# Clinical and Histopathological Profile of Primary or Secondary Osteosarcoma of the Jaws

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**Abstract.** *Osteosarcoma of the jaw is a rare disease; we report two cases, one in which the primary osteosarcoma had occurred in the sacrum and ileum, the second at the mandible. Dissemination of osteosarcoma to other organs, especially early dissemination to the lung, is common, but metastasis to the jaw has only rarely been reported. About 10% of osteosarcomas occur in the head and neck, most in the mandible or maxilla. Clinically, both patients presented swelling, and pain at the jaw in the premolar-molar region. At radiography, extensive bone erosion and soft-tissue swelling were apparent. A biopsy was taken and a diagnosis of osteosarcoma rendered in both cases. Histological examination revealed a proliferation of atypical osteoblast-like cells with hyperchromatic nuclei and formation of scattered neoplastic osteoid tissue. Immunohistochemistry for a panel of antibodies showed strong positivity for CD99, weak positivity for S-100, but was negative for desmin, vimentin, and cytokeratins. The diagnosis for both cases was of osteogenic osteosarcoma, chondroblastic subtype. Unfortunately, both patients died, one before the planned chemotherapy regime could begin, the second during the chemotherapy course. Our report aims to highlight the importance of the diagnostic profile in formulating a diagnosis of osteosarcoma, and that this tumor, although very rare, may be primary or may metastasize to the jaws.*

Osteosarcoma (OS) is the commonest primary neoplasm of the bone, typically affecting the metaphysis of the femur or tibia in children and young adults (1); it is the third commonest malignancy in adolescents (2). About 10% of OS occurs in the head and neck (3); those occurring in the jaws account for 4% (4).

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OS of the jaws presents some differences compared to its counterpart in the long bones. In the jaws, there is typically an equal gender predilection, whereas in the long bones, a slight male preponderance is found. Likewise, the age of onset differs: cases in the jaws are diagnosed on average two decades later than their long-bone counterparts, which have a peak incidence between the ages of 10 and 14 years (5-7).

Several different factors are considered significant in the etiology of this tumor, including irradiation, pre-existing benign bone disorders, and trauma (8). Tumorigenesis has been linked to alterations in several genes. The first association with an inherited predisposition was observed in patients with bilateral retinoblastoma. This association was confirmed by identification of the retinoblastoma susceptibility gene (*RB*1) on human chromosome 13, which showed a high number of mutations in osteosarcoma cases (9). The second gene associated with OS was the *p53* gene, mutations in which have been reported in sporadic cases of OS (10-11).

The commonest signs and symptoms associated with jaw OS, as reported in the literature, consist of persistent pain, swelling, and paresthesia/anesthesia (12, 13). Imaging studies in patients with OS should include panoramic radiographs and computed tomographic (CT) scans of the head and neck, which are used to evaluate cortical bone involvement and possible lymphadenopathy. In addition, magnetic resonance imaging (MRI) is useful to assess the extent of marrow spread. Chest and abdominal CT, as well as isotope bone scan to rule out metastasis to other bones, are required for staging.

We report two cases, in both of which the tumor metastasized to both lungs; we trace the clinical profile and immunohistochemical studies that are needed in order to improve diagnosis.

## Case Reports

*Case 1.* A 62-year-old man complained of persistent pain of the palate, present for approximately 4 months. The patient noticed swelling of the right side of the face and presented for treatment. There was no other contributory past medical or

family history, such as trauma or irradiation. Extraoral examination revealed facial asymmetry related to the enlargement of the right maxilla. The right swelling extended from the zygomatic arch to the inferior border of the mandible, and the overlying skin was normal and nonindurated.

Intraoral examination revealed a mass measuring 3.5 cm × 3.0 cm on the buccal gingiva of the maxillary area, which was bony-hard and reddish in color. There were no abnormal findings in the cervical lymph nodes or any other part of the body. A panoramic radiograph revealed mixed radiolucent and radiopaque lesions, with poorly circumscribed borders in the maxilla.

CT detected a heterogeneously sclerotic lesion. Chest radiograph and abdominal ultrasound examination were all normal.

At clinical examination, there was cortical bone expansion and perforation intraorally. Panoramic radiography showed extensive bone destruction in the maxilla area. An incisional biopsy was performed, and a diagnosis of chondroblastic subtype osteogenic OS rendered. The patient was referred to an oncologist and a head and neck surgeon and was submitted to hemimandibulectomy, followed by 30 sessions of radiotherapy. However, the patient died approximately two months after diagnosis and before the planned chemotherapy course could begin.

