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Review Article

Craniofacial osteosarcomas – The challenges in the diagnosis of a biologically distinct entity**Mourougessine Vimal*** and Anandabaskar Nishanthi*Sri Manakula Vinayagar Medical College and Hospital, Puducherry, India*

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Puducherry, India***Article History:****Received:** 11/01/2017**Revised:** 16/03/2017**Accepted:** 16/03/2017**DOI:** <https://dx.doi.org/10.7439/ijbr.v8i3.3849>**Abstract**

Osteosarcoma is the second most common primary neoplasm arising from bone next to Multiple myeloma and is common in metaphysis of long bones. Osteosarcoma of the jaw bones is a biologically distinct entity in contrast with Osteosarcoma of the long bones. This review highlights the challenges in the diagnosis of craniofacial osteosarcoma and emphasizes the need for appropriate diagnosis of this entity for proper management.

Keywords: Osteosarcoma, Chondroblastic osteosarcoma, Osteoid, Maxilla, Craniofacial region.**1. Introduction**

Although Osteosarcoma is the second most common primary neoplasm arising from the bone, it is relatively a rare entity in the craniofacial region accounting for only 6.5 to 7% of all osteosarcomas. [1] Mandible is the most common site of occurrence of osteosarcoma in the craniofacial region. [2] This review highlights the clinical and histopathological aspects of this tumour to emphasise the importance of regarding Osteosarcoma of the craniofacial region as a biologically distinct entity in contrast to Osteosarcoma of the long bones and importance of making correct diagnosis of this entity for proper management.

2. Review

Osteogenic sarcoma is a highly aggressive primary malignant neoplasm of bone directly producing osteoid and bone from mesenchymal tumour cells. [3,4] Osteosarcoma is the second most primary malignant bone tumour after Multiple myeloma. The most common site of osteosarcoma is in the metaphysis region of distal Femur, Proximal Tibia and Humerus. [5] In spite of sharing common histological appearances, osteosarcoma of the long bone differs

considerably from that of the craniofacial region in its biological behaviour. Osteosarcoma of long bones has a bimodal age presentation, common in adolescents and in fifth decade whereas osteosarcomas of the craniofacial region occur in the third and fourth decades of life. [6-8] Long bone osteosarcoma presents as a painful swelling of distal femoral metaphysis, proximal tibia and humeral metaphysis with prominent veins, distal edema and micrometastasis at the time of diagnosis. Osteosarcoma of the craniofacial region occurs in mandible at the body, symphysis and ascending ramus and in the maxilla they occur at anterior alveolus and antrum and presents with a painless swelling with neuroparesthesia and with less evidence of micrometastasis. [9]

The most common presenting feature is a rapidly growing swelling. [10] The other symptoms may be loosening and displacement of teeth, epistaxis, paresthesia and nasal obstruction. Longer period of skeletal growth can attribute to slight male preponderance of this lesion but mandibular tumours are common in women than men. [11]

In 2002, World Health Organisation (WHO) divided the osteosarcoma into primary and secondary. The

primary group includes 7 subtypes including conventional, low grade central, periosteal, paraosteal, high grade surface, telangiectatic and high grade surface. The secondary group includes syndrome associated and radiation associated. [12] Osteosarcoma can arise from pre existing benign bone lesions such as Fibrous dysplasia, Retinoblastoma, Pagets disease, Osteonecrosis, Chronic osteomyelitis or at previous site of irradiation. [13-15] Osteosarcoma has also been associated with joint prostheses and metallic implants. [16-18] A complete clinical evaluation should rule out syndromes like Li-Fraumeni, Rothmund-Thompson, Bloom and Werner. Patients with mutations of p53 and retinoblastoma, Li-Fraumeni syndrome, Von Recklinghausen disease are at higher risk of developing radiation induced osteosarcoma. [19,20]

