CASE REPORT

CHONDROBLASTIC OSTEOSARCOMA OF MAXILLA-A CASE REPORT AND REVIEW OF LITERATURE

Authors:
Skariah Ks[1],
Ambika K[2],
Niveditha Baiju[3],
Pramod P. Mathews[4],
Jithin Jose[1]

[1]Senior Lecturer,
Department of Oral Pathology and Microbiology,
Indira Gandhi Institute of Dental Sciences,
Nellikuzhy P. O., Kothamangalam 686 691,
Kerala, India.

[2]Principal and Professor
Department of Oral Pathology and Microbiology,
Indira Gandhi Institute of Dental Sciences,
Nellikuzhy P. O., Kothamangalam 686 691,
Kerala, India.

[3]Professor and Head,
Department of Oral Pathology and Microbiology,
Indira Gandhi Institute of Dental Sciences,
Nellikuzhy P. O., Kothamangalam 686 691,
Kerala, India.

[4]Professor, Department of Oral Pathology and Microbiology,
Indira Gandhi Institute of Dental Sciences,
Nellikuzhy P. O., Kothamangalam 686 691,
Kerala, India.

Address for correspondence:
Dr. Skariah K. S.,
Senior Lecturer,
Department of Oral Pathology and Microbiology,
Indira Gandhi Institute of Dental Sciences,
Nellikuzhy P. O., Kothamangalam 686 691,
Kerala, India. E mail: abinskariah2@yahoo.com.

ABSTRACT

Tumors of jaw bones are among the most uncommon of all types of neoplasms. Osteosarcoma of jaw bones represents a distinct group of lesions from the conventional type commonly occurring in long bones. We present a case of chondroblastic variant ofosteosarcoma (COS) of the maxilla in an 32 year-old lady and the relevant review of literature with regard to etiopathogenesis, clinical, radiographic findings, role of Immunohistochemistry (IHC), staging, grading, treatment and prognosis are being presented in this report.

Key words: Osteosarcoma, Neoplasm, Maxilla,

J Odontol Res 2014;2(1):52-60

INTRODUCTION

Osteosarcoma (OS) is a malignant mesenchymal tumor characterized by formation of osteoid tissue[1]. Craniofacial osteosarcomas constitute only about 6.5-7% of all osteosarcomas[2].The maxillary tumors show predilection for posterior portion of the alveolar process and the antrum, whereas the body is most commonly involved in the mandible followed, by angle, symphysis, and ascending ramus.[3]This article is presented to share our experience with a case of chondroblastic variant of osteosarcoma of maxilla in a young lady and to review the relevant literature.

Case report

A 32-year-old female patient presented to the department of Oral Medicine with the chief complaint of a slow growing asymptomatic swelling in the right upper buccal vestibule since 2 weeks. She had no significant medical and family history.

On examination the patient was apparently healthy except for a mild swelling on the right side of her cheek. She also complaints about the blockage of right nostril. No cervical lymphadenopathy was evident, and there was no sign of involvement of cranial nerves. The mouth opening was adequate. Intraorally a solitary well circumscribed roughly oval to round swelling measuring 3x2cm in diameter was located in the right upper buccal vestibule extending from the distal aspect of second premolar till the mesial aspect of the second molar Fig: 1. The swelling obliterated the entire buccal vestibule and had a palatal extension in the region of the second premolar to first molar region. All the teeth in the quadrant were clinically normal and vital. It was a well demarcated swelling with erythematous gingiva on buccal aspect of second premolar. On palpation it was non tender, bony hard in consistency and fixed to the underlying structures.

There were no signs and symptoms of distant metastasis.

Maxillary occlusal view and an intraoral periapical view were taken. The radiographs revealed poorly defined mixed radiolucent radiopaque lesion in the maxillary alveolus with sun burst appearance. Fig 2

A CT scan of the right maxillary sinus region showed osteosclerotic and lytic

lesion extending from right maxillary sinus to the right maxillary alveolus. Posteriorly the lesion is extending into the floor of right orbit. Fig 3.