*Case 2*. A 58-year-old woman was referred with a painful, non-tender submucosal swelling over the mandible in the second premolar and first molar area that had been present for approximately one month. Intraoral examination showed a clearly demarcated mass measuring 2.5 cm × 3 cm, covered with oral mucosa of normal appearance. CT revealed a hard-tissue mass above the right mandible with bone involvement. The patient reported a history of OS affecting the left part of her sacrum, which had been diagnosed approximately six years previously. This had been treated with chemotherapy alone, without surgical intervention or radiotherapy. About six years after onset of the primary tumor, the OS metastasized at the mandible and, on the basis of MRI data, it was strongly suspected that the primary tumor had metastasized first to the lungs and then had further metastasized to the mandible. To confirm this hypothesis, an incisional biopsy of the affected area was taken under local anesthesia and sent for microscopic analysis. A diagnosis of chondroblastic OS with fibroblastic area was rendered. Wide excision with negative margins was the treatment; however, the patient died during the chemotherapy course.

## Histology

In both cases, histological examination of the specimens revealed a proliferation of atypical osteoblast-like cells with hyperchromatic nuclei, and formation of scattered neoplastic osteoid tissue beneath the stratified squamous cell epithelium. The tumor was formed exclusively of homogeneous cells of large aspect, with polarized nuclei and abundant cytoplasm, a trabecular pattern predominating that was formed of two rows of cells showing scarce intercellular material. Typical osteoid material involved by and containing malignant cells was seen in a few areas of the tumor. Nuclear pleomorphism was evident but not aberrant, and mitotic figures were visible.

Both chondroblastic subtypes, necrosis, fibrosis, cartilaginous tissue, and spindle cells were present. In the first case areas of proliferating fibroblasts along with bundles of collagen fibers were observed (Figure 1 and Figure 2 A,B).

A panel of antibodies was used for immunohistochemical evaluation and the results are summarized in Table I.

CD99 cytoplasmic expression was stronger in most of the neoplastic cells, and reaction for extracellular matrix was also strong in many areas, but also negative in the osteoid material (Figure 2C). S-100 staining was positive in the cytoplasm of cartilaginous cells, preferentially so in the adjacent areas of calcification and also faintly stained the extracellular matrix close to the osteoid material, but was negative in the osteoid material itself (Figure 2D). The Ki-67 (MIB-1) labeling index was 40%, calculated after analyzing approximately 1000 cells in 5 high-power fields in the region of the tumor with greatest density of staining.

Both tumors were similar for all markers tested. The tumor cells stained positively for CD99, MIB-1 and S-100, showing focal nuclear and cytoplasmic positivity in most cells, but were negative for cytokeratin AE1-AE3 (monoclonal anticytokeratin) and smooth muscle actin (SMA).

Taken together, these data confirmed the diagnosis of mixed osteogenic OS for case 2 and chondroblastic subtypes for case 1, affecting the mandible and the maxilla.

## Discussion

Primary OS of the jaws is rare, and metastasis to the mouth and jawbone is extremely rare, accounting for 1% of all malignancies (14). Multiple metastases of OS commonly occur, and frequently involve the lungs (14); this occurred in one of our patients, who also developed jaw metastases. In this patient, the primary OS had metastasized to the lung without any other detectable distant metastases; in the second case, multiple metastases were present in the lung and lumbar vertebrae.

The prevailing symptom was swelling, which both patients reported, followed by loosening teeth and pain. Radiologically, both cases showed a well-delimited lucent lesion and tooth displacement.

The histological diagnosis of osteosarcoma was formulated in both cases with conventional H&E staining and immunohistochemical staining. Histopathologically, OS of the long bones and that of the jaw bones share common features. The diagnosis of OS is based on the recognition of osteoid production by the tumor cells (15). Depending on the

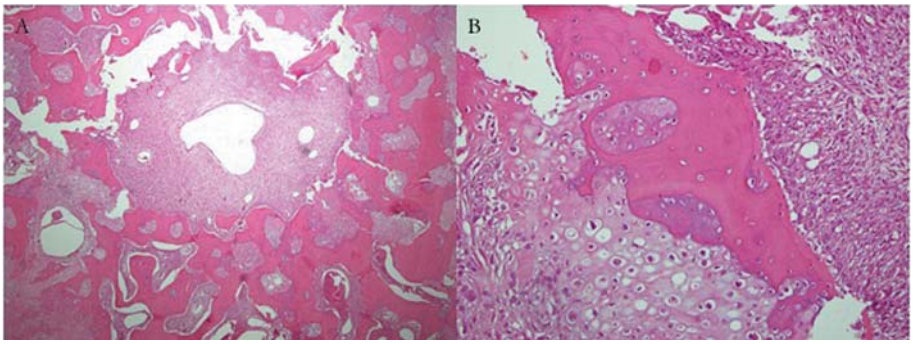


Figure 1. *Mixed osteosarcoma A: A panoramic view of the lesion where cellular areas are scattered throughout abundant bone matrix (H&E, ×40). B: Higher magnification demonstrating the different areas of chondroblastic and fibroblastic appearance in the context of osteosarcoma. The chondroblastic component appears as cartilaginous matrix with a malignant features; the fibroblastic component may mimic fibrosarcoma (H&E, ×200).*

