Abstract: Background. Osteosarcomas of the jaws account for less than 10% of reported neoplasms of this type. Patients with osteosarcoma in this region tend to be in the late-third to mid-fourth decades of life. The osteoblastic, chondroblastic, and fibroblastic variants constitute the majority of lesions.

Methods. A mass was observed in the maxilla of a 50-year-old male who presented for a complete odontectomy. Over the ensuing weeks, the mass substantially increased in size, despite multimodality treatment efforts.

Results. Radiographic findings revealed a mixed density mass of the left maxilla. Histologic, immunohistochemical, and electron microscopy examination of the tumor showed a malignant mesenchymal neoplasm consisting of sheets of epithelioid and spindle cells exhibiting focal osteoid formation.

Conclusions. We report a rare and aggressive case of epithelioid osteosarcoma arising in the maxillofacial complex.

Keywords: osteosarcoma; epithelioid; maxilla; jaws; sarcoma

This tumor demonstrates a slight overall male predilection, and most often arises in the second decade of life, with another, lower peak incidence in the late seventh to early eighth decades.¹

In contrast, jaw osteosarcomas, which represent 6% to 10% of all reported osteosarcomas,¹,² affect men twice as often as women,² and tend to occur in the late third³ to the middle of the fourth decades of life.² The maxilla and mandible are affected with nearly equal frequency.²,³ This tumor is known for its heterogenous histomorphology, with some of the rare subtypes potentially creating considerable difficulty for the pathologist to arrive at a diagnosis.⁴ We report a case of a rare variant of osteosarcoma arising in the maxilla, which to our knowledge is the first to be reported at this anatomic location.

CASE REPORT

A 50-year-old black man presented to the Oral and Maxillofacial Surgery service of the University of Texas Health Science Center at San Antonio for removal of multiple decayed and broken teeth. Additionally, he complained of pain in the left maxillary vestibule and sinus region. Physical
examination revealed multiple extensively decayed maxillary and mandibular teeth. He also had a small, nontender, nonfluctuant swelling of the left maxillary vestibule. Panoramic radiographic exam revealed the additional finding of clouding of the left maxillary sinus. Initial diagnosis was a nonrestorable dentition and an odontogenic infection with secondary sinus involvement. He underwent removal of all his remaining teeth and alveoloplasty. Postoperatively, he was placed on antibiotics and told to return in 2 weeks for a follow-up examination.

Follow-up examination revealed a large, red, friable, fungating mass protruding from the left maxillary extraction sites. He was admitted to University Hospital, placed on IV antibiotics, and CT scans were obtained. CT scan revealed a large, expansile mass of mixed density involving the left maxilla. The lesion occupied the left maxillary sinus and was causing extensive bony destruction. It further extended into the infratemporal fossa and nasopharynx (Figure 1). Over the next 24 hours, the mass visibly increased in size. At this point, it was difficult for the patient to close his mouth. To establish a diagnosis and provide some sense of comfort, the patient underwent biopsy and debulking of the lesion. Intraoperative frozen section revealed a high-grade malignancy. Additional imaging studies were negative for metastatic disease.

Over the next 24 hours, the tumor again noticeably increased in size, despite considerable debulking. Because of the aggressive nature, extensive size, and involvement of anatomic structures, the lesion was deemed unresectable. At this time, a multidisciplinary consult determined that chemotherapy was the best option to control tumor expansion. A regimen of doxorubicin and cisplatin was instituted at once.

Unfortunately, the tumor did not respond to chemotherapy, and continued to grow larger. Seventeen days after admission and upon completion of his initial chemotherapy regimen, the patient left the hospital against medical advice.

The patient was readmitted 7 days later exhibiting epistaxis, hemoptysis, and rapid expansion of the tumor into the neck. He was febrile, with chills and a weight loss of 50 pounds over the previous 3 weeks. Steadily increasing tumor size over the following week necessitated the placement of a tracheostomy due to airway encroachment. Radiation therapy was initiated, with a regimen of irradiation twice a day, 5 days per week. Seventeen days following the commencement of radiation therapy, areas near the periphery of the port showed evidence of radiation toxicity. The lips exhibited edema, excoriations, and desquamation. The left eye showed conjunctival erythema. As this increased in severity over the following 2 weeks, radiation treatment was held, after a total dose of 5450 cGy, to allow for resolution of his cutaneous symptoms.

