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Case Report

Primary chondroblastic osteosarcoma with glandular areas - An extremely rare case of divergent differentiation

B Deepthi[1,*], **B Soumia**[1], **G Swyritha**[1], **N Rukmangadha**[1], **Aruna K Prayaga**[1]

[1]*Dept. of Pathology, Sri Venkateswara Institute of Medical Sciences, Tirupati, Andhra Pradesh, India*

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ABSTRACT

Malignant bone tumors with epithelial differentiation are extremely rare. A primary carcinosarcoma arising in bone is characterised by the presence of both epithelial and mesenchymal differentiation. Herein we report an extremely rare case of primary chondroblastic osteosarcoma with true divergent glandular differentiation in a twenty-nine year old female. Microscopic sections reveal a high-grade chondroblastic osteogenic sarcoma with definite areas showing neoplastic osteoid formation and nests, cords and acinar (glandular) structures with cytokeratin positivity suggesting definitive epithelial glandular differentiation. Our case illustrates the ability of osteosarcomas to show epithelial differentiation characterized both by cytokeratin expression and differentiation to adenocarcinomatous cells displaying distinct glandular differentiation

1. Introduction

Malignant bone tumors with epithelial differentiation are extremely rare. Osteosarcoma (OS) is a primary malignant bone tumor with a worldwide incidence of 3.4 per million people peryear.[1,2] OS is a rare sarcoma that has the histological findings of osteoid production in association with malignant mesenchymal cells.[1,3] The combination of a primary osteosarcoma of bone and a second cell type with morphologic characteristics of epithelial cells has been recognised.[4–8]

A primary carcinosarcoma arising in bone is extremely rare and is characterised by the presence of both epithelial and mesenchymal differentiation. Most of the published cases describes combination of primary chondrosarcomas of the bone with squamous cell differentiation.[5,6,8,9] This type of divergent differentiation in osteosarcoma is certainly a rare phenomenon and, defined as the development in these tumours of morphologically, immunohistochemically and/or ultrastructurally recognizable epithelial differentiation. Only one case of malignant bone tumor with distinct true glandular differentiation has been reported.[4]

Herein we report the second case of primary chondroblastic osteosarcoma with true divergent glandular differentiation.

2. Clinical Summary

A 29 year-old woman with history of swelling and progressive pain over left lower leg since three months and associated with pain while walking. Physical examination revealed a firm to hard mass measuring approximately 5x3cms, in lateral aspect of left leg, 2cm below the knee joint. The X-ray revealed a large, poorly defined high density shadow in the right upper fibula occupying the epiphysis and metaphysis with cortical destruction and extension into adjacent soft tissue (Figure 1A). MRI features suggestive of focal altered signal intensity with

* *Corresponding author*.
E-mail address: drbdeepthi@gmail.com (B. Deepthi).

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slight expansion involving the left fibular head extending from subarticular location upto metadiaphysis, hypointense on T1W1, faintly hyperintense onT2W1, hyperintense on STIR images. There is interrupted periosteal reaction with tiny cortical break inanterolateral cortex of fibula with involvement of adjacent extensor digitorum longus muscle (Figure 1B)Three phase bone scintigraphy reveals solitary ltyic lesion with soft tissue component in proximal end of left fibula. No other osteoblastically active skeletal lesions noted(Figure 1C). The resection of the proximal fibula along with lateral compartment of soft tissues and musculature was received. Grossly, the resection specimen showed an irregular mass of sclerotic white tan lesion present in the metaphyseal region of the fibula measured 5 X 3 cm in greatest dimension in the medullary canal (Figure 2). The tumor destructed the cortical bone and encroached the contiguous soft tissues.

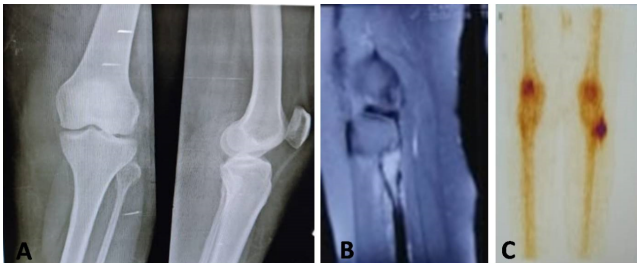

Fig. 1: A: X rayhigh density shadow in the right upper fibula occupying the epiphysis and metaphysis with cortical destruction; **B:** MRI **C:** Three phase bone scintigraphy showing solitary lytic lesion.