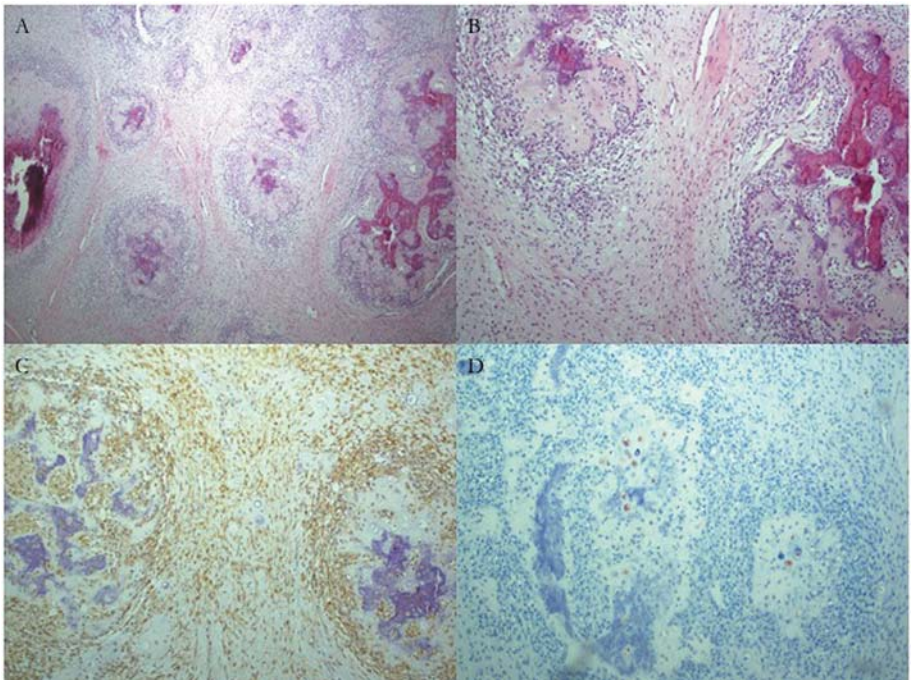


Figure 2. *Chondroblastic osteosarcoma. A: Chondroblastic osteosarcoma: a panoramic view shows the tumor composed of lobules of cartilage with central bony trabeculae (H&E, ×40). B: Higher magnification demostrating a condensation of spindle cells at the periphery of cartilaginous nodules. There is a gradual transition from the chondroid areas to spindle cell areas (H&E, ×200). C: The spindle cell areas stained for CD99 (×20). D: The cartilaginous component stained with S-100 protein (×20).*

predominant type of extracellular matrix present, OS is categorized histopathologically into osteoblastic, chondroblastic, or fibroblastic subtypes (16). It is difficult to differentiate some tumors from malignant fibrous histiocytomas (17); other less frequent types are osteogenic, fibroblastic, telangiectatic, low-grade intraosseous, parosteal, and periosteal tumors (5, 14, 18, 19).

Immunohistochemistry was an important aid in diagnosis; S-100 and CD99 markers were evaluated to confirm the diagnosis. CD99 was constantly positive, with S-100 showing focally positivity in the cytoplasm of cartilaginous cells. Positivity for MIB-1 gave a proliferative index of 40% of the tumor cells. Such challenging cases often pose a problem in deciding upon definitive surgical treatment.