The lesion also showed dense foci of calcifications within it. Her hematological and biochemical profile including serum alkaline phosphatase were normal. FNAC was inconclusive, an incisional biopsy was done under local anesthesia from the right buccal cortical plate. Fig 4

The histopathology examination revealed hyaline type of cartilaginous tissue with varying cellularity. Many mildly pleomorphic round/oval cells with dispersed chromatin, prominent nucleoli enclosed in lacunae wereseen in haphazardly arranged sheets and in lobules. Scattered binucleated and multinucleated cells and foci of calcification are also seen. Intervening the proliferating mesenchymal tissue there are spindle cells, chondrocytes with indistinct focal osteoid formation.The picture was suggestive of a chondroblastic variant of osteosarcoma Fig: 5,6 &7.The patient was taken up for surgery at Regional Cancer Center, Thiruvananthapuram.

Discussion

Osteosarcoma (OS) is a tumor composed of malignant connective tissue cells, directly producing osteoid and bone[1].Craniofacial osteosarcoma is a relatively rarer entity and osteosarcomas of the jaws(OSJ) constitute only about6.5-7% of all osteosarcomas [2.] OSJ differs from OS of long bones in its biological behavior, though they share common histological features. The average age of onset of jaw lesions is in the4th decade, with a mean age of 34 years, but cases have been reported in patients of all ages. The common presenting feature is a rapidly growing swelling with localized pain[4]. August et al.[5]in a study of 30 patients with OSJ reported that the most common presenting symptom was swelling without pain. Other signs and symptoms include displacement and loosening of teeth, paresthesia, epistaxis and nasal obstruction.

The average duration of symptoms before diagnosis is 3-4 months. The most frequent locations in the craniofacial region are alveolar ridge and antrum in the maxilla, the body, symphysis and ascending ramus in the mandible [4,6]

Standard radiographies and CT shows 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 as sunburst pattern resulting from radiating spicules of bone. Widening of the periodontal ligament could be present. However these finding are not specific for osteosarcoma. 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 spindled 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 immuno histochemical 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.[7]

Review of literature

Etiopathogenesis

There are numerous variants of osteosarcoma of jaw bones ,but these are generally classified into two types primary and secondary.[8]The etiology of primary type is unknown; may be due to genetic influence or other environmental factors. Secondary craniofacial osteogenic sarcomas occur in older patients of skeletal Paget's disease,[9]fibrous dysplasia of bone and as a late sequela to craniofacial irradiation[10]A number of risk factors had been attributed for the cause of osteosarcoma which includes rapid bone growth as the incidence increases during adolescent growth spurt and because of the typical location of tumor near the metaphyseal growth plate of the long bones.[2]However, osteosarcoma of jaws peaks one or two decades after adolescence which excludes rapid bone growth as the major etiologic factor. Environmental factors such as ionizing radiation and chromic oxide, a radioactive scanning agent have been incriminated.

Genetic mutations in tumor suppressor gene P_{53} and mutated retinoblastoma gene have been claimed to be amongst other etiologic factors. In older patients, this lesion has been found secondary to benign bone lesions such as Paget's disease and fibrous dysplasia.

Clinical Features

They affect the most rapidly growing parts of the skeleton; metaphyseal growth plates in femur, tibia and humerus being the commonest sites. Patients of primary craniofacial osteosarcomas are younger (mean age 48 years). Majority of craniofacial osteosarcomas occur in skeletally mature patients in contrast to those that affect the appendicular skeleton. Osteosarcoma of jaw bones have some distinct features such as older age at presentation, longer median survival, rare metastases and local recurrences difficult to control, typically leading to death of the patients.[6]They comprise only 6.5% of all osteosarcomas.[2]In maxilla and mandible, the presentation of the tumor at later age (around fourth decade) and its higher survival rate helps to differentiate it from osteogenic sarcomas in other locations. Mean age according to Garrington*et al*[2]ranges from 34 to 36 years. Distant metastases are less frequent according to some but Garrington and his colleagues reported distant metastases in approximately 50% of the cases. Men seem to be more commonly affected. August *et al*[5] reported gender predilection for males and found male:female ratio to be 1.1:1. In a study by Fortez*aet al*[6]on 81 cases of osteosarcoma, maxillary osteosarcomas occurred in females with the ratio of 4:1 whereas mandibular lesions occurred only in males. Few reports state even distribution of the lesion between maxilla and mandible. Clinically, osteosarcoma of long bones presents as pain during activity compared to osteosarcoma of jaw bones where swelling rather than pain is the commonest finding. [2]In a study by Nissanka*et al*[11]most patients related the occurrence of tumor to previous dental treatment, most commonly, dental extractions. The reason for this is most likely to be rapid growth of tumor immediately after tooth extraction, a phenomenon often shown by bone tumors.

