


Pan-Cytokeratin Positive Fibroblastic Osteosarcoma of Jaw: An Extremely Rare Entity in a Pediatric Patient

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ABSTRACT: Osteosarcoma (OS) of jaws is a rare entity characterized by malignant osteoid formation and is most commonly seen in third to fourth decade of life. Here, we present a rare and intriguing case of a 14-year-old pediatric patient, who reported with a chief complaint of swelling in the left maxilla, which was rapidly increasing in size. Both cytokeratin AE1/3 and vimentin-positive spindled cells were seen arranged in storiform pattern with minimal areas of osteoid formation on histopathologic examination. The diagnosis of fibroblastic OS was confirmed by fluorescent in situ hybridization after excluding monomorphic synovial sarcoma. The patient underwent segmental resection of left maxilla and is on close follow-up. A PubMed search revealed that only 5 pediatric cases of fibroblastic OS have been published since 1991. Here, we highlight the diagnostic challenges encountered in reaching the histopathologic diagnosis.

KEYWORDS: Osteosarcoma, synovial sarcoma, immunohistochemistry, fluorescent in situ hybridization, pediatric, oncology

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Introduction

Osteosarcoma (OS) can be defined as a heterogeneous neoplasm of bone with histopathologic evidence of malignant osteoid formation by atypical mesenchymal cells. The essential criterion for its diagnosis is the evidence of direct osteoid formation, though minimal, by neoplastic osteoblasts that confirms its diagnosis.¹

OS is a rare entity in the head and neck region with jaw bones being the most common site of involvement. It has a male preponderance. The jaw OSs are seen in an older age group (third to fourth decade), are less aggressive with low incidence of metastasis, and are associated with better prognosis when compared with their long bone counterparts.¹

OS has been histologically classified as conventional OS (fibroblastic, osteoblastic, and chondroblastic), small cell, telangiectatic, osteoblastoma-like, chondroblastoma-like, fibrohistiocytic, and giant cell-rich.² This report describes an unusual case of pan-cytokeratin (AE1/3)-positive fibroblastic OS in the left maxilla that showed positivity for both cytokeratin and vimentin and negative expression for epithelial membrane antigen (EMA) with histopathologic features mimicking monomorphic synovial sarcoma.

Case Report

A 14-year-old female patient reported to the Department of Oral Pathology with a chief complaint of swelling on the left side of the face since 4 months. She had a previous history of a similar lesion at the same site 9 months back, which was excised by a private practitioner and was histopathologically reported as neurofibroma. The swelling appeared again after 5 months, which was initially small and gradually increased in size over a

period of 4 months. There was evidence of rapid growth in the past 1 month. The patient took non-conventional medicine for the same, but the swelling kept on increasing in size. It was associated with mild and intermittent pain, the intensity of which increased with time. The patient's medical, family, and habit history were unremarkable. On extraoral examination, diffuse swelling was present on the left side of the face extending from midline to 4 cm posteriorly toward the outer canthus of eye and from corner of mouth to 4.5 cm superiorly toward the inferior orbital margin and was causing deviation of the nasal septum to the right side (Figure 1A). The swelling was firm and tender with normal color and texture of the overlying skin. The mouth opening was found to be normal and lymph nodes were not palpable.

Intra-oral examination revealed a well-defined soft tissue swelling of size 3 cm × 3.5 cm in the maxillary anterior region extending from distal aspect of 11 to distal aspect of 24 with erythematous overlying labial mucosa that was fixed to the swelling. It was firm in consistency and tender on palpation causing palatal displacement of 11, 21, 22, and 23. Grade I mobility was observed in these teeth (Figure 1B).

Orthopantomogram showed no bony changes, except displacement of teeth 21 and 22. Contrast-enhanced computed tomography (CECT) revealed heterogeneously enhancing mass measuring 4 cm × 4.5 cm × 5 cm in size anterior to the left maxillary sinus with destruction of its anterior and medial wall. The lesion was extending into the left maxillary sinus. It was indenting over the left inferior turbinate and extending into the left anterior nasal cavity (Figure 1C).

