Case Report

Osteosarcoma: A case report and evaluation

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Abstract

Osteosarcoma (OS) comprises 2.1% of all malignant oral and maxillofacial tumors. OS arising from the jaw OS differs from OS of the long bones in its biological behavior, presenting a lower incidence of metastasis and a better prognosis. The morphologic and behavioral heterogeneity observed in OS and the perplexity of the varied histological features mimicking other primary and metastatic bone tumors has emphasized the need of advanced molecular techniques in its diagnosis. Hereby, we present a case of OS which was diagnosed by immunohistochemical analysis, aiding in establishing its histogenetic origin.

Keywords: Immunohistochemistry, osteocalcin, osteonectin, osteosarcoma

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INTRODUCTION

Osteosarcoma (OS) is a rare but highly malignant bone tumor. It is also the most common primary malignant lesion of bone in patients under 40 years, excluding multiple myeloma.[1] OS of the jaws OS (JOS) is infrequent as compared to their skeletal counterparts comprising nearly about 6%–13% of all known cases of OS and 2.1% of all malignant oral and maxillofacial tumors.[2-4] Incidence of new cases of JOS is said to be around 0.07 in 100,00/year.[4]

Varied types of OSs have been acknowledged by the World Health Organization (WHO) based on their clinical behavior, radiographic features and degree of cellular atypia.[4-6] OS is histologically classified by the WHO into central, intramedullary and surface variants with a number of subtypes. The central OS is further subdivided into conventional/classic, telangiectatic, small cell and low-grade OS. The conventional OS predominantly comprises the osteoblastic, chondroblastic and fibroblastic variants depending on cellular atypia and type of extracellular matrix, produced by the tumor cells.[3] Despite histopathological similarities of JOS with OS of the long bones, it is biologically different. JOS is known to have a comparably higher survival rate and a lower incidence of metastasis than OS occurring in other areas of the body.[1,4,6,7] Early diagnosis and adequate surgical resection is the key to its better prognosis.[4] This could also be attributed to a better histological differentiation of JOS and a higher mean age group of its occurrence.

The etiology of OS remains unknown. However, pre-existing conditions such as Paget's disease, fibrous dysplasia, ionizing radiations, trauma and retinoblastoma have been considered to be the predisposing factors.[4] Most cases of JOS do not have any suggestive history, but a co-relation with linear bone growth and genetic and environmental factors is being researched upon. Patients with

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chromosomal aberrations in the p53 and the retinoblastoma genes which are localized to 17p13 and 13q14 and patients with Li-Fraumeni syndrome or hereditary retinoblastoma have an increased risk for developing OS.[4]

The morphologic and behavioral heterogeneity observed in OS and the perplexity of the varied histological features mimicking other primary and metastatic bone tumors has emphasized the need of advanced molecular techniques in its diagnosis. The diagnostic algorithm of tumors of bone such as OS is, and always has been a collaborative effort in which clinical, radiologic and pathologic features have played a role, to which a fourth element of immunohistochemistry (IHC) can now be considered a gold standard.

Hereby, we present a case of OS which was diagnosed by immunohistochemical analysis, aiding in establishing its histogenetic origin.

CASE REPORT

A 56-year-old male reported with a chief complaint of painless swelling in the left front region of the lower jaw for 2 years. The swelling was asymptomatic with an increase in size over the past 4 months. There was no history of trauma and a noncontributory medical and surgical history. Extraorally, a diffuse swelling was evident on the lower left region of the face leading to its disfigurement. Mentolabial fold was partially obliterated [Figure 1a]. On palpation, a smooth surfaced, nontender and bony hard swelling was noted. The overlying skin was freely mobile with no local rise in temperature. Lymph nodes were nonpalpable.

Intraoral examination revealed a well-defined swelling extending anteriorly from the left mandibular canine (#33) region to the left second molar (#37) region posteriorly, causing labial vestibular obliteration. Teeth #33–#36 were missing because of prior extraction 5 years back. The overlying mucosa appeared normal [Figure 1b].