Radiographic Features

Osteosarcoma shows varied radiographic appearance ranging from osteolytic to mixed to osteogenic pattern of bone. If the tumor invades the periosteum, many thin irregular spicules of new bone may develop outward and perpendicular to the surface of the lesion producing the so-called 'sun ray appearance.' Lindquist *et al*[12]reported that the widening of periodontal ligament space and inferior dental canal, together with sunburst effect are almost pathognomonic of osteosarcoma of jaw bone. Not all the lesions show such peculiar characteristics. Fortez*aet al*[6]reported that the presence of destructive unicentric lesion with poorly defined margins and a predominantly sclerotic, lytic or mixed radiographic pattern should lead one to suspect an osteogenic sarcoma.

The preoperative diagnosis of these neoplasms is often difficult because of its nonspecific nature. The importance of special investigations such as computerized tomography (CT) and magnetic resonance imaging (MRI) lies in assessing the size of the lesion for staging, intramedullary and extramedullary involvement, tumor calcification and invasion into adjacent tissues.

Histopathologic Features

The varied radiographic appearance of this lesion highlights the importance of histopathological analysis in the diagnosis of osteosarcomas. The diagnosis of osteosarcoma is based on recognition of osteoid production by tumor cells.[13]Depending upon the predominant type of extracellular matrix present, osteosarcomas are categorized histopathologically into osteoblastic, chondroblastic, fibroblastic subtypes.[8,14]The osteoblastic variety consists of tumor osteoid surrounded by bizarrely arranged fibroblast like cells.

In chondroblastic osteosarcoma, tumor cells lie in the lacunae and form lobules. The center of the lobule has bony trabeculae producing a feathery appearance, and towards the periphery, the tumor becomes hypercellular. Most of the times, an area of atypical chondroid tissue is also seen with large chondrocytes. Fibroblastic osteosarcoma is the least common variant where the tumor cells are spindle-shaped and characteristically arranged in herring bone pattern typically resembling fibrosarcoma. The formation of tumor osteoid differentiates this variant of osteosarcoma from fibrosarcoma[15]

Mardinger*et al*[16]reported the highest prevalence for chondroblastic osteosarcoma (42%), osteoblastic osteosarcoma being lesser (33%). Histologic diversity of osteosarcomas points to the fact that histology alone is insufficient for the diagnosis of osteosarcoma. Therefore, combined clinical, radiographic and histopathologic analysis before definitive diagnosis is prudent.

Immunohistochemistry

Immunohistochemistry (IHC) plays an important role in the differentiation between chondrosarcoma and chondroblastic osteosarcoma. IHC will show chondrosarcoma to be positive for S100 and Vimentin and negative for cytokeratin and EMA (Epithelial Membrane Antigen). Chondroblastic

osteosarcoma will be positive for Vimentin, EMA, S100 and rarely cytokeratin.[17]

Recently, Yoshida *et al* reported that the combination of MDM2 and CDK4 by immunohistochemical analysis shows 100% sensitivity and 97.5% specificity for the diagnosis of low-grade osteosarcoma. They concluded that MDM2 and CDK4 immunostains therefore reliably distinguish low-grade osteosarcoma from benign histological mimics, and their combination may serve as a useful adjunct in this difficult differential diagnosis.[18]

In a study by Hu *et al*, the expressions of IDH1 and p53 in formalin-fixed paraffin-embedded tissue sections from 44 osteosarcoma patients were determined by immunohistochemistry, and the correlation between them and clinicopathological features were analyzed. They concluded that osteosarcoma patients with High IDH1 expression have a very high p53 expression. Thus IDH1 may correlate with p53 and be a candidate biomarker for osteosarcoma.[19]

Staging and Grading

Cellularity is the most important criterion used for histological grading. In general, the more cellular the tumor, the higher the grade. Irregularity of the nuclear contours, enlargement and hyperchromasia of the nuclei are correlated with grade. Mitotic figures and necrosis are additional features useful in grading.