The histopathologic examination of the incisional biopsy taken from the lesion revealed highly cellular tumor tissue



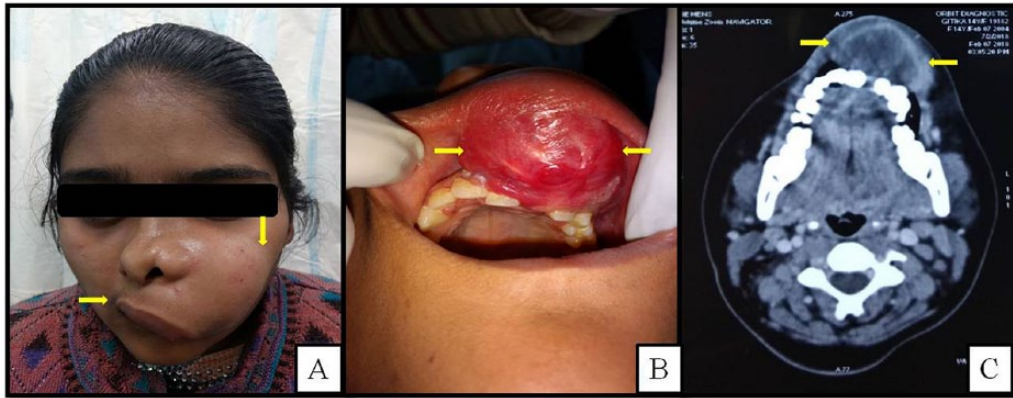


Figure 1. (A) Extra oral photograph shows swelling on the left side of the face causing nasal deviation; (B) intra-oral photograph shows swelling involving the left maxilla, crossing the midline and obliterating the labial vestibule; and (C) CECT shows heterogeneously enhancing mass involving the left maxilla. CECT indicates contrast-enhanced computed tomography.

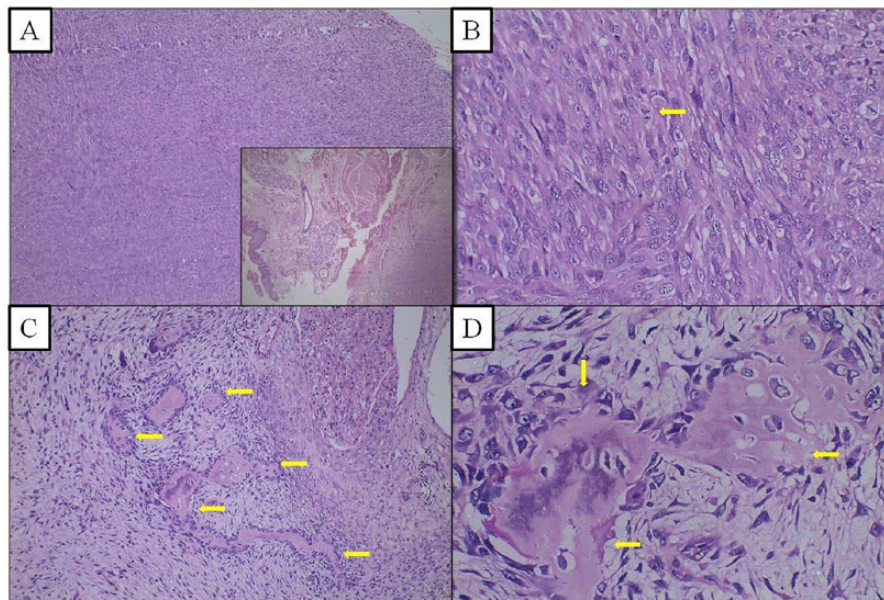


Figure 2. (A) Microphotograph shows spindle-shaped cells arranged in whorls and storiform pattern (10 \times) (inset 4 \times); (B) microphotograph shows abnormal mitosis (arrow) in tumor cells (40 \times); (C) microphotograph shows foci of osteoid formation (10 \times); and (D) microphotograph shows tumor osteoid lined by atypical osteoblasts (40 \times).

composed of intersecting fascicles of spindle-shaped cells. Cells in cross section showed vesicular nuclei with vacuolar degeneration of the cytoplasm (Figure 2A). Few hyperchromatic nuclei and mild nuclear pleomorphism were also observed. Increased and abnormal mitotic activity was observed throughout the lesion. The nuclei varied from ovoid to blunt-ended with spherical nuclei also observed at places. The minimal supporting stroma was fibro collagenous with variable vascularity. The tumor tissue was separated from overlying parakeratinized stratified squamous epithelium by fibrous tissue. Tumor cells were diffusely positive for pan-cytokeratin (AE1/3) and vimentin and negative for S100, smooth muscle actin (SMA), Desmin, bcl-2, and CD99 (Figure 3A to G). Absence of osteoid with these findings pointed toward the diagnosis of monophasic variant of synovial sarcoma.

