

Osteosarcoma of jaws: Challenges in diagnosis

Sonalee Shah¹, Biswajit Mishra², Nidhi Tiwari¹, Anand Nikunj²

Departments of ¹Oral Pathology and ²Oral Surgery, Government Dental College, Raipur, Chhattisgarh, India

Abstract

Osteosarcoma (OS) accounts for about 20% of all sarcomas with gnathic involvement seen in about 6%–10% of all OSs. The clinical presentation of OSs in the jaws is different from that of long bones as swelling is the most common complaint in patients with jaw OS followed by pain. The histopathologic variables seen are more favorable in OSs of jaws. Low-grade tumors are Stage I, high-grade tumors are Stage II and metastatic tumors (regardless of grade) are Stage III. A 17-year-old male patient reported with a complaint of the presence of an intra-oral growth gradually increasing in size in the right buccal mucosa region soft tissue enveloping the occlusal aspect of the right mandibular second molar. Extraorally swelling was present on the right side of the face for 4 months. Radiographically, there was a radiolucency from the distal aspect of right Mandibular second molar extending into the ramus region of the mandible with ill-defined borders. Hemi-mandibulectomy was done with the removal of the right mandible from the premolar region to condyle and coronoid processes. Microscopic evaluation of the sections after hematoxylin and eosin staining revealed interlacing fascicles of spindle-shaped cells arranged in a biphasic pattern and some areas of attempted bone formation evident in deeper sections. Tumor was an osteoblastic variety consisting of tumor osteoid surrounded by bizarrely arranged fibroblast-like cells. It showed positive staining with α -smooth muscle actin and Vimentin, suggesting a malignant tumor of mesenchymal cells with high myofibroblastic activity. Our case had small-cell histology; therefore, differential diagnosis was important.

Keywords: Chondroblastic, fibrosarcoma, osteoblastic, osteosarcoma, small-cell type osteosarcoma

Address for correspondence: Dr. Sonalee Shah, Department of Oral Pathology, Government Dental College, Raipur - 492 001, Chhattisgarh, India.
E-mail: drsonaleeshah@gmail.com

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INTRODUCTION

Osteosarcoma (OS) accounts for about 20% of all sarcomas and is the most common primary malignant bone tumor (excluding bone marrow tumors) in children and adults and it constitutes about 1% of all head and neck malignancies. The OSs of jaws account for only about 6%–10% of all OSs. Although rare, these tumors, are the seventh most common malignancy of childhood and they have high mortality rates.^[1,2] These mandibular and maxillary primary OSs behave differently than OSs of

long bones and have a slightly better prognosis than them.^[1] They usually affect patients who are 10–20 years older than those afflicted by long bone OSs. The incidences of distant metastasis are lesser in jaw OSs (JOSs). The histopathologic variables seen are more favorable and the survival rates are higher. The difference in the clinical presentation of OSs in the jaws from that of long bones is in the fact that swelling is the most common complaint in patients with JOS followed by pain, while bone pain during activity is characteristic of long bone OSs. Thus, the biological behavior of JOS differs from OSs involving long bones.^[2]

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OS within the medullary cavity of the bone is histologically classified into the conventional OS, telangiectatic OS, small cell OS and low-grade central OS, according to the WHO Classification of Tumours of Soft Tissue and Bone in human medicine, fourth edition. Conventional OS accounts for 80%–90% of all OSs and has a broad spectrum of morphology divided into three main histologic subtypes based on the prominent matrix they secrete with minimal prognostic significance. These are-osteoblastic, chondroblastic, fibroblastic. Other morphologic variants include Giant cell-rich, osteblastoma-like, epithelioid variant, clear cell, chondroblastoma-like, chondromyxoid-fibroma like and small cell variant [Table 1].^[3,4]

JOS is more frequent in men than in females. Bone growth, hormonal changes and growth during puberty are likely to be involved in OS etiology, partly explaining the slightly higher overall incidence in males. Head-and-neck OSs tend to recur locally, leading to increased mortality, and frequent symptoms of recurrence are: swelling at the site of disease, facial dysesthesia, and loosening of the teeth. According to Garrington *et al.*, distant metastases are also seen in about 50% of cases. The histopathological characteristic of OS is the presence of aggressive malignant mesenchymal cells producing osteoid or immature bone.^[5-7]

