; G4, undifferentiated.

Lesions frequently manifest as a swelling or mass over the jaw or cheek; numbness could be present; pain and dental symptoms are less common. Serum alkaline phosphatase levels are elevated in 50% of patients with osteosarcoma. Elevated serum alkaline phosphatase levels in patients with any of the associated conditions may signal malignant transformation.^[22] Radiologic examination is necessary for evaluation of the tumor.^[23] Standard radiographies and CT show destructive lytic or sclerotic bone lesions, which sometimes involves the adjacent soft tissue. Subperiosteal formation of new bone could occur adjacent to areas of bone loss. It has been described a sunburst pattern resulting from radiating spicules of bone. However, this finding is not specific for osteosarcoma. Widening of the periodontal ligament could be present; this finding is not specific for osteosarcoma, but it is highly suggestive of malignancy. At gross examination, tumors may appear soft and granular (osteolytic) or sclerotic and dense (osteosclerotic), depending on the degree of mineralization. Soft tissue extension is frequent. At histologic examination, osteoid tissue (a precursor of bone) is present within a sarcomatous stroma. The stromal cells may have anaplasia; their shape varies from spindle to round, and the cells contain hyperchromatic nuclei. The degree of vascularization varies considerably from scant to abundant. The presence of osteoid tissue is the distinguishing feature of this tumor, but osteoid may be absent in small unrepresentative biopsy specimens. Osteoid is eosinophilic with hematoxylin-eosin staining and may resemble collagen when it is present in small quantities; immunohistochemical stains can help in differentiating the two. Unlike collagen, osteoid reacts positively with immunohistochemical stains for osteocalcin, a bone-specific protein produced by osteoblasts, and osteonectin, a bone-specific phosphorylated glycoprotein. On the basis of the predominant component of the stroma, lesions can be subtyped as osteoblastic, chondroblastic, or fibroblastic. A giant cell-rich osteosarcoma subtype has been confirmed with osteocalcin staining. Osteoblastic tumors occur most frequently and have osteoclastic activity and increased vascularity. The high-grade tumors show a higher incidence of local recurrence often within 12 months.^[9] Junior^[10] by immunohistochemical analysis founded positivity for p53 in 52% of the cases, 24% for MDM2, 84% for CDK4, 92% for PCNA, and 88% for Ki-67. Hoang^[24] has indicated expression of LDL receptor-related protein 5 (LRP5) as a novel marker for disease progression in high-grade

osteosarcoma. Cervical metastases are present in fewer than 10% of patients. They usually result from direct extension rather than true lymphatic spread. Distant metastases occur in 33% of patients; most frequently, they involve the lungs. Surgical excision is the main treatment for osteosarcoma.^[3,13,22,25,26] Local recurrence occurs in approximately 60% of patients, most commonly within the first year after treatment. Extragnathic sites of involvement fare worse than gnathic sites. Reported mean 5-year survival rates are 43% for gnathic osteosarcoma and 9% for skull lesions, which are associated with a higher incidence of local recurrence and distant metastasis. Multifocal tumors are uniformly fatal. Patients with increased alkaline phosphatase levels appear to have a worst prognosis, as do patients with concomitant Paget disease. Alkaline phosphatase levels, when elevated preoperatively, can be used to monitor patients for recurrences. Like other uncommon tumors of the head and neck, therapy for HNOS often was based on previous case reports or small case series that span several years. Consequently, the treatment for HNOS has been based largely on experience with osteosarcoma of sites outside of the head and neck. Based on relevant data Smith *et al.*,^[5] provided important elements of therapeutic orientation, based on age, staging (histologic subtype, size of tumor, grade), and status of surgical margins. Luna-Ortiz *et al* noted in their cases that disease-free survival according to surgical margin and overall survival were not statistically significant with 29% disease-free survival at 5 years, and 50% and 25% overall survival at 5 and 10 years, respectively.

Patients older than 60 years were most likely to undergo surgery alone. If multimodality therapy was administered to patients in this age group, then it most likely was surgery and radiotherapy. The most common multimodality treatment for patients aged 60 years and younger was the combination of surgery and chemotherapy. Patients who had tumors that measured ≤ 3 cm were equally likely to undergo surgery alone or surgery with adjuvant therapy, whereas patients who had tumors that measured > 3 cm were more likely to undergo surgery and adjuvant therapy than surgery alone. The histologic type of HNOs influenced the treatment with surgical therapy being commonly employed while multimodal therapy (surgery with radiotherapy) was reserved for the poorly differentiated HNOs. Significant differences were found with respect to grade and disease stage. Surgery alone was used most often to manage low-grade tumors and localized disease, whereas combined surgery and chemotherapy were used more often to manage high-grade tumors and metastatic disease. Even in the presence of distant metastases, surgery was included as part of treatment in almost 70% of patients. Currently, oncogenetic pattern of tumor is also considered in treatment planning.^[24]

CONCLUSIONS

OS of the jaws (JOS) are relatively uncommon tumors. Mixed, chondroblastic, and fibroblastic type is very rare. Clinically the tumor may be central or peripheral (periosteal) and histologically can be divided into three subtypes: osteoblastic, fibroblastic, and chondroblastic. In the maxillofacial region, the neoplasm starts as localized disease. Distant metastases are rare. Loco-regional adenopathies appear in 10%-15% of the high-grade cases. Surgery with clear margins is an important factor in successful therapy for patients with JOS. OS are very aggressive tumors, and it is necessary to apply an integrated and multimodal protocol

of treatment, as we have done in this reported case, with good results despite the histological high-grade.

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