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Mesenchymal Chondrosarcoma of the Maxillary Alveolar Bone in a 6-Year-Old Girl

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Malignant small round blue cell tumors encompass a diverse group of aggressive neoplasms that share overlapping histological features, making diagnosis challenging based on morphology alone. We share a case of mesenchymal chondrosarcoma to illustrate this challenge and discuss the differential diagnosis.

Soft, cream-tan tissue fragments with tan, grainy surfaces were submitted from an incisional biopsy taken from the left maxillary alveolar bone of a 6-year-old female. Microscopically, the tumor

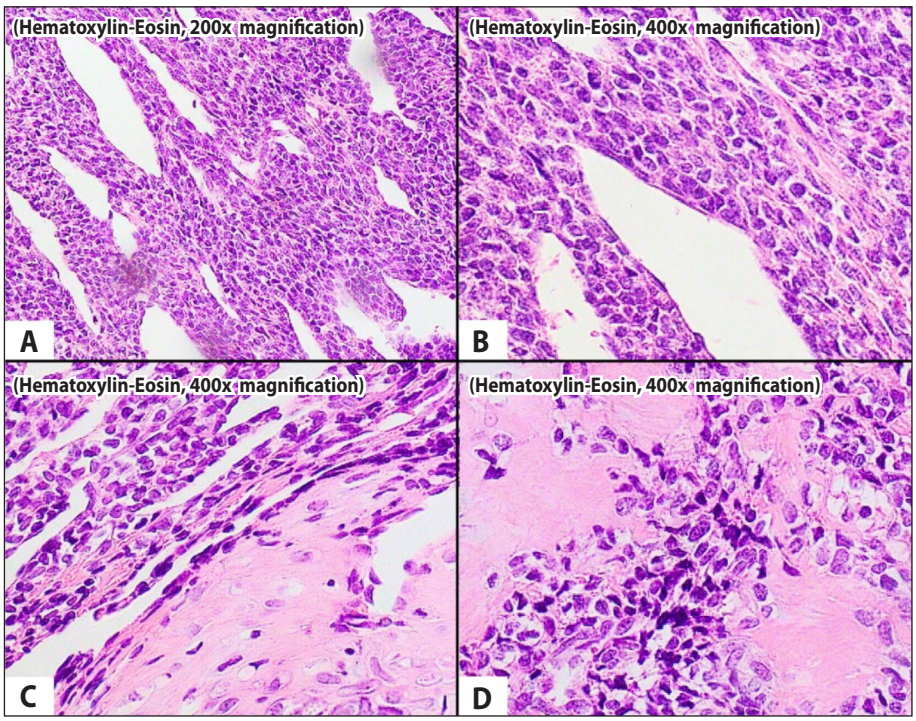

Figure 1. The tumor is predominantly composed of sheets of undifferentiated monomorphic small round blue cells with interspersed slit-like spaces resembling staghorn vessels. (Hematoxylin and Eosin: **A.** 200X magnification, **B.** 400X magnification). Some areas show an abrupt transition to islands of mature hyaline cartilage. (**C.** and **D.** Hematoxylin and Eosin, 400X magnification)