Staging incorporates the degree of differentiation as well as local and distant spread, in order 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.[20,21] It is based on the grade (G) of the tumor, the local extent of the primary tumor (T), and whether or not it has metastasized to regional lymph nodes or other organs (M).

The grade is divided into 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 give an overall stage (Table 1)

Table 1: Grading and staging of osteosarcomas

Stage	Grade	Tumor	Metastasis
IA	G1	T1	M0
IB	G1	T2	M0
IIA	G2	T1	M0
IIB	G2	T2	M0
IIIA	G1 or G2	T1	M1
IIIB	G1 or G2	T2	M1

In summary, low-grade tumors are stage I, high-grade tumors are stage II, and metastatic tumors (regardless of grade) are stage III.

There are no known specific laboratory parameters. Increase in alkaline phosphatase or lactic dehydrogenase (LDH) serum levels are observed in a considerable number of patients. Although they do not correlate reliably with disease extent, they may have negative prognostic significance.

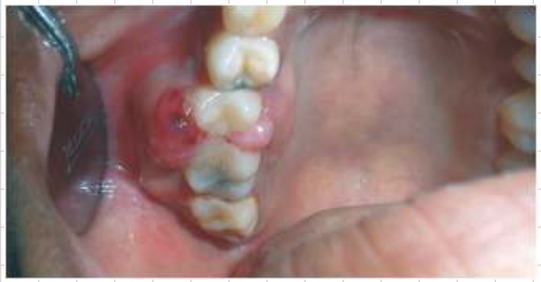
Histopathologic grading of this neoplasm is done according to Broder's grading system developed for epitheliomas, based on degree of cellular anaplasia shown by tumor cells. Mardinger*et al*[16] stated that nearly 50% of the jaw osteosarcomas are low grade and according to Unni,[22] the most common form is grade II.

Treatment and Prognosis

Wide radical resection is the treatment of choice for osteosarcoma of jaws with clearance margins of 1.5-2 cm. Surgery and adjuvant chemotherapy and radiotherapy may be required sometimes. The presence of micro metastases decides the need of adjuvant therapy. Obturators have been prescribed for the defect created.

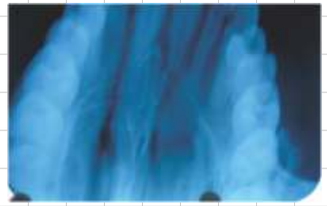
Smeele*et al*[23] investigated the value of chemotherapy in the treatment of craniofacial osteosarcoma by analyzing 201 reviewed cases. They found that the overall and disease free survival rates significantly improved with chemotherapy. Raymond *et al*[24] reported 33% 5-year survival for patients treated with adjuvant chemotherapy and surgery and 41%

Fig 1



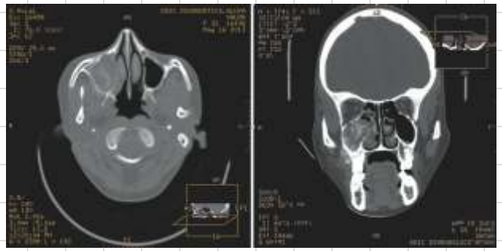
Clinical picture showing a firm swelling the right maxilla

Fig 2



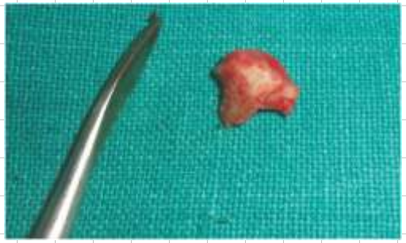
Occlusal radiograph showing sun burst appearance

Fig 3



CT Scan showing tumor mass in the right maxillaextending from sinus into the cortical plate of right maxillary alveolus.Posteriorly the lesion is extending into the floor of right orbit