A repeat CT scan revealed progression of the tumor, now involving the left ethmoid and sphenoid sinuses, orbital floor, and infratemporal and middle cranial fossa. The tumor also spread in an anteroposterior direction, involving the anterior maxilla and deep cervical space. Since the necessity of increasing the area of the radiation port to include the sphenoid sinus would likely result in the loss of his left eye, the patient refused further radiation therapy. He did consent to additional chemotherapy.

Continued treatment was determined to be ineffective due to the relentless increase in tumor size and anatomic extent. It was therefore decided that the patient was no longer a candidate for fur-
ther treatment. Two months following his second admission, the patient was sent home with hospice care, where he died shortly thereafter.

PATHOLOGIC EXAMINATION

The gross surgical specimen consisted of multiple fragments of tan, hemorrhagic soft tissue showing a homogeneous tan surface upon sectioning.

Histologically, the tumor represented a poorly differentiated malignant neoplasm consisting of diffuse infiltrating sheets and organoid nests of pleomorphic epithelioid cells (Figure 2), exhibiting eosinophilic cytoplasm with poorly defined cell borders and irregular, vesiculated nuclei with margined chromatin and prominent nucleoli (Figure 3). The neoplastic cells displayed a brisk mitotic rate with a large proportion of abnormal mitotic figures. Portions of the tumor showed a storiform pattern due to spindling, which blended into the surrounding well-vascularized stroma. A population of multinucleated giant cells was distributed throughout the neoplasm. Focally, the tumor cells produced irregular trabeculae of osteoid extracellular matrix material (Figure 4). Scattered zones of necrosis and interstitial hemorrhage were observed, in addition to overlying areas of mucosal ulceration and epithelial reactive atypia. A search through the epithelium did not reveal any areas of dysplasia, carcinoma in situ, or a malignant epithelial neoplasm.

Immunohistochemical studies were significant for a strong, diffuse positivity for vimentin. Stains for cytokeratin, S-100, HMB-45, epithelial membrane antigen, desmin, Factor VIII, chromogranin, placental alkaline phosphatase, CD 3, CD 20, CD 30 (Ki-1), CD 43, and \( \kappa \) and \( \lambda \) light chains were negative. Focal equivocal staining was present for CD 45RB (LCA) and CD 68 (KP1). The multinucleated giant cells exhibited intense staining for CD 68 (KP1).

Additional studies using transmission electron microscopy were performed, which showed primitive tumor cells with complex interdigitating cell membranes, focal intercellular junctions, rough endoplasmic reticulum, mitochondria, lysosomes, irregular nuclear membranes, peripherally clumped chromatin, and multiple nucleoli. Scant intercellular collagen was seen. There were no apparent melanosomes, tonofilaments, complex desmosomal attachments, thick/thin/intermediate filaments, or Z-band material.

**FIGURE 2.** The majority of the tumor consisted of infiltrating sheets of ovoid to polygonal epithelioid cells (hematoxylin-eosin stain, original magnification \( \times 100 \)).

**FIGURE 3.** The neoplastic epithelioid cells exhibited variably sized irregular vesicular nuclei with 1 or more prominent nucleoli. Mitotic figures were common (arrows) (hematoxylin-eosin stain, original magnification \( \times 400 \)).

**FIGURE 4.** Epithelioid osteosarcoma. Zones of mineralizing osteoid (asterisks) were found arising from the neoplastic cells (hematoxylin-eosin stain, original magnification \( \times 400 \)).
On the basis of the radiographic, histopathologic, immunohistochemical, and electron microscopic characteristics, it was concluded that this tumor represented the epithelioid variant of osteosarcoma.

DISCUSSION

Osteosarcoma of the jaws accounts for up to one-tenth of all osteosarcomas. They occur approximately twice as often in men than in women, and typically arise later in life than their extragnathic counterparts, with a median age of 28 years, contrasting with an overall median age of 19 years. Expansion with or without pain in the involved site is the most common presenting symptom, with destruction of the periodontium and subsequent loosening of the teeth observed in tumors encompassing the alveolar ridge. The radiographic features of osteosarcoma of the jaws include cortical destruction and perforation, expansion of the periodontal ligament space, calcifications above the level of the alveolar crest, tooth resorption, and a radiolucent, radiopaque, or mixed pattern. A cortical sunburst pattern may also be seen.