Thus when there is a bony hard swelling centered over the mandible, it should be investigated, keeping in mind the possibility of diagnosing a malignant bone tumor. Surgical excision is the standard method of care for treating mandibular OSs when they occur. This is because, OS of Head and Neck is a distinct subtype of OS that should be managed with radical surgical excision with consideration for adjuvant radiotherapy for close/positive surgical margins.^[8]

Table 1: Histologic Classification of Osteosarcomas

Central (Medullary)	High-grade central OS Conventional OS Telangiectatic OS Small cell OS Epithelioid OS Osteblastoma-like OS Chondroblastoma-like OS Fibrohistiocytic OS Giant cell OS
Surface (Peripheral)	Low grade(well-differentiated) central OS Paraosteal(Juxta cortical) OS Low grade (well-differentiated) OS Intermediate grade OS Periosteal OS High grade surface OS
Intra-Cortical Gnathic	
Extra-Skeletal	High grade Low grade

Three main factors generally are proposed to be etiologically significant in the development of OSs-irradiation, pre-existing benign bone disorders and trauma. OS tumorigenesis has been linked to alterations in several genes also.^[9]

Aggressive ossifying fibroma and osteblastoma must be considered in the clinical differential diagnosis, which can resemble OS in clinical presentation and aggressive biologic behavior.^[9,10]

Role of the pathologist

The role of the pathologist in the management of bone tumors is essential. Accurate diagnosis of a given neoplasm determines not only the patient's general prognosis but, more importantly, the type of therapeutic modality needed to achieve optimal results. Unfortunately, little is known about the antigenic specificity of normal bone tissue and bone neoplasias, and although several candidate antigens have been explored, reagents to detect bone-specific antigens are not yet available. However, immunohistochemistry (IHC) evaluation may help to confirm the diagnosis made from hematoxylin and eosin (H&E) stained slides by ruling out other lesions with similar histologic appearance and thereby increase the confidence in the diagnosis, allowing a more accurate determination of cell of origin for most poorly differentiated neoplasms.^[11]

Mesenchymal marker

Vimentin

Although of limited value in the differential diagnosis, vimentin is an abundant antigen that can be demonstrated in most properly fixed tissues and survives most decalcification procedures. This is because all sarcomas stain positive for Vimentin as it is the mesenchymal cell intermediate filament. The pleomorphic neoplastic cells of OS show positive intracytoplasmic staining for vimentin.

Epithelial markers

Epithelial membrane antigen

Epithelial membrane antigen is expressed in approximately 75% of the epithelial-like sarcomas (epithelioid and synovial sarcomas) and in malignant peripheral nerve sheath tumors, leiomyosarcomas, histiocytes and neoplasias of histiocytic origin.

Neuronal, nerve sheath and melanocytic markers

S-100 Protein (S-100)

Widely distributed in peripheral and central nervous systems, the S-100 protein localizes to both the nucleus and the cytoplasm and in the appropriate context, is one of the most useful markers. S-100 is expressed diffusely in neurofibromas and neurilemmomas, liposarcomas, ossifying

fibromyxoid tumor, chondrosarcomas and in 90% of clear-cell sarcomas.

Endothelial/vascular markers

CD34

A sensitive marker for endothelial differentiation, CD34 is expressed by 70% of angiosarcomas, 90% of Kaposi's sarcomas and 100% of epithelioid hemangioendotheliomas.^[11]