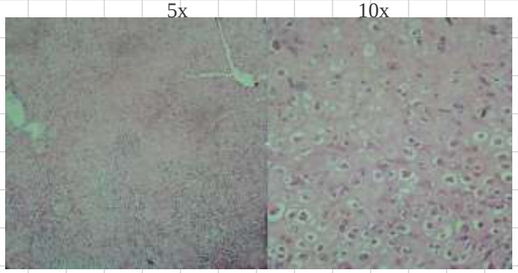
Fig 4



Macroscopic specimen

Fig:5: Microscopic picture

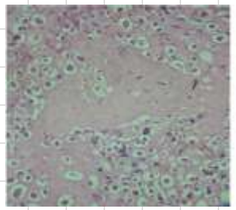
5x 10x



Proliferating chondroblasts with hyperchromaticnuclei. Abnormal mitotic figures

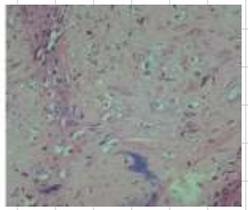
Lobular arrangements of tumor cells under

Fig 6 20x



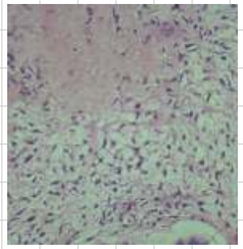
Osteoid deposits in ill-defined trabecular pattern

20x



Foci of calcification in osteoid

Fig7 20x



Foci of osteoid with star and spindle shaped tumor cells at the periphery

5-year disease free survival for those treated with surgery alone. Radiotherapy must be confined for the treatment of residual, recurrent and unresectable tumors.

Unni KK has reported a 40% 5-year survival for jaw osteosarcomas compared to conventional osteosarcomas (20.3%).[22]Clark *et al*[25]attributed this to occurrence of predominantly chondroblastic low grade osteosarcomas in the jaws.

A number of potential prognostic factors have been identified which include the expression of HER2/CerbB2, tumor cell ploidy, and specific chromosome gains or losses, loss of heterozygosity of the RB gene, loss of heterozygosity of the p53 locus, and increased expression of p-glycoprotein. The only feature that consistently predicts outcome is the degree of histologic necrosis following induction chemotherapy. Patients with more than 95% necrosis in the primary tumor after induction chemotherapy have a better prognosis than those with smaller amounts of necrosis.[26,27,28] The prognosis for patients with metastatic disease appears to be determined largely by the site(s), the number of metastases, as well as the surgical resectability of the metastatic disease. The most common site for the metastases is lung accounting for almost 20%. Prognosis appears more favorable for patients with unilateral rather than bilateral pulmonary metastases, and for patients with fewer nodules rather thanmany nodules. The degree of necrosis in the primary tumor after induction chemotherapy remains prognostic in metastatic osteosarcoma. Patients with skip metastases (≥2 discontinuous lesions in the same bone) have been reported to have inferior prognoses. Patients with multifocal osteosarcoma (>1 bone lesion at diagnosis) have a poor prognosis [28]

Conclusion

Jaw osteosarcoma presents a wide spectrum ofclinical, histological and radiological features. Therefore all these features have to be correlated toreach a conclusive diagnosis. It has a better prognosisif diagnosed and treated at an early stage.

Acknowledgement: I sincerely acknowledge the contributions of Dr. Anis Ahmed, Senior Lecturer, Department of Oral Medicine and Radiology, Dr. Mohammed Yasin, Department of Oral and Maxillofacial Surgery, Dr. Mohammed Shereef, Department of Periodontology and Oral Implantology, Indira Gandhi Institute of Dental Sciences, Kothamangalam.