Taking into consideration the clinical extent of the lesion, an orthopantomogram (OPG) was advised, which revealed an ill-defined radiolucency occupying the mandibular body extending anteriorly from the canine premolar region up till second molar region posteriorly with destruction of the inferior border of the mandible [Figure 2].

Computed tomography (CT) of the neck with contrast showed an ill-defined heterogeneously enhancing mass in the left gingivobuccal region measuring 5.8 cm × 5.7 cm × 5.6 cm in size along with erosions in the mandible. The mass extended anteriorly up to the midline and infiltrated the adjacent skin involving the left buccinator muscle and anguli oris muscle, closely abutting the left mylohyoid muscle [Figure 3a and b]. Multiple enlarged heterogeneously enhancing lymph nodes were seen at levels Ia, Ib, II bilaterally and level III.

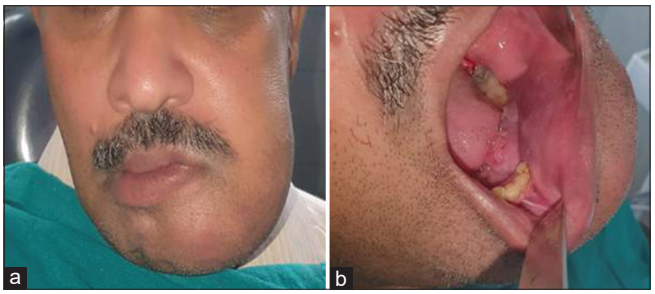

Figure 1: (a) Extraoral photograph showing swelling in the lower left part of the face with partially obliterated mentolabial fold. (b) Intraoral photograph reveals a well-defined swelling extending anteriorly from the left mandibular canine (#33) region to the left second molar (#37) region posteriorly, causing labial vestibular obliteration

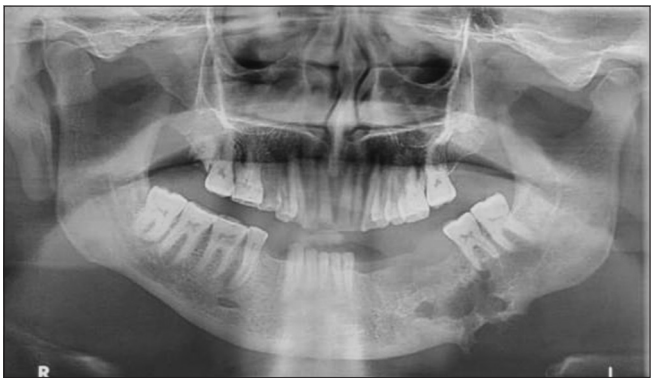

Figure 2: An ill-defined radiolucency occupying the mandibular body extending anteriorly from canine premolar region up till second molar region posteriorly with destruction of the inferior border of the mandible

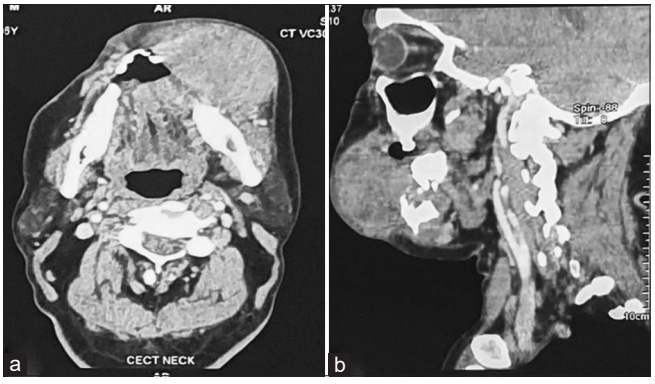

Figure 3: An ill-defined heterogeneously enhancing mass in the left gingivobuccal region, along with erosions in the mandible. The mass extended anteriorly up to the midline and infiltrated the adjacent skin involving the left buccinator muscle and anguli oris muscle, closely abutting left mylohyoid muscle (a) Axial section (b) Sagittal section

Based on these features, a provisional clinical diagnosis of a malignant mesenchymal tumor/intraosseous carcinoma was made. Differential diagnoses included squamous cell carcinoma, fibrosarcoma, OS, chondrosarcoma, central hemangioma, metastatic carcinoma and lymphoma. The patient was referred for incisional biopsy.