Smooth muscle marker

α -Smooth muscle actin staining

The pattern of immunoexpression is intense and diffuse throughout the sarcomatous stroma. To support the dysregulated expression of growth factors such as transforming growth factor (TGF), insulin-like growth factor and connective tissue growth factor, which are the major secretory products of myofibroblasts and are also known to affect the OS malignant cells. The major cytokines secreted by α -smooth muscle actin staining (α -SMA) positive myofibroblasts include interleukin (IL)-1, 4, 6, 8 and IL-11, of which IL-6 and 8 are seen to be significantly higher in malignant bone tumors as OS. The degraded bone matrix releases TGF- β which activates IL-6 and IL-11 leading to osteoclastic activation, facilitating further invasion and the release of pro-resorptive cytokines. This indicates the pivotal direct or indirect role of myofibroblasts in the molecular pathogenesis of OS oncogenesis through its diverse key molecular factors affecting OS cells and endothelial cells in the tumor progression correlating with poor prognosis. The reason being that myofibroblasts have a dual role, i.e. role in host-defense mechanism in limiting the extent of the lesion by desmoplasia and role in progression of the lesion by stromal modulation including the growth of the lesion, degradation of the extracellular matrix, angiogenesis and metastasis.^[12]

Osteosarcoma and immunohistochemistry

The differential diagnosis of OS from other sarcomas (e.g., malignant fibrous histiocytoma, fibrosarcoma, Ewing's sarcoma [EWS]) is important because of the specific therapy required for OS patients. Most OSs express vimentin and according to some authors, some tumors focally express cytokeratin and desmin, although these findings have not been widely confirmed. Bone matrix proteins, such as osteocalcin, alkaline phosphatase and osteonectin, are expressed in OSs. However, their presence has also been detected in chondrosarcomas, EWS, fibrosarcomas and malignant fibrous histiocytomas. Caution needs to be exercised in the interpretation of the focal expression of a variety of markers (e.g., S-100,

actin, epithelial membrane antigen) found occasionally in otherwise typical OSs. Extraskelatal OSs of the fibroblastic subtype often have sparse amounts of osteoid and can be differentiated from malignant fibrous histiocytoma based on strong expression of alkaline phosphatase. Chondroblastic OS and chondrosarcoma, however, cannot be distinguished immunohistochemically. It also remains to be seen, if the expression of CD31 or CD34 helps in the differential diagnosis between telangiectatic OS and angiosarcoma. Owing to the fact that different types of collagen present in the bone matrix are also produced by other tumors, they have no application in the differential diagnosis of OS.^[11]

CASE REPORT

A 17-year-old male patient reported with a complaint of intra-oral growth in the right buccal mucosa region and swelling of the right side of face for 4 months with a gradual increase in size.

On extra-oral examination, there was a diffuse, nontender swelling on right side of the face in cheek region around 5 cm \times 4 cm in size. There was a palpable solitary right submandibular lymph node present.

On intra-oral examination, there was swelling on the right side body of mandible with anteroposterior extension from lingual to the right first premolar region and its superio-inferior extension was from the alveolar region of teeth to inferior border of mandible. The swelling had smooth margins and on palpation was firm and soft. The soft-tissue mass projecting from the alveolar region of teeth covered the first molar across buccolingual aspect. On palpation, buccal and lingual cortical plate expansion was evident, which was hard in consistency. Thus the Intra-osseous lesion had expanded extra-osseously and involved the gingival tissue of the region.

Radiographically, there was a radiolucency from the distal aspect of Right mandibular second molar extending into the ramus region of the mandible. The lesion showed a mixed picture with ill-defined borders. Radiographically, the lesion showed sunray appearance near the angle of mandible, periodontal widening was not noted, but bone resorption around teeth apices was seen. Also widening of the mandibular canal was noted with fuzzy, irregular outline [Figure 1].

The patient was treated surgically with right mandible hemimandibulectomy from premolar to coronoid and condyle area.

Gross specimen was of a tumor mass attached to the mandibular cortex from molar to coronoid area. It was soft, brownish, size - 4 cm × 3 cm × 3 cm covering occlusal area and displacing right mandibular first molar. The cut surface of the tumor was whitish in appearance [Figures 2 and 3].

Microscopic evaluation of the sections after H&E staining revealed interlacing fascicles of spindle-shaped cells arranged in a biphasic pattern set in a collagenous stroma. Spindle cells were seen with oval, round and tapering nuclei with pale eosinophilic cytoplasm. These cells were seen alternating with closely packed cells that had small rounded nuclei and eosinophilic cytoplasm. Vascular spaces mimicking the hemangiopericytoma pattern were also observed along with cellular atypia. Foci of forming bone were also evident in deeper tissue sections. Tumor was an osteoblastic variety consisting of tumor osteoid surrounded by bizarrely arranged fibroblast – like cells [Figure 4].