The patient underwent segmental resection of the left maxilla. On histopathologic examination of the resected tissue, hypercellular, and hypocellular areas were noted. The hypercellular areas were composed of spindled to plump fibroblasts. At areas, these cells showed Herring bone pattern intersecting at right angles with scarce cytoplasm, vesiculated nuclei, and exhibiting cellular and nuclear pleomorphism and nuclear hyperchromasia. Two to four abnormal mitotic figures were observed per 10 high power fields (Figure 2B). Malignant osteoid formation was seen only at foci (Figure 2C and D). A few tumor giant cells were seen in close approximation with the tumor osteoid.

The remaining connective tissue stroma was hypocellular, showing loosely arranged collagen fibers in whorled pattern. Mild diffuse infiltration of chronic inflammatory cells was seen

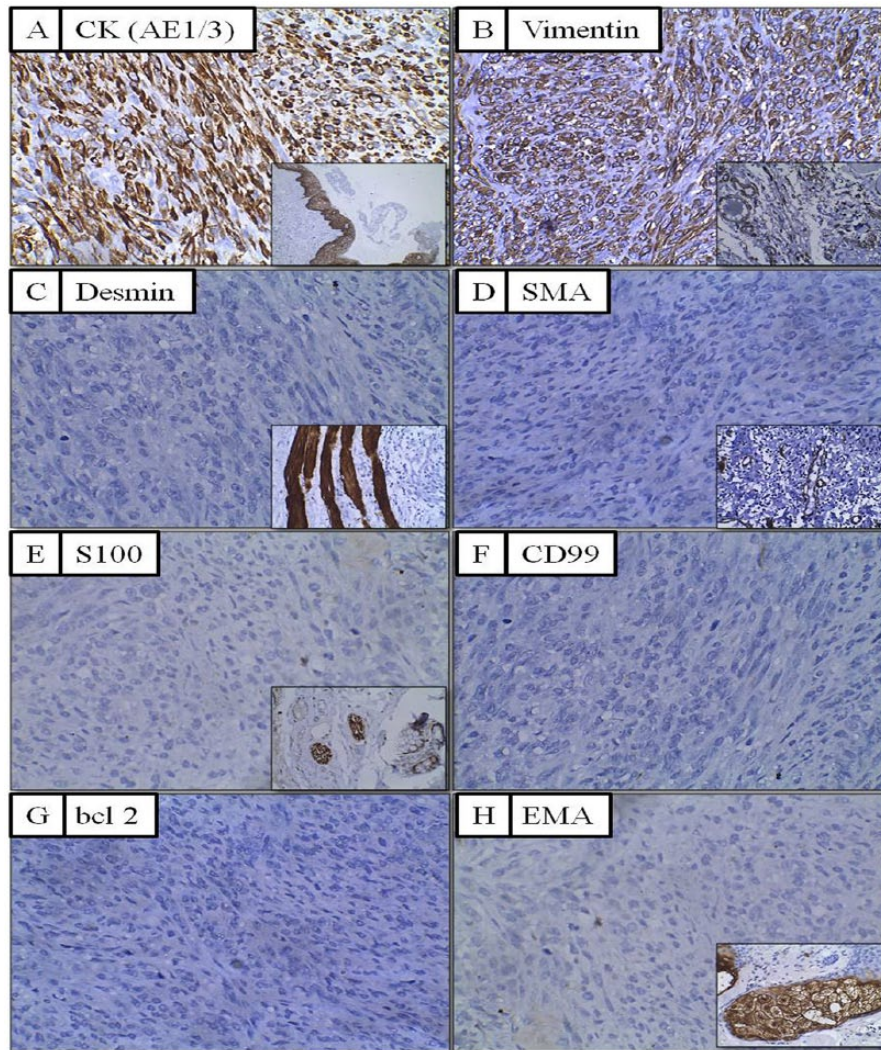


Figure 3. Microphotographs showing immunopositivity for Cytokeratin AE1/3 and vimentin (A and B, respectively) and immunonegativity for Desmin, SMA, S100, CD99, bcl-2, and EMA (C to H, respectively) (inset: controls). CK indicates cytokeatin; EMA, epithelial membrane antigen; SMA, smooth muscle actin.