Histopathological examination revealed the presence of bizarre-shaped (fusiform/epithelioid/spindle) tumor cells in the stroma arranged in sheets to a lobular pattern. These tumor cells revealed marked anisonucleosis, anisocytosis, hyperchromatism, prominent nucleoli and atypical mitotic figures. The fibrovascular connective tissue stroma was mucoid in areas [Figure 4a-d].

Based on these findings, a diagnosis of poorly differentiated mesenchymal tumor was reached upon. To establish the histogenetic origin of the tumor from a therapeutic and prognostic point of view, IHC was advised. On IHC, the tumor was found to be immunoreactive for vimentin, S100, osteocalcin, osteonectin, pancytokeratin (AE1/AE3) (focally) and immunonegative for CD31/ERG [Figure 5a-f]. A definitive diagnosis of OS Grade 3/4 was made.

The patient was referred to an oncology center, and the treatment regimen which was prescribed was radical surgical resection along with a margin of the normal surrounding tissue, followed by chemotherapy/radiotherapy.

DISCUSSION

The term "Osteosarcoma" introduced by Alexis Boyer in 1805[3] refers to a heterogeneous group of primary malignant neoplasms affecting bone-forming or mesenchymal tissue that have histopathologic evidence of osteogenic differentiation. OS of the head and neck is considered by most clinicians to be distinct clinically from OS that arises in the long bones. The mean age of patients with JOS is higher than those reported for OS of the long bones (<20 years), confirming the occurrence of this type of jaw tumor in the elderly age group.[1] A more frequent occurrence is seen in men than women with a ratio of about 1.5:1 and mandibular lesions reported more often than maxillary though some studies suggest equal distribution in both.[7-10] In the present case, the patient was a 56-year-old male presenting with a mandibular lesion, which is in accordance with the literature.

The characteristic clinical presentation of OS of long bones is bone pain. In jaw lesions pain is not a prominent feature and swelling and paresthesia of the involved region is the commonest presenting complaint.[6] Painless swelling was the only complaint in the present case.

The radiographic appearance varies, depending on the interrelationship between the destruction of the pre-existent cortical or medullary bone, calcification or new bone production and periosteal new bone formation.

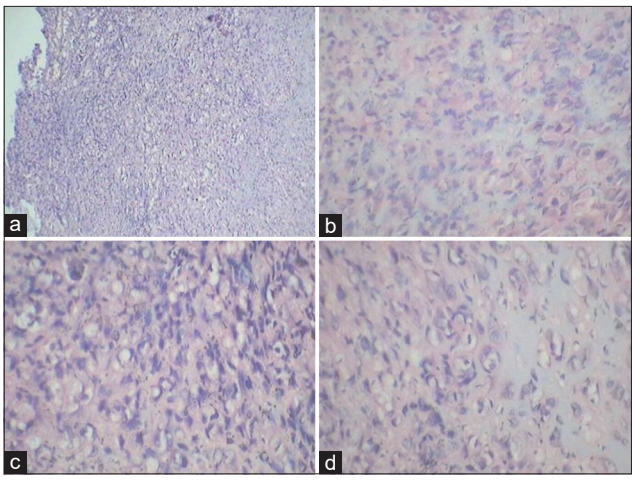

Figure 4: Histopathological examination showing the presence of bizarre shaped (fusiform/epithelioid/spindle) tumor cells in the stroma arranged in sheets to a lobular pattern (a; H & E, ×100). These tumor cells revealed marked anisonucleosis, anisocytosis, hyperchromatism, prominent nucleoli and atypical mitotic figures (b-d; H & E, ×400)