Keywords: *HEY1-NCOA2; maxilla; mesenchymal chondrosarcoma; NKX3.1*

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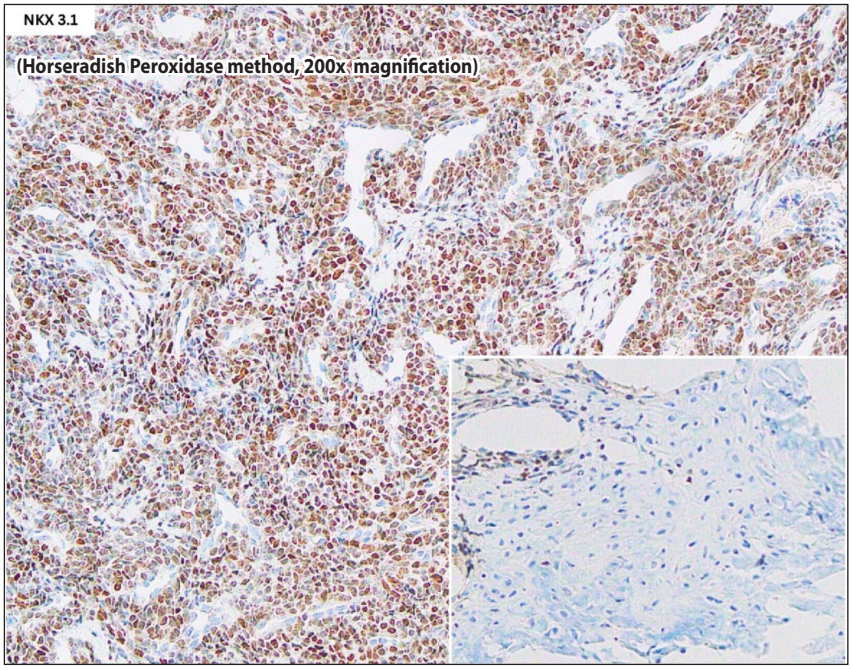

Figure 2. The undifferentiated component shows diffuse nuclear positivity for NKX 3.1 while the cartilaginous component (inset) is negative. (Horseradish Peroxidase method, 200X magnification)

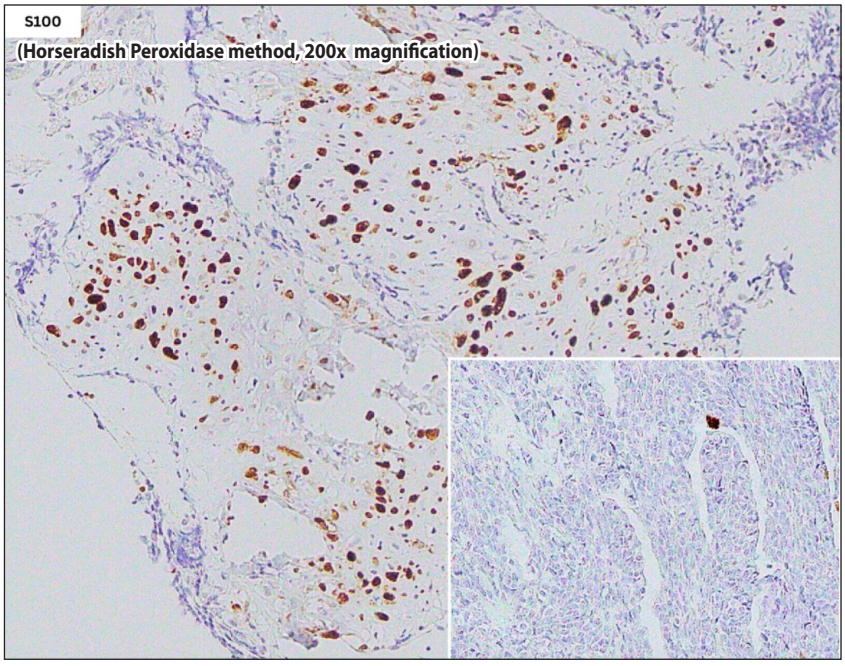

Figure 3. The cartilaginous component is strongly positive for S100, confirming chondrocytic differentiation. Inset: The undifferentiated component is negative. (Horseradish Peroxidase method, 200X magnification)

was composed primarily of sheets of morphologically undifferentiated monomorphic small blue round cells with hyperchromatic nuclei, scant cytoplasm, and poorly defined cell borders interrupted by staghorn-shaped vascular structures. Admixed within the sheets of tumor cells were abrupt transitions to islands of mature, well-differentiated hyaline cartilage. *(Figure 1)*

Immunohistochemistry studies were performed for SATB2, NKX3.1, S100, pancytokeratin, and desmin. In the undifferentiated round

cell component, NKX3.1 showed moderate to strong diffuse nuclear staining. *(Figure 2)* Strong, diffuse nuclear and cytoplasmic staining of S100 was observed in the cartilaginous component, confirming chondrocytic differentiation. *(Figure 3)* SATB2 was weakly positive in the undifferentiated component but negative in the cartilaginous component. Pancytokeratin and desmin were both negative.