References

1. Schajowicz F, Sissons HA, Sobin LH. The WorldHealth organization's Histologic Classification of boneTumors: a Commentary on the Second Edition. Cancer 1995; 75: 1208-14.
2. Garrington GE, Scofield HH, Cornyn J, Hooker SP. Osteosarcoma of jaws, analysis of 56 cases. Cancer 1967;20:377-91
3. Balwani SR, Tupaki JV, Barpande SR. Parostealosteosarcoma of the mandible. J Oral MaxillofacPathol2006;10(1):10-4
4. Clark J, Unni KK, Dahlin DC, DevineKD (1983) Osteosarcoma of the jaw. Cancer 51(12): 2311–6
5. August M, Magenni SP, Dewitt D (1997)Osteogenic sarcoma of the jaws: Factors influencing prognosis. Int J OralMaxillofacSurg 26(3):198–204
6. Forteza G, Colmenero B, Lopez-Barea F(1986) Osteogenic sarcoma of the maxilla and mandible. Oral Surg Oral Med OralPathol 62(2): 179–84
7. Bertoni F, Dallera P, Bacchini P, Marchetti C, Campobassi A. The Istituto Rizzoli-Beretta experience with osteosarcoma of the jaw. Cancer. 1991;68:1563–91
8. Rajendran R. Benign and Malignant tumors of the oral cavity. In: Rajendran R, Sivapathasundharam B, editors. Shafer's textbook of Oral Pathology. India: Elsevier, a Division of Reed Elsevier India Private Limited; 2006. p. 113-308. 9.Brackenridge CJ. A statistical study of sarcoma complicating Paget's disease of bone in three countries. Br J Cancer 1979;40:194-200.
10. Huvos AG, Woodard HQ, Cahan WG, Higinbotham NL, Stewart FW, Butler A, *et al*. Postradiationosteogenic sarcoma of bone and soft tissues. A pathological study of 66 patients. Cancer 1985;55:1244-55.
11. Nissanka EH, Amartunge EA, Tilakaratne WM. Clinicopathological analysis of osteosarcoma of jaw bones. Oral Dis 2007;13:82-7.
12. Lindquist C, Teppo L, Sane J, Holmstrom T, Wolf J. Osteosarcoma of mandible: Analysis of 9 cases. J Oral MaxillofacSurg 1986;44:759-64
13. Schajowicz F. Histological typing of bone tumours. 2nd ed. Berlin: Springer-Verlag; 1993.
14. Frei C, Bornstein MM, Stauffer E, Iizuka T, Buser D. Osteosarcoma of the maxilla and the maxillary sinus: A case report. Quintessence Int 2004;35:228-33.
15. Neville BW, Damm DD, Allen CM, Bouquot JE. Bone Pathology. In: Neville BW, DammDD, Allen CM, Bouquot JE, editors. Bone Pathology, editors. Oral and Maxilofacial Pathology. Philadelphia: Saunders, an imprint of Elsevier; 2002. p. 574-7.
16. Mardinger O, Givol N, Talmi YP, Taicher S. Osteosarcoma of the jaw- The Chaim Sheba Medical Center Experience. Oral Surg Oral Med Oral Path Oral RadiolEndod 2001;91:445-51.
17. Akpolat N, Yildirim H, Poyraz K. Sacral chondroblastic osteosarcoma misdiagnosed as chondrosarcoma and chordoma. Turk J Med Sci 2007;37:243-9.
18. Yoshida A, Ushiku T, Motoi T, Shibata T, Beppu Y, Fukayama M, *et al*. Immunohistochemical analysis of MDM2 and CDK4 distinguishes low-grade osteosarcoma from benign mimics. *Mod Pathol* 2010;23:1279-88.

