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Challenges Faced During Diagnosis of Fibroblastic Variant of Osteosarcoma

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Perspective

Although the incidence of osteosarcoma (OS) in malignancies is low, it is still the most common primary tumor of bone [1]. It belongs to a family of lesions that show considerable diversity in histological features and grades. Jaw-derived OS accounts for 2.1% of all oral and maxillofacial malignancies. Jaw OS, unlike long bone OS in its biological behavior, has a low incidence of metastasis and a good prognosis with a 5-year survival rate of about 40% compared to 20% for non-jaw lesions [2]. In the early stages of the disease, OS can manifest itself as inconspicuous, slowly progressing bone swelling, but in the later stages of the disease it becomes overly aggressive and malignant, poses challenges for accurate diagnosis [1]. Histologically, OS is divided into three subtypes: osteoblasts, chondroblast, and fibroblasts. However, it exhibits varying degrees of differentiation and can generate different types of extracellular matrix, creating significantly different histological patterns not only in each case, but also in each region within the same case. OS is thought to result from neoplastic differentiation of immature bone-forming cells or other immature mesenchymal cells into osteoblasts. It is generally said that the three main factors of radiation, pre-existing benign bone disease, and trauma are etiologically important in their development [3]. OS tumor formation is associated with changes in several genes. The first association between OS and genetic predisposition was observed in patients with bilateral retinoblastoma. This association was confirmed by the identification of the retinoblastoma susceptibility gene (RB1) on human chromosome 13, which had a high proportion of mutations in OS. The second OS-related gene is the p53 gene, and mutations in the p53 gene were first observed in sporadic OS [4]. OS is a malignant tumor that mainly produces bone and most commonly occurs in long bones. Jaw OS usually occurs 10 to 20 years later than OS in other regions. Patients with OS usually present with non-specific clinical symptoms, the most common of which is swelling-related pain, which manifests over weeks or months. It has a bimodal age distribution, with a major peak at 20 years and a slightly smaller peak after age 50. However, the bimodal distribution of jaw lesions differs from the distribution of the limb skeleton, with the first peak occurring 30 years later. This case, with significant clinical manifestations of pain and swelling, is consistent with the literature on jaw OS in which patients present clinical manifestations at 30 and 40 years of age. In the early stages, these neoplasms often exhibit typical behavior in the form of unobtrusive swelling, but become overly aggressive in the later stages of the disease [5]. This was also observed in our case where the initial swelling was an inconspicuous swelling, leading to a tentative diagnosis of periapical pathology. However, the swelling became significantly more aggressive in a short period of time, reaching emergency management of the lesion.

Histologically, although OS of jaws are almost similar to that of long bones, they are always better differentiated than the latter. It has been reported that production of osteoid by malignant cells, even in small amounts, is diagnostic of OS. Depending on the relative amounts of osteoid, cartilage, or collagen fibres present in the extracellular matrix, OS are categorized histopathologically into osteoblastic, chondroblastic, or fibroblastic subtypes [6]. In reality, most OS exhibit varying amounts of these three cell types and matrix [1]. Therefore, division into any one of these types is arbitrary and is generally meant to signify greater than 50% prevalence of any of these histologic types [1]. OS are known to vary in histologic pattern within same case with areas showing storiform pattern of fibrosarcoma to atypical elongated histiocytic like cells representing histiocytic tumours. Storiform pattern of fibroblasts with proliferating fibroblasts along with bundles of collagen fibers led to the diagnosis of fibrosarcoma in the initial biopsy in the present case. Further, there was a predominance of spindle cell proliferation in sweeping fascicles along with infrequent mitosis, occasional atypia and with focal areas showing giant cells, which again favored a diagnosis of fibrosarcoma.

Immunohistochemistry forms an integral part of pathologic diagnosis that aids in arriving at an accurate histopathological diagnosis. Vimentin, S100 and CD68 markers were used to help in reaching the diagnosis. Vimentin was constantly positive with S100 showing negativity, thus ruling out the possibility of neural tumours. Focal positivity with CD68 added on to the fibrohistiocytic nature of the tumours as quoted in the literature, to be one of the variants of OS. Such challenging cases often pose a problem in executing a definitive surgical treatment option. Radiographic evaluation is important in diagnosing OS as clinical symptoms like pain; swelling, paresthesia, and loosening of teeth are not specific. Better knowledge of the radiological features can lead to an earlier diagnosis thus improving its prognosis. Characteristic radiographic features include cortical plate destruction, periodontal ligament enlargement, and vertical needle-like patterns of new periosteal bone formation. However, because these features are often absent, the OS is difficult to interpret because it has a variety of appearances, from pure osteocytic or osteoblastic lesions to mixtures of both [6]. The relapse of the lesion, along with its aggressive nature, was confirmed by CT scan. CT scans facilitated thorough sampling of lesions by expanding into the orbit. The classic appearance of tumor bone was a characteristic finding that led to the diagnosis of OS. X-rays suggested lytic destructive lesions, but CT findings ruled out metastases.

The recurrence rate in large, bulky tumours is 80% within 24 months. Early diagnosis and radical surgery are the key factors for the better survival rate in this condition. Treatment of this lesion is radical surgery consisting of complete resection along with a margin

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of normal surrounding tissue, usually accompanied by chemotherapy. The best survival rate of five years was noted with radical surge. Anatomic limitations in face can cause some difficulties in achievement of uninvolved margins. The combination of closed margins and poor histologic response appears to be the reason for high local recurrence of these lesions. The prognosis for patients after local recurrence of OS is poor.

Recent studies have focused on new markers for early detection of OS. Park et al. in their recent study showed by immunohistochemistry that high-grade OS of the jaws had a higher expression rate of proteins involved in regulation of growth and metastasis of cancer cells (ezrin and Metastatic tumour antigen) suggesting that their positivity can be used as additional prognostic markers in OS of the jaw. Another study analyzed the clinicopathological features and immunohistochemical expression of p53, MDM2, CDK4, PCNA and Ki67 proteins in 25 head and neck OS and found 52% positivity for p53, 24% for MDM2, 84% for CDK4, 92% for PCNA and 88% for Ki67 suggesting PCNA as one of most favorable prognostic marker. Another study suggested the role of 12q1315 genes in OS of the jaws with amplification and overexpression of these genes might help in detecting high-grade tumors.

Response to chemotherapy (CT) is best seen in fibroblastic subtypes and poorest in chondroblastic subtype. Multimodality therapy using chemotherapy and radiation treatment (RT) has shown improvement in survival rates in the OS of the extremity, from 20% to 70%, which is better than the 40% survival rate reported for jaw OS. A recent study which was performed to evaluate the outcomes of multimodality treatment in patients with OS of the jaw/craniofacial region with positive/uncertain resection margins, found that combined modality treatment, comprising of surgery and RT (median dose, 60 Gray) significantly improved local control ($P = 0.006$) and overall survival ($P < .0001$) as compared to surgery alone. In the cases shown here, the patient underwent partial maxillary resection in combination with RT and CT, and at the time of writing, a one-year follow-up reported one episode of tumor recurrence. However, multidimensional approaches, including traditional surgical and prosthetic procedures, need to be considered for individual patients and specific defects.

Conclusion

Various new therapies are being researched for the treatment of jaw OS. Recent studies have focused on the relationship between the expression of inducible nitric oxide synthase (iNOS) in the jaw mouth and tumor angiogenesis and clinicopathological features. They concluded that iNOS promotes tumor angiogenesis in jaw OS and may be an important target for antitumor therapy. The development of microvascular tissue transplantation now offers a variety of reconstruction options, significantly improving the outcome of central facial reconstruction.

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