throughout the connective tissue. Peripheral area showed degenerated muscle fibers exhibiting fragmentation and loss of striation. The lesional tissue was moderately vascular with deeper area comprising intact muscle tissue and many neurovascular bundles. All surgical margins were negative for tumor tissue. The tumor cells were positive for vimentin and pan-cytokeratin and negative for EMA (Figure 3A, B, and H). A differential histopathologic diagnosis of monophasic synovial sarcoma and fibroblastic OS was considered. Furthermore, the tissue was subjected to fluorescent in situ hybridization (FISH), which was negative for SYT gene translocation. Hence, the final diagnosis was signed out as fibroblastic variant of OS. The patient was referred to an oncology center for further treatment involving chemotherapy.

Discussion

OS is the most common primary malignant tumor of bone after exclusion of plasma cell tumors. The OS can be classified as primary or secondary depending on the causal factors. The

cause of primary OS is unknown and may be attributed to genetic or environmental factors, whereas secondary OS arises in precedent bone diseases like Paget or fibrous dysplasia.³

It most commonly affects the appendicular skeleton, but cases in head and neck region have also been documented.³ The OS in our case was seen in second decade of life, which is in contrast with the general finding of head and neck OSs having a predilection for fourth decade.¹ The head and neck OSs are commonly seen in male population.³ The present case was seen in the maxilla of a female patient, which is in accordance with the study by Forteza et al, where maxillary OS was seen in female patients with a ratio of 4:1.³

Radiologic examination plays an important role in its diagnosis and usually shows a varied radiographic presentation ranging from lytic to mixed to osteogenic pattern. Widening of periodontal membrane space (Garrington sign) and inferior alveolar canal together with sunray appearance is pathognomonic of the diagnosis.⁴ Our case presented as osteolytic lesion with displacement of teeth in the anterior maxilla.

Table 1. Total number of cases of fibroblastic osteosarcoma of jaw published from 1991 to 2017 (PubMed data).

S. NO.	REFERENCES	YEAR	AGE (YEARS)/SEX	NO. OF CASES
1.	Jeong et al ⁶	2017	1. 35/F 2. 10/F	2
2.	Peddana et al ⁷	2017	1. 35/F	1
3.	Argon et al ⁸	2015	1. 51/M	1
4.	Nirmala et al ⁹	2014	1. 10/F	1
5.	Cutilli et al ¹⁰	2011	1. 62/M	1
6.	Desai et al ⁴	2010	1. 42/F	1
7.	Ajura and Lau ¹¹	2010	1. 43/M 2. 6/F 3. 16/M 4. 7/F 5. 18/F 6. 42/M	6
8.	Ogunlewe et al ¹²	2006	1. 17/M 2. 35/F 3. 11/M 4. 21/F 5. 25/M 6. 22/M	6
9.	Mardinger et al ¹³	2001	1. 78/F 2. 22/F 3. 38/M 4. 35/M	4
10.	Bertoni et al ¹⁴	1991	1. 38/M 2. 41/M 3. 45/F 4. 35/F	4
Total cases				27

Bold values depict pediatric patients in respective studies.

The dilemma in diagnosis of incisional biopsy arose due to the small size of the biopsy specimen that was taken from the periphery of the lesion. The lesional tissue showed spindle cells that were positive for Cytokeratin AE1/3 and vimentin, and was devoid of tumor osteoid. These findings led to the consideration of synovial sarcoma as diagnosis. Hence, this emphasizes the importance of procuring biopsy tissue from the most representative site or from the center of the lesion.

The excisional tissue showed spindle-shaped cells along with minimal osteoid formation. The tumor cells were positive for Cytokeratin AE1/3 and vimentin. The common tumors positive for both Cytokeratin AE1/3 and vimentin are epithelioid sarcoma, sarcomatoid carcinoma, and synovial sarcoma. The epithelioid sarcoma affects young adults in their second and third decade of life, and presents as a single nodule, whereas sarcomatoid carcinoma mostly develops in men at sixth to seventh decade of life. The tumor cells in epithelioid sarcoma are usually epithelioid in nature with minimal spindle-cell component. Furthermore, sarcomatoid carcinoma necessitates that there is invasion of tumor cells from the surface epithelium with tumor cells varying from spindle to epithelioid shape.