19. Hu X, Yu AX, Qi BW, Fu T, Wu G, Zhou M, *et al*. The expression and significance of IDH1 and p53 in osteosarcoma. J ExpClin Cancer Res 2010;29:43.
20. Staging of musculoskeletal neoplasms. Musculoskeletal Tumor Society. Skeletal Radiol 1985;13:183-94.
21. Hoffman S, Jakoway JR, Krolls SO. Malignant odontogenic tumors of jaws. In. intraosseous and Parosteal tumors of jaws. Atlas of tumor pathology. Washington, D.C: AFIP; 1987. p. 170- 80.
22. Unni KK, Dahlin DC. Grading of bone tumors. SeminDiagPathol 1984;1:165-72.
23. Smeele LE, Kostense PJ, van der waal I, Snow GB. Effect of Chemotherapy on survival of craniofacial osteosarcoma: A systematic review of 201 patients. J ClinOncol 1997;15:363-7.
24. Raymond AK, Spires J, Ayala A, Chawla S, Lee YY, Benjamin RS, *et al*. Osteosarcoma of head and neck. Lab Invest 1989;60:76a
25. Clark JL, Unni KK, Dahlin DC, Devine KD. Osteosarcoma of the jaw. Cancer 1983;51:2311-6.
26. Bruland OS, Høifødt H, Saeter G, Smeland S, Fodstad O. Hematogenousmicrometastases in osteosarcoma patients. Clin Cancer Res 2005;11:4666-73.
27. Gorlick R, Huvos AG, Heller G, Aledo A, Beardsley GP, Healey JH, *et al*. Expression of HER2/erbB-2 correlates with survival in osteosarcoma. J ClinOncol 1999;17:2781-8.
28. Kusuzaki K, Takeshita H, Murata H, Hirata M, Hashiguchi S, Ashihara T, *et al*. Prognostic value of DNA ploidy response to chemotherapy in human osteosarcomas. Cancer Lett 1999;141:131-8.

authors for the manuscripts. **The maximum number of authors for original research articles is six and for case reports and reviews is four.**

Conflicts of Interest/ Competing Interests

All authors of must disclose any and all conflicts of interest they may have with publication of the manuscript or an institution or product that is mentioned in the manuscript and/or is important to the outcome of the study presented. Authors should also disclose conflict of interest with products that compete with those mentioned in their manuscript.

Submission of Manuscripts

All manuscripts must be submitted on-line to the e-mail jorigids@gmail.com. Authors will have to pay for submission, processing or publication of articles. If you experience any problems, please contact the editorial office by e-mail. The submitted manuscripts that are not as per the “Instructions to Authors” would be returned to the authors for technical correction, before they undergo editorial/ peer-review. Generally, the manuscript should be submitted in the form of two separate files:

[1] **Title Page/First Page File/covering letter**:

This file should provide

1. The type of manuscript (original article, case report, review article, Letter to editor, Images, etc.) title of the manuscript, running title, names of all authors/ contributors (with their highest academic degrees, designation and affiliations) and name(s) of department(s) and/ or institution(s) to which the work should be credited, . All information which can reveal your identity should be here. Use text/rtf/doc files.
2. Source(s) of support in the form of grants, equipment, drugs, or all of these;
3. Acknowledgement, if any..
4. Conflicts of Interest of each author/ contributor. A statement of financial or other relationships that might lead to a conflict of interest, if that information is not included in the manuscript itself or in an authors' form
5. The name, address, e-mail, and telephone number of the corresponding author, who is responsible for communicating with the other authors about revisions and final approval of the proofs, if that information is not included on the manuscript itself.

[2] **Blinded Article file**: The main text of the article, beginning from Abstract till References (including tables) should be in this file. The file must not contain any mention of the authors' names or initials or the institution at which the study was done or acknowledgements. Page headers/running title can include the title but not the authors' names. Manuscripts not in compliance with the Journal's blinding policy will be returned to the corresponding author. Use rtf/doc files. Do not zip the files. **Limit the file size to 1 MB**. Do not incorporate images in the file. The pages should be numbered consecutively, beginning with the first page of the blinded article file.

[3] **Images**: Submit good quality color images. **Each image should be less than 4 MB in size**. Size of the image can be reduced by decreasing the actual height and width of the images (keep up to 1800 x 1200 pixels or 5-6 inches). Images can be submitted as jpeg files. Do not zip the files. Legends for the figures/images should be included at the end of the article file.

[4] **The contributors' / copyright transfer form** has to be submitted in original with the signatures of all the contributors within two weeks of submission via courier, fax or email as a scanned image. High resolution images (up to 5 MB each) can be sent by email.

Preparation of Manuscripts

Manuscripts must be prepared in accordance with "Uniform requirements for Manuscripts submitted to Biomedical Journals" developed by the International Committee of Medical Journal Editors (October 2008). The uniform requirements and specific requirement of Journal of Odontological Research are summarized below. Journal of Odontological Research accepts manuscripts written in English. For further details regarding the guidelines in drafting the manuscript for publication, log on to www.igids.org