The optimal treatment for jaw metastases of OS is radical surgical mandibular resection (19). Likewise, the most important curative therapy for primary jaw OS has been found to be radical resection with clear margins (18, 20-24). Clear margins may be technically difficult to achieve, particularly in the maxilla and at the skull base, where

Table I. *Immunohistochemical findings of the current cases.*

| Antibody | Clone | Dilution | Supplier city/state/country | Reactivity case (1) | Reactivity case (2) | Antigen retrieval |
|---|---|---|---|---|---|---|
| CD99 | 12E7 | 1:50 | Dako,Copenhagen, Denmark | ++ | ++ | None |
| CKs | AE1/AE3 | 1:50 | Dako,Copenhagen, Denmark | – | – | Microwave Citrate PH 6 |
| S-100 | Polyclonal | 1:1000 | Dako,Copenhagen, Denmark | + | + | None |
| SMA | HHF35 | 1:100 | Bio-Optica, Milan, Italy | – | – | None |
| Ki-67 | MIB-1 | 1:200 | Dako, Copenhagen, Denmark | + | + | Microwave Citrate PH 6 |

CKs: Cytokeratins; SMA:smooth muscle actin.

positive margin rates of 31% to 52.4% have been reported (20, 22, 23). On the contrary, for OS in the long bones, a multi-modal treatment protocol has been established. In long-bone OS, chemotherapy is given as induction, neoadjuvant and adjuvantly after surgical therapy (25). The benefits of chemotherapy for long-bone OS have been clearly defined, and have led to a dramatic improvement in disease-related survival rates, from 20% in the 1960s to 60-70% in the 1980s (26, 27), whereas neoadjuvant chemotherapy, although often applied in head-and-neck OS, has not been conclusively established as being superior to prompt postoperative chemotherapy.

The results of published studies are contrasting (13, 28). The most commonly used chemotherapeutic agents are doxorubicin, cisplatin, adriamycin and high-dose methotrexate. Chemotherapy has not proved as effective in OS, for several reasons: One is that the distant metastatic rate of 18% for the jaws contrasts with the 80% rate for microscopic subclinical metastatic disease in long-bone OS (28). Again, high-grade OS is reported in 85% for long-bone cases, but in the jaw, only 56% to 79% of cases are high grade (29, 30). In addition, the histological response to neoadjuvant chemotherapy is below 25% for OS of the jaws (31) compared with 41% for long-bone OS (32). Lastly, most cases of OS of the jaws are of the chondroblastic type, as opposed to long-bone OS, in which the osteoblastic type predominates; the osteoblastic type has a worse prognosis (33). All these factors may play roles in explaining the different rates of metastasis.

With regard to postoperative radiation therapy (RT), although OS is generally considered a radioresistant tumor, this treatment has nevertheless been employed (31), although Delgado *et al*. (6) reported no improvement in survival for patients with positive margins who were treated with RT. Multimodality therapy using chemotherapy and RT has shown improvement in survival rates in the OS of the extremities, from 20% to 70% (34). A recent study conducted to evaluate the outcomes of multimodality treatment in patients with OS of the head and neck region with positive resection margin found that combined modality treatment, comprising surgery and RT considerably improved local control as compared to surgery alone (35).

A new treatment investigated the expression of inducible nitric oxide synthase (iNOS) in OS of the jaw, its relationship with tumor angiogenesis and clinicopathological characteristics, indicating that iNOS may promote tumor angiogenesis in OS of the jaw and may represent an important target in antitumor therapy (36).

In the present case, we were unable to follow any therapeutic protocol because one patient died very shortly after diagnosis of the metastatic lesion, before the planned chemotherapy treatment could begin, and the second died during therapy.

Jaw OS has a better prognosis than conventional osteosarcomas. Clark *et al*. (30) attributed this to the occurrence of predominantly chondroblastic low-grade OS in the jaws. For conventional OS, the 5-year survival rate is 20.3%, whereas for jaw OS it is 40% (16). OS spreads microscopically along marrow spaces and the mandibular dental canal; extracted tooth sockets may enhance extraosseous spread. Local recurrence is the commonest complication of OS (8, 29, 30), whereas distant metastases are rare (33). Uncontrollable local spread is the main cause of death due to OS. Local recurrence and distant metastasis, mainly to the lungs, are common, while nodal involvement is rare (6).

The biological behavior of OS differs from that of tumors involving other skeletal bones, not only in regard to the average age at onset, OS typically having onset 10 to 20 years later than that reported for skeletal lesions, but also because survival rates are higher (37, 38).

Head- and -neck OS is associated with a lower metastatic rate than is long-bone OS, and has a better 5-year survival rate, ranging between 27% and 84% (5, 8). One of our patients died due to uncontrollable local recurrences, and the other from distant metastases.

To sum up: clinicians should consider not only the possibility of a primary lesion, but also of metastases ot the jaw from OS. While being an uncommon finding, the latter remains a clinical possibility in patients with known primary OS. However, it is essential to take a biopsy in order to reach a definitive diagnosis. Immunohistochemistry is an important aid in formulating a diagnosis of OS. An early diagnosis of OS is fundamental for the rapid institution of adequate treatment.

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