There is some uncertainty pertaining to the frequency of histologic subtypes of osteosarcoma. The largest group (approximately 49%) of a combined total of 89 jaw osteosarcomas reported by Clark et al and Delgado et al were represented by the chondroblastic subtype, characterized by the presence of lobules of atypical cartilage, often showing focal mineralization, produced within zones of invasive malignant mesenchyme, which contains areas of osteoid formation. Nearly one-third of gnathic osteosarcomas consist of the osteoblastic subtype, which exhibits osteoid production by atypical polygonal mesenchymal cells. The remainder of the tumors consist of the fibroblastic subtype, showing focal osteoid production upon a background of atypical spindle cells. However, a smaller series of 18 jaw osteosarcomas reported by Slootweg and Müller contradict the earlier findings, with the osteoblastic, fibroblastic, and chondroblastic subtypes constituting one half, one third, and one sixth of cases, respectively. Other recognized histologic subtypes of osteosarcoma are small cell, malignant fibrous histiocytoma-like, osteoblastoma-like, giant cell-rich, telangiectatic, low-grade intraosseous, and epithelioid.

Epithelioid osteosarcoma is a rare subtype of osteosarcoma characterized by a neoplastic population of ovoid to polygonal cells of nearly uniform size, with conspicuous cytoplasm that morphologically mimic epithelial cells, with focal osteoid formation. Constituent cells of the tumor may be uniformly eosinophilic, as in our case, or there may be variable numbers of clear cells. Periodic multinucleated giant cells resembling osteoclasts have also been encountered among the tumor cells. The bland morphology of the osteoblasts in this variant is similar to that of other subtypes of osteosarcoma.

Many high-grade large-cell malignancies show cellular features similar to the neoplastic cells of epithelioid osteosarcoma, such as epithelioid carcinomas and sarcomas, melanoma, and large-cell lymphoma. The potential for diagnostic confusion necessitates histochemical and immunohistochemical studies to further delineate the phenotype of this variant. The morphologic and immunohistochemical features of this tumor have been described in scattered case reports and case series.

One frequently cited case report and immunohistochemical analysis of a designated epithelioid osteosarcoma instead represents a carcinosarcoma, a fact the authors recognize as they use the terms...
interchangeably in the text. Examination of the supplied photomicrographs reveals the tumor in question to indeed be a carcinosarcoma, with the error in nomenclature most likely due to the paucity of well-described cases of epithelioid osteosarcoma in the literature at the time of publication.

Our case involves a 50-year-old man with a mass of the left maxilla showing brisk growth and subsequently diagnosed as epithelioid osteosarcoma. This, to our knowledge, is the first reported instance of this rare tumor in the maxillofacial complex. Difficulty was encountered in establishing a diagnosis because of the poor differentiation of the neoplasm, which displayed histologic features consistent with undifferentiated carcinoma, melanoma, and lymphoma. The tissue sampled at biopsy was superficial and corresponded to the radiolucent periphery of the tumor; yet, close histologic examination revealed foci of neoplastic cells producing osteoid, leading to the diagnosis of osteosarcoma. An immunohistochemical panel revealed unequivocal staining of tumor cells for vimentin only.

The treatment and management of osteosarcoma consists of a combination of surgery, chemotherapy, and radiation therapy.\textsuperscript{13,14} Surgical excision of the tumor is a mainstay of treatment. Clear surgical margins are associated with a considerably higher 5-year survival rate.\textsuperscript{13} Chemotherapy is usually employed before and after surgery, although its ability to increase survival has yet to be unequivocally demonstrated. Preoperative use of such agents as doxorubicin, cisplatin, and methotrexate may shrink the tumor and facilitate the establishment of clear surgical margins. Postoperative radiation therapy has been used in instances of extensive and/or high-grade disease and in cases with presence of tumor at the surgical margins, although its efficacy is questionable.\textsuperscript{13} The 5-year survival rate for osteosarcoma of the head and neck approaches 55%.\textsuperscript{13}

The limited number of detailed case reports\textsuperscript{7–9} shows the prognosis for epithelioid osteosarcoma to be dismal. Out of the compiled 8 patients, 7 were dead of disease within 5 to 52 months of initial surgery or hospital admission. This was despite treatment regimens consisting of chemo-therapy with or without surgery or radiotherapy. One patient\textsuperscript{9} showed no evidence of disease 4 months after initial surgery.

In conclusion, we report a case of epithelioid osteosarcoma arising in the maxillofacial region. The presentation of this tumor in a 50-year-old man, well outside the typical age range for an osteosarcoma of the head and neck area, was unusual. Despite surgery, chemotherapy, and radiotherapy, the tumor grew relentlessly and resulted in the patient's death less than 3 months following initial presentation.

**REFERENCES**