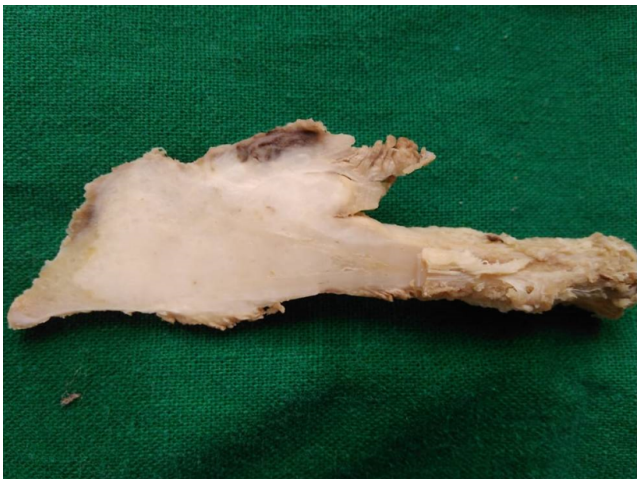

Fig. 2: Sclerotic white tan lesion present in the metaphyseal region of the fibula

Microscopic sections reveal a high-grade chondroblastic osteogenic sarcoma with predominant areas showing proliferation of irregular-shaped lobules of chondromyxoid cellular areas permeating into the bone trabeculae (Figure 3

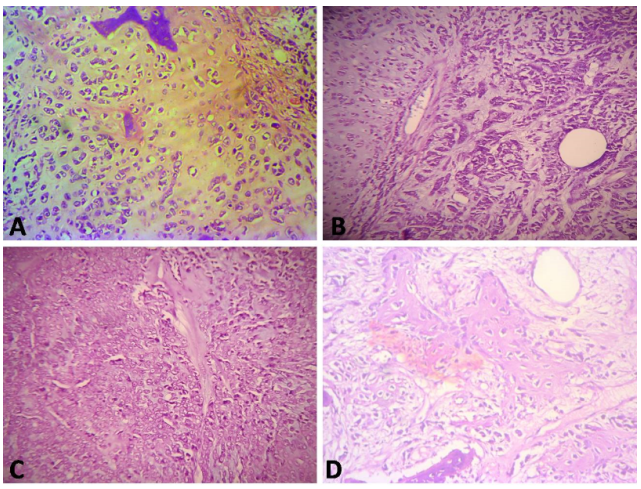

Fig. 3: High-grade chondroblastic osteogenic sarcoma permeating the bone trabeculae (**A,B,C**) with lacy, eosinophilic, homogenous, glassy matrix and osteoblastic rimming by neopastic cells(**D**).

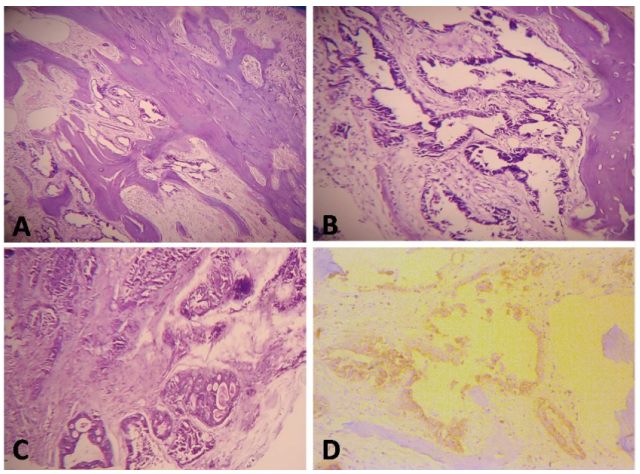

Fig. 4: Areas showingepithelial glandular differentiation forming trabeculae, nests, cords and acinar (glandular) structures (**A,B,C**) Highlighted by IHC with cytokeratin (**D**).

A).These chondroblasts are large round to polygonal cells with high nucleocytoplasmic ratio, pleomorphic round vesicular nucleus ,very prominernt amphophilic nucleoli and moderate to abundant eosinophilic cytoplasm (Figure 3B).The cells are seen embedded within and floating in abundant blue chondromyxoid matrix (Figure 3C).The non chondroid cellular areas comprising large polygonal cells with definite areas showing neoplastic osteoid formation seen as lacy , eosinophilic, homogenous, glassy matrix with irregular contours with osteoblastic rimming by neopastic cells (Figure 3D). The presence of osteoblasts directly apposed over thin rims of osteoid is seen.In addition there were foci of distinct areas containing pleomorphic cells with prominent nucleoli arranged in cohesive clusters and nests forming trabeculae, nests , cords

and acinar (glandular) structures, suggesting definitive epithelial glandular differentiation (Figure 4A,B,C). Immunohistochemistry with cytokeratin showed distinct strong positivity only within the glandular epithelial component (Figure 3D). A diagnosis of chondroblastic osteosarcoma with divergent epithelial glandular differentiation was made. Immunohistochemistry with cytokeratin showed distinct strong positivity only within the glandular epithelial component.

3. Discussion

Most sarcomas exhibit only one line of histologic differentiation,while a minority may display a strikingly diverse phenotype in addition to the main lineage.[10] This phenomenon not only presents a diagnostic problem but also raises questions about the commitment of tumor cells toward a specific phenotype. Sarcomas which display divergent differentiation with atleast two components (not patterns) were called malignant mesenchymomas. This term advocated by Stout was proposed to recognise the complexity of composition of such tumors and avoiding specifying all their different elements