Immunohistochemical staining was done to confirm the nature of tumor. It showed positive staining with α -SMA and Vimentin while it showed negative staining with S-100, EMA, CD34 and Desmin [Figures 5-8].

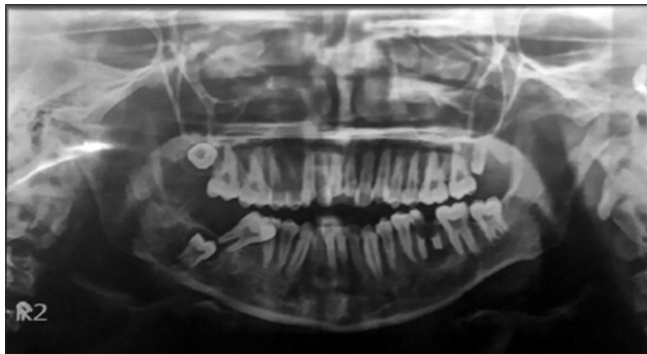


Figure 1: Radiolucency from distal aspect of right mandibular second molar into Ramus region of mandible



Figure 3: Lingual aspect of resected jaw

DISCUSSION

OS is a mesenchymal tumor having evidence of osteoid or bone production by malignant stromal cells in some portion of the tumor. Bizarre tumor cell morphology and divergent differentiation are common. The histologic diagnosis of OS rests solely upon demonstration of unequivocal osteoid being laid down by malignant cells; however, the amount varies widely between tumors. OS is capable of divergent differentiation. It often shows chondroid and fibrous areas besides the pathognomic osteoid deposition by malignant tumor cells. Typical OS may also be accompanied by areas rich in giant cells (giant cell-rich OS), large blood-filled



Figure 2: Buccal aspect of resected jaw

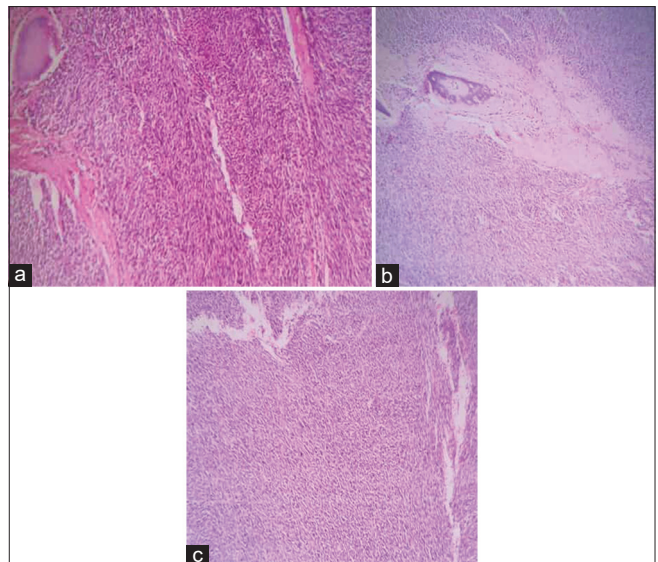


Figure 4: (a) Interlacing fascicles of spindle-shaped cells with oval, round and tapering nuclei showing bone formation ($\times 10$). (b) Interlacing fascicles of spindle-shaped cells with oval, round and tapering nuclei alternating with small round nuclei cells arranged in a biphasic pattern set in a collagenous stroma showing bone formation ($\times 10$). (c) Interlacing fascicles of spindle-shaped cells with oval, round and tapering nuclei alternating with small round nuclei cells arranged in a biphasic pattern ($\times 10$)