Radiologically, osteosarcoma of the long bone presents either as a lytic, blastic or mixed lesion (Moth eaten or cumulus cloud appearance). [18] Destruction of the cortex and spreading into the soft tissue is usually evident. But in contrast Osteosarcoma of jaw bones lacks a florid periosteal reaction. [21] A panoramic radiograph may reveal widening of the periodontal ligament space around the affected teeth with tumour infiltration causing tooth roots resorption (Garrington's sign). [4,17]

Grossly the tumour appears soft and granular in osteolytic lesions and firm dense in osteosclerotic lesions. Evidence of soft tissue extension is evident in many cases. The histological diagnosis of Osteosarcoma is usually made when the sarcomatous stroma is directly producing osteoid or primitive bone. [22] Osteoid appears as homogenous eosinophilic which may resemble collagen when present as scant in the biopsy specimens. Osteoid is positive for immunohistochemical markers like osteocalcin and osteonectin (both are bone specific proteins). The stromal cells morphologically have round to spindle cell in appearance with varying degree of anaplasia. The vascularity of the tumour varies with different cases. Craniofacial osteosarcomas are cytologically difficult to distinguish from fibrous dysplasia and osteoblastoma. [23] The reactive proliferation of the stroma which occurs in fractured callus, cellular forms of Pagets disease can sometimes cause diagnostic difficulties. [24,25]

Based on the predominant tumour matrix, conventional osteosarcoma is subdivided by the World Health Organisation (WHO) into three subtypes. The Osteoblastic variant with osteoid and predominant bone in the midst of stroma, Fibroblastic variant characterized by predominance of spindle cell growth with minimal matrix and Chondroblastic subtypes. WHO defines chondroblastic osteosarcoma as an entity characterized by a predominant chondroid matrix (more of hyaline cartilage) and with presence of non chondroid elements like osteoid or bone

matrix. [26] Although the histopathological subtypes have not been shown to have prognostic significance, [5,10] few authors were of the opinion that chondroblastic variant has better prognosis than others. [27] The other less common histological variants are small cell, giant cell, large cell, myxomatous, telangiectatic, fibrous histiocytoma like and epithelioid variant of osteosarcoma. [28,29]

The subtypes of osteosarcoma arising in jaw and skull are similar. But higher grade tumours are usually observed in skull and craniofacial bones when compared to gnathic sites. [30] Metastatic osteosarcoma is a very rare occurrence in craniofacial region. [31,32] Broder designed a grading system based on the degree of cellular anaplasia and higher grades correlate with a poor prognosis. [33] In the craniofacial region, chondroblastic variant is the most common one followed by osteoblastic.

The main differential diagnosis of Chondroblastic variant of osteosarcoma is Chondrosarcoma or fibrosarcoma especially in small incisional specimen biopsies. The presence of Osteoid formation within the tumour is the most important histomorphologic clue to the diagnosis in such cases. Chondrosarcoma can have a spectrum of histopathological presentation varying from a well differentiated lesion resembling benign cartilaginous tumours to a very aggressive high grade malignant neoplasm. [6] Chondrosarcoma of the head and neck region is a rare occurrence. Dedifferentiated chondrosarcoma usually contains a high grade sarcomatous area adjacent to a well differentiated chondrosarcoma. Many authors suggest that a lesion with malignant cartilage should be designated as osteosarcoma if it contains significant malignant osteoblasts and tumour osteoid. The main differentiating features between Chondroblastic variant of osteosarcoma and Chondrosarcoma are shown in Table. 1.