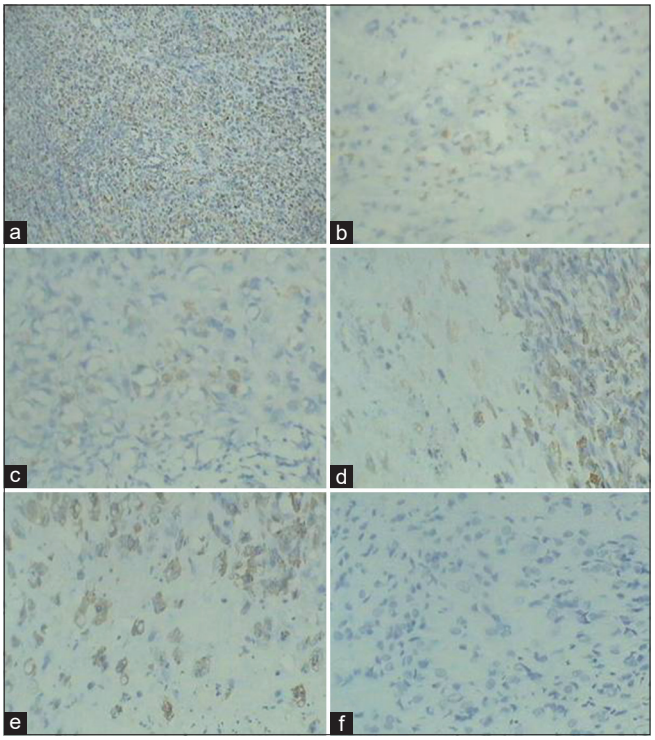

Figure 5: Immunohistochemistry showing immunoreactivity for vimentin (a; ×100), S100 (b; ×400), pancytokeratin (AE1/AE3) (Focally) (c; ×400), osteocalcin (d; ×400), osteonectin (e; ×400) and immunonegativity for CD31 (f; ×400)

Accordingly, the radiographic appearance may be purely osteolytic, mixed or osteogenic (sun-ray appearance).[6] OPG in our case revealed an ill-defined radiolucency with destruction of the inferior border of the mandible, while the CT findings demonstrated the extent of the lesion. Classic radiologic features showing "sunray appearance," "codman's triangle" and "garrington sign" were absent.

The essential microscopic criterion is the direct production of osteoid by malignant mesenchymal cells. In addition to the basic neoplastic cell, the osteoblast-like tumor cell, chondroblast-like, fibroblast-like, histiocyte-like, myofiroblast-like, osteoclast-like and angioblast- like cells have also been reported. Depending on the predominant type of matrix, the osteoid, cartilage or collagen fibers produced by the tumor, OSs are subclassified into osteoblastic, chondroblastic and fibroblastic types. Nearly, 60% of JOS are osteoblastic, 34% fibroblastic and <10% chondroblastic.[2]

Accurate diagnosis of OS is important because they are treated with specific protocols that have been associated with improved survival. Most OSs are easily diagnosed by light microscopy, but their identification can be difficult for the following reasons: (1) their varied histologic features can be mimicked by other primary and metastatic bone tumors, (2) neoplastic bone is not always present in small biopsy specimens, and (3) hyaline-like dense connective tissue can resemble neoplastic bone when examined by light microscopy.[11] In our case, histologically, the tumor showed the presence of bizarre-shaped cells arranged in sheets to a lobular pattern exhibiting atypical features. At this point, a definitive diagnosis could not be inferred as the tumor histologically masqueraded several malignant mesenchymal lesions. Hence to accurately distinguish and classify this lesion, its antigenic profile was done to establish the histogenetic origin. The results of immunohistochemical analysis revealed a better histological distinction and classification of this tumor. Positivity for vimentin (mesenchymal marker) demonstrated the sarcomatous nature of the lesion. A faint localized positivity for S100 revealed a neuronal component in the tumor. The tumor was also subjected to pancytokeratin (AE1/AE3) which showed a focal reactivity. Epithelial markers like cytokeratin are expressed in carcinomas and in vast majority, if not all, of epithelial-like sarcomas (epithelioid and synovial sarcomas). Certain tumors express profiles of cytokeratin subsets that have been reported to be more or less specific, although this is rarely helpful in routine diagnosis.[12]