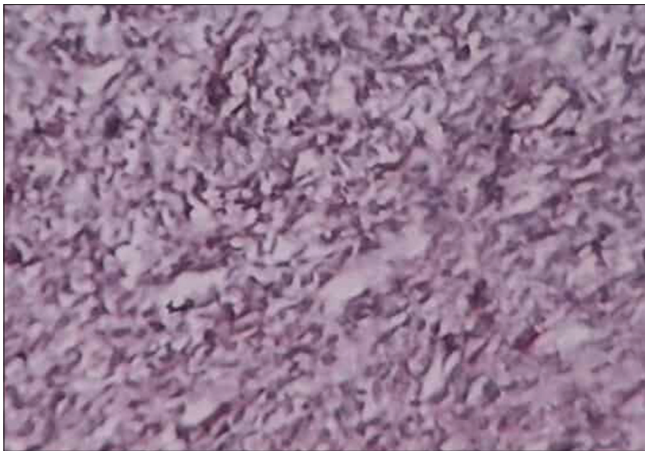


Figure 5: α -Smooth muscle actin positive $\times 10$

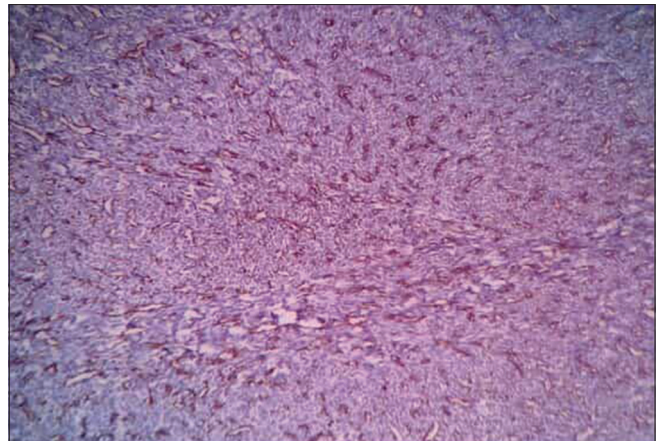


Figure 6: Vimentin positive $\times 10$

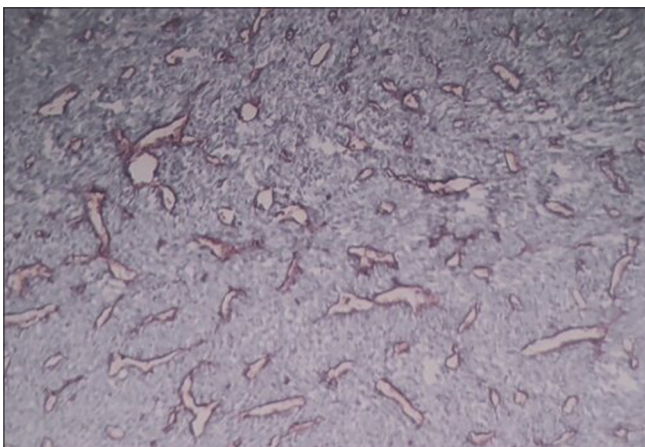


Figure 7: CD34 negative $\times 10$

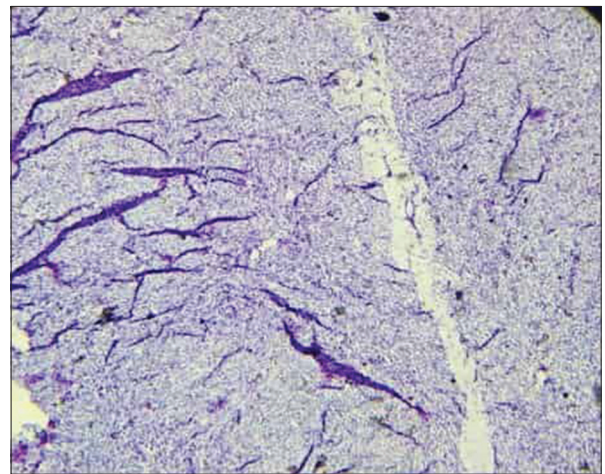


Figure 8: Desmin negative $\times 10$

spaces (telangiectatic OS), or small cells with minimal osteoid production (small cell OS). These tumors are likely to be misdiagnosed as giant cell tumor of bone, aneurysmal bone cyst and EWS, respectively.^[5,6]

Etiologically, JOSs are of many types that are broadly grouped as:

- Primary
- Secondary.