Cartilaginous neoplasms harbor mutations in the metabolic enzyme genes – Isocitrate dehydrogenase (IDH1 and IDH2). The presence of these gene mutations can confirm the diagnosis of dedifferentiated chondrosarcoma with osteosarcomatous differentiation and distinguish it from chondroblastic osteosarcoma. [34] Ezrin, a cytoskeleton linker protein is expressed in conventional osteosarcomas with a specificity of 100% which can serve as a diagnostic immunohistochemical marker to differentiate it from conventional chondrosarcoma. [35]

The frequent expression of Galectin-1 (GAL - 1) in chondroblastic osteosarcoma can be a valuable diagnostic marker to differentiate it from conventional chondrosarcoma. [36-38] A recent marker called “cbfa 1” – an intranuclear osteocalcin promoter, is positive in malignant bone tumours. Further detection of alkaline phosphatase activity in the imprint smears before formalin

fixation is characteristic of osteosarcoma [27,39] and chondrosarcoma is negative for this marker.

Junior *et al*[40] found that the craniofacial osteosarcomas were also positive for markers like PCNA, p53, Murine Double Minute type 2 (MDM2), Cyclin Dependent Kinase 4 (CDK4). Hoang *et al* [41] found that LDL receptor-related protein 5 (LRP5) can serve as a useful marker to assess the disease progression in high-grade tumours.

The high grade tumours are more prone for local recurrence within a year. [42] Craniofacial osteosarcomas have fewer tendencies for metastasis when compared to long bone osteosarcomas. But cases of post radiation osteosarcomas have relatively more incidence of osteosarcomas [1,29,43] Adult patients can have increased resistance to the tumour and may have better prognosis than children. [1,7] Patients with elevated alkaline phosphatase and those with Pagets disease have a worst prognosis.

The expression of Vascular Endothelial Growth Factor (VEGF) on the tumour carries poor prognosis. The

results of clinical trials investigating Endostatin therapy (Anti angiogenic) are fruitful. [44-46]

Radical surgery with adjuvant chemotherapy is the main stay of treatment for osteosarcoma of long bones and radiation therapy does not appear to have significant benefit. The main cause of mortality in craniofacial osteosarcoma of jaw is locoregional recurrence and meticulous radical surgery is the main stay of treatment. Obtaining a tumour free surgical resection margin is the key factor in determining the prognosis. Maxilla is more of cancellous bone when compared to mandible and spread of tumour cells and encasement of vital structures is more rapid which limits the prognosis in maxillectomy resections. [28,47,48]

The results with the combined surgery and of adjuvant chemotherapy had been variable[5].The tumour stage at the time of the diagnosis, selection of chemotherapy regimen, anatomic location, size of the tumour and percentage of tumour cell necrosis following neo adjuvant chemotherapy are the other factors influencing the outcome of the tumour. [49,50]

Table.1 Differentiating features between Chondroblastic variant of osteosarcoma and Chondrosarcoma

| Features | Chondroblastic variant of Osteosarcoma | Chondrosarcoma |
|----------------------|--|--|
| Age group | Adolescents and early adults | Elderly (4 th -6 th decade) |
| Location | flat bones of the trunk and proximal appendicular skeleton | Predominantly in the appendicular skeleton |
| Histopathology | Tumour – Neoplastic osteoid in addition to cartilaginous differentiation | Tumour matrix - uniformly and entirely chondroid in nature |
| Immunohistochemistry | Positive for S100 and Vimentin and negative for cytokeratin and Epithelial Membrane Antigen (EMA)[50]. | Positive for vimentin, Epithelial Membrane Antigen , S100 and rarely Cytokeratin[50] |
| Prognosis | Poor[5] | Better[5] |
| Metastatic tendency | Apparent metastatic disease is present in 10-20% of all patients at the time of diagnosis[5]. | Lower[5] |
| Treatment | Adjuvant chemotherapy with surgery | Surgical excision |

3. Conclusion

Although the histopathological morphology of osteosarcoma of long bones and jaw bones are similar, their management is entirely different because both are biologically different entities. The diagnosis of craniofacial osteosarcoma is made histopathologically and it can be easily confused with chondrosarcoma. Thus much emphasis should be made on the need for making appropriate diagnosis of osteosarcoma in the craniofacial region and its differentiation from Chondrosarcoma.

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