The round cell neoplasm demonstrated a characteristic biphasic morphology and immunophenotypic profile, strongly supporting a diagnosis of mesenchymal chondrosarcoma (MCS). Ancillary molecular testing for the HEY1::NCOA2 fusion, which may offer additional diagnostic support, was not performed due to the unavailability of the assay at the local institution.

MCS is considered a rare type of sarcoma accounting for 2-10% of all chondrosarcomas, 20-30% of which arise in the head and neck.[1] Adolescents and young adults are affected with a slight female predominance. Grossly, it is a grey-white, lobulated tumor.[2] The first described histological features of MCSs are marked by bidirectional differentiation of tumor cells, resulting in a biphasic tumor composed of small, round, or spindle-shaped undifferentiated mesenchymal cells and islands of mature hyaline cartilage. The undifferentiated cells have round or oval nuclei, thick nuclear membranes, granular chromatin, modest nucleoli and scant cytoplasm. Mitosis is frequent and often atypical with possible necrosis and inflammation. In the cartilage areas, the cells are polygonal with cytoplasmic vacuoles, round nuclei, granular chromatin and distinct nucleoli. Solid areas of small round cells resemble "Ewing-like" features, while spindle-shaped cells around blood vessels are termed "hemangiopericytoma-like". The cartilaginous and undifferentiated regions are well-defined or intertwined.[3]

The diagnosis of MCS is more readily apparent if both components are present, as the biphasic histology is quite distinctive. However, the absence of cartilage in a limited biopsy sample can cause this tumor to be confused with other small, round, blue-cell tumors, particularly those that preferentially affect the pediatric age group. The differential diagnosis for the undifferentiated component includes Ewing's Sarcoma (ES), desmoplastic small round cell tumor (DSRCT), small cell osteosarcoma, and rhabdomyosarcoma. Mesenchymal chondrosarcoma typically expresses CD99, NKX2.2, S100, and SOX9.[4] Weak positivity of SATB2 in the index case excludes small cell osteosarcoma while pancytokeratin and desmin negativity exclude DSRCT and rhabdomyosarcoma, respectively. CD99 and NKX2.2 are found in ES while CD99 is also positive in DSRCT. Due to this overlapping immunologic profile, distinguishing MCS from its differentials is challenging. A recent study identifies NKX3.1 as a useful immunohistochemical marker for mesenchymal chondrosarcoma. Located on chromosome 8p21, NKX3.1 is a prostate-specific gene commonly used in diagnosing metastatic prostate adenocarcinoma. It plays a role in axial skeleton development through chondrogenic differentiation and ossification.[5] NKX3.1 is absent in ES, DSRCT, small cell osteosarcoma, and rhabdomyosarcoma, making it helpful in distinguishing MCS from other small round blue cell tumors. Other than MCS, NKX3.1 expression is only seen in *EWSR1-NFATC2* sarcomas.

The *HEY1-NCOA2* gene fusion has become a reliable molecular diagnostic marker for MCS, aiding in diagnosing cases without the typical histological features, especially in small biopsies where the cartilaginous component may not have been sampled. Studies recommend FISH testing for *HEY1-NCOA2* fusion in tumors with nested round cell morphology and staghorn vasculature but lacking a clear cartilaginous component.[3]

MCS is an aggressive neoplasm and patients usually require long-term follow-up after treatment. Tumors of craniofacial origin and those occurring in children and adolescents tend to follow a more favorable course following complete resection and chemotherapy.[1] This case underscores the diagnostic complexity of MCS due to its mixed histological features. Key immunohistochemical markers, specifically NKX3.1, may aid in distinguishing it from other small round blue cell tumors. Due to its rarity and overlapping features with other sarcomas, a comprehensive approach combining histology, immunohistochemistry, and molecular testing is crucial for accurate diagnosis.

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