Tumor cells also showed positivity for osteocalcin and osteonectin. Osteocalcin is a well-characterized bone-specific protein produced by osteoblasts. Its three γ-carboxyglutamic acid (Gla) residues in each molecule bind Ca^{++} and cause a conformational change, possibly playing a role in mineralization; osteocalcin is also known to have a high affinity for hydroxyapatite crystals.[11] Osteonectin, also well characterized, is present in higher concentration in bone than in any other tissue. It is homologous (or identical) to several other proteins including secreted protein acidic and rich in cysteine, basement membrane 40 in mouse basement membranes and carcinoma, 43-kDa protein (bovine parietal endothelial cell culture) and platelet osteonectin.[11] Since it selectively binds hydroxyapatite and type I collagen, it also may have a role in mineralization. Osteocalcin has been associated with 70% sensitivity and 100% specificity, compared with 90% sensitivity and 54% specificity reported for osteonectin in OS.[11,12] The tumor was immmunonegative for endothelial/vascular marker CD31 and ERG, thus excluding central hemangioma/angiosarcoma.

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, Ewing's sarcoma, fibrosarcomas and malignant fibrous histiocytomas. Caution should also be used in the interpretation of focal expression of a variety of markers (e.g., S100, epithelial membrane antigen [EMA] and actin) found occasionally in otherwise typical OSs.[12] Fanburg *et al*.[11] in their study concluded that osteocalcin has 100% specificity in cytoplasmic reactivity of bone-forming tumors. Although they could not distinguish between benign and malignant bone tumors, it was helpful in distinguishing OS from malignancies of other phenotypes. Staining of a matrix using osteocalcin and osteonectin concurrently could not distinguish between neoplastic and reactive bone but may help distinguish neoplastic matrix from dense collagen which is essential in the diagnosis of OS.

Differentiating chondrosarcoma from chondroblastic OS can also be done based on molecular studies. IHC shows chondrosarcoma to be positive for S100 and vimentin and negative for cytokeratin and EMA. Chondroblastic OS will be positive for vimentin, EMA, S100 and rarely cytokeratin. Fibroblastic OS will be positive for vimentin and S100 negative, thus ruling out the neural tumors.[2]

Intense and diffuse positivity for cytokeratin, mainly seen in epithelial tumors, is rarely seen in OS. In cases of epithelioid

OS with intense and diffuse expression of cytokeratin, the differential diagnosis between OS and metastatic carcinoma is a difficult diagnostic problem. Okada *et al*.[13] in their study concluded that clinical history of cancer, existence of other cancers in the visceral region, osteoid formation on histological slides and negativity for EMA may be useful.

Guadagnolo *et al*.[14] described the outcome of the treatment in OS patients. Combined treatment in the form of radical surgery, followed by radiotherapy and/or chemotherapy, was found to result in a good prognosis. Similar findings with respect to treatment have been reported by various authors in their respective case studies.[6] However, radiotherapy and chemotherapy remain as unsatisfying modes of treatment as far as JOS is concerned.[15] They are recommended for the patients, if the surgical margins of the lesions are questionable or positive. It is well known that JOS of various histological types shows local recurrences more frequently than distant metastasis.[7,15] OS, in this case, was graded as 3/4 based on morphologic observation, which is considered a high grade by the WHO and requires periodic follow-up postsurgery and chemotherapy/radiotherapy.

CONCLUSION

JOS is a rare entity with an unusual presentation showing diversity in histopathological patterns. Overlapping clinical appearance, radiological features and histopathology with other lesions may pose a diagnostic dilemma in correct diagnosis from a therapeutic and prognostic point of view. For the distinction of primary tumors versus metastases of non-osseous origin and for the characterization of a small subset of neoplasias, such as those with similar morphology, IHC remains the technique of choice and the preferred gold standard.

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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