Primary tumors have unknown etiology and may occur due to genetic influences as well as other environmental factors. Secondary tumors usually occur in older patients with H/O of skeletal Paget's disease, Fibrous dysplasia of bone or as a late consequence of craniofacial irradiation.

The risk factors with a causative role in the occurrence of OS are many and include:

- Rapid bone growth as during adolescent growth spurt
- Ionizing radiation
- Chromic oxide, a radioactive scanning agent
- Mutated Retinoblastoma gene

- Mutations in tumor suppressor gene P53 as in Li-Fraumeni syndrome
- Hormonal factors^[13]
- Mutations in DNA Helicase genes as in Rothmund Thomas syndrome, Werner syndrome and Bloom syndrome.^[5]

The cells of origin of OS are believed to be immature bone-forming cells or they may also arise through neoplastic differentiation of other immature mesenchymal cells into osteoblasts.

In our case, it appears that the causation of the tumor is probably related to a disturbance of bone growth and maturation during periods of high osteoblastic activity. Experimental support for this concept has been offered by Baserga *et al.*, who found no correlation between the degree or distribution of radiation damage and the incidence of tumors but did find a positive correlation between the incidence of tumors and the growth rate of tissue at the time of irradiation in rats.^[7]

Grading and staging

Grading

The most important criterion used for histological grading is the cellularity of the tumor tissue. The more cellular the tumor, the higher is its grade in general. Nuclear abnormalities like: irregularity of the nuclear contours, enlargement and hyperchromasia of the nuclei also correlate with grade. Mitotic features and necrosis are additional features useful in grading.

Staging

The criteria used for staging, include, both the degree of differentiation as well as local and distant spread, to estimate the prognosis of the patient. The universal TNM staging system is not commonly used for sarcomas because of their rarity to metastasize in lymph nodes. The system used most often to formally stage bone sarcomas is known as the Enneking system.

In the Enneking system, the grade (G) of the tumor, the local extent of the primary tumor (T), and whether or not there is metastasis to regional lymph nodes or other organs (M) is considered. So, the grade is divided into a low grade (G1) and high grade (G2).

The extent of the primary tumor is classified as either intracompartmental (T1), meaning it has basically remained in place, or extracompartmental (T2), meaning it has extended into other nearby structures.

Tumors that have not spread to the lymph nodes or other organs are considered M0, while those that have spread are M1. These factors are combined to derive the overall staging of the tumor.

Briefly speaking, low-grade tumors are Stage I, high-grade tumors are Stage II, and metastatic tumors (regardless of grade) are Stage III.^[9]

These tumors, which are a rare malignant condition, usually present later in life i.e., 4th–5th decade.^[13] However, our case was a young, adolescent male with a mandibular tumor.

The average interval between the first symptoms and the first treatment ranged from 1 to 36 months, with an average of about 6.5 months.^[13] In our case, the duration of the lesion as per given history was 4 months.

From both jaws, the mandible is more commonly involved as noted by most authors and in mandible, it tends to involve the body and angle of mandible more often. In our case also, the involvement was of the body of the mandible.

The presenting complaint as reported by various authors, was swelling and it was also the presenting complaint in our case.^[7,13,14]

The average size of the tumors was 5.9 × 4.1 × 3.6 cm in a review by Bertolli *et al.* in Cancer 1991. In our case also the size was 4 cm × 3 cm × 3 cm.

In OS, the radiological features depend on the behavior of a tumor in the form of bone destruction and bone formation and may vary from purely osteogenic (sun-ray appearance) to osteolytic or a mix of both with periosteal reaction. Periodontal ligament space widening and lamina-dura attenuation around a tumor are other features that may be present in JOSs. In the present case, the OPG showed a mixed radiographic picture with the loosening of the first molar of the right mandibular quadrant with irregular and indefinite margins of the radiolucency as well as of mandibular canal.^[11]

These lesions usually have low histologic grade, less frequent metastases, higher incidence in males, common osteoblastic histology and better prognosis.^[15] In our case also, the tumor was of a low histologic grade.