These features were not apparent in the case studied and hence both were ruled out. The negativity for EMA, bcl-2, and CD99 eliminates synovial sarcoma and tilted the diagnosis toward OS as there were foci of osteoid formation.

Further to complicate the diagnosis, the osteoid formation was not typical of tumor osteoid. It resembled more of reactive bone formation with association of few tumor giant cells in the vicinity. Hence, FISH was carried out, which was negative for SYT gene translocation. The negativity for EMA and FISH ruled out the monophasic variant of synovial sarcoma. Therefore, a diagnosis of fibroblastic OS was given.

The deposition of even small amount of osteoid by malignant cells is a diagnostic of OS. It can be classified into osteoblastic, chondroblastic, and fibroblastic depending on the relative amount of osteoid, cartilage, or collagen fibers in the extracellular matrix. The division is arbitrary as varying amount of these cell types and matrix can be seen. It generally signifies more than 50% prevalence of any of these histologic types.⁵

Fibroblastic OS is the least common variant in the head and neck among the 3 variants as only 27 cases (Table 1) including only 5 pediatric patients have been published from 1991 to

2017 according to PubMed data. Histologically, spindle-shaped cells arranged in storiform to Herring bone pattern resembling fibrosarcoma are seen. Formation of malignant osteoid is the distinguishing feature between the 2 entities.

In a case series by Okada et al, 6 out of 131 cases of OS involving the extremities were found to be positive for cytokeratin immunostaining. Three cases showed intense epithelioid differentiation and showed strong immunopositivity for cytokeratin. The remaining cases showed focal positivity in spindled pleomorphic cells in cases of fibroblastic OS, and chondrocytes in cases of chondroblastic subtype. However, in our case, diffuse strong positivity for cytokeratin in spindled pleomorphic cells was observed.¹⁵

Kramer et al discussed several hypotheses regarding biphenotypic nature of malignancies and suggested that the most accepted theory as given by Brooks et al states that these tumors arise from primitive mesenchymal cells whose differentiation proceeds in a non-random fashion that results in biphenotypicity. The uncommitted multipotent stem cells can acquire epithelial morphology and express a variety of epithelial products including cytokeratins, hence showing immunopositivity for both pan-cytokeratin and vimentin.¹⁶

OS of jaws are less aggressive and have better prognosis due to their better histologic differentiation.⁹ The correlation between histologic subtype and prognosis is still controversial,⁶ although few studies have reported the chondroblastic variant to be associated with poor prognosis.^{8,11} Patients with maxillary OS are reported to have a shorter median survival period when compared with those with mandibular involvement.⁹ It has also been reported that the EMA-positive OSs have poorer prognosis in comparison with cytokeratin positive OSs.¹⁵ Our patient is on close follow-up considering the fact that maxilla was involved.

Multidisciplinary treatment modalities are involved in treating OS and include surgery followed by adjuvant chemotherapy and palliative radiotherapy. These have resulted in improved outcome versus surgery only.^{17,18} Complete surgical resection of the tumor mass is essential for local control, recurrence-free, and disease-specific survival.¹⁷ Neoadjuvant chemotherapy has been reported to have reduced the chances of recurrences irrespective of the tumor margins and enhanced the survival rate and disease-specific survival.¹⁸ Mandibular cases have been reported to have better prognosis when compared with maxillary lesions. This can be attributed to the fact that tumor margins are positive in cases of maxillary lesion due to the location, which results in difficulty in resection and inability to involve normal tissue at the tumor margins.¹⁷

Conclusions

OS is the most common tumor originating in bone after hematopoietic neoplasms. A presumptive diagnosis of OS can be reached if typical radiographic presentation is evident, but histopathology is the gold standard for confirmatory diagnosis. The histopathologic diagnosis was, however, complicated in

this case. Therefore, a complete correlation between clinical details, radiographic examination, and histopathologic examination should be carried out. This case highlights the diagnostic dilemma encountered with spindle-cell lesions that are pan-cytokeratin positive.

Author Contributions

ABU, PK, JA and BN have worked on the diagnosis of the case. ABU and BN drafted the manuscript and made edits. PK and JA made suggestions and edits. All authors reviewed and approved the final submission.

Informed Consent

Informed consent was taken from patient's father regarding use of pre-operative photographs for scientific or educational purposes.

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