OS is a primary malignant bone tumor in which the mesenchymal neoplastic cells produce osteoid or immature bone. Therefore, the observation of osteoid is the key for the diagnosis of OS.^[7,13,14] Besides the production of osteoid and immature bone, other histological features evident are the presence of neoplastic cells showing anaplasia with epithelioid, plasmacytoid or spindle aspects and the growth with a permeative pattern, filling the marrow space surrounding and eroding pre-existing trabeculae. As mentioned earlier, depending upon the predominant type of extracellular matrix present, conventional OS is classified histopathologically into osteoblastic, chondroblastic and fibroblastic subtypes. The osteoblastic subtype consists of osteoid or immature bone surrounded by haphazardly arranged fibroblast-like or epithelioid cells as seen in the present case.^[5]

Pathologically, high-grade intramedullary OS is the classic or conventional form comprising nearly 80% of the tumors. Low-grade intramedullary OS constitutes <2%, and the other pathological types include parosteal and periosteal OS, which has juxtacortical or surface variants, account for <5%. Consistent with the above distribution, majority of mandibular OSs are conventional as was the case we have reported here. It spreads microscopically through the narrow spaces between bone tissue with other possible routes being the mandibular canal and the structures which connect the intraosseous components

and soft tissues, such as the periodontal ligament and the mental and inferior alveolar nerves. These structures may facilitate the extraosseous spread also of an intraosseous lesion which, can also occur through a recently extracted tooth socket or by perforation of the cortical plates.^[15]

The impact of histology on patient outcomes is modest. Fibroblastic differentiation is considered to be a better prognostic histology as it is a significant predictor of connective tissue related necrosis.^[16]

Recent reports suggest that the basic calponin gene, a smooth muscle differentiation-specific gene that encodes an actin-binding protein involved in the regulation of smooth muscle contractility, is expressed in OSs and that this expression may have favorable prognostic implications. The subtype of OS that most likely will benefit from the application of an immunohistochemistry panel is the “small-cell” type. The diagnosis of this entity is difficult due to the paucity of osteoid and the similarity to other small round cell tumors. Although the antigenic profile of small-cell OS is unknown, nonexpression of markers specific for other small-cell tumors helps in ruling out this diagnosis.^[11]

Thus, histologically the diagnosis of OS in the jaw is not always straightforward, and multiple sequential biopsies are commonly done.^[14] We also had to do the same to be able to diagnose the case, as, osteoid was evident only in very few regions in deeper sections.

Immunohistochemical evaluation was done in our case due to the small cell morphology and it revealed positive labeling for Vimentin but negative for EMA, S100, CD34 and Desmin ruling out endothelial, nerve cell or epithelial origin of the lesion. However, it was positive for α -SMA suggesting an abundance of myofibroblasts.

The lesion in our case was considered as primary, as the patient did not have any predisposing factors known in the literature, such as Paget’s disease, previous exposure to radiation, fibrous dysplasia.

CONCLUSION

To conclude, it seems essential that a triple diagnostic approach, i.e., clinical, radiological and histopathological is relied on essentially in all cases for apt diagnosis and improved prognosis.

Clinically, although the rate of growth varies, it is usually quite rapid. The only significant associated clinical

laboratory finding is an elevated serum alkaline phosphatase value, but it is not a constant occurrence. However, alkaline phosphatase may be demonstrated histochemically in tissue sections if proper fixation procedures have been employed. An OS can be diagnosed radiographically as a malignant lesion with a fair degree of accuracy, but radiographic criteria are not always reliable for a more definitive differential diagnosis.^[7]

Multiple sequential biopsies are often required for the diagnosis of osteosarcoma.^[14] Furthermore, the application of IHC panel is likely to be most beneficial in the diagnosis of “small-cell” type OS due to the paucity of bone formation and osteoid in these lesions.^[11]

Regardless of treatment, the prognosis is poor. Reported 5-year survival rates range from about 5% to 23%. Notable is the fact that OS of the jaws has been reported to have a better prognosis than OS of other bone, the highest reported 5-year survival rate being about 25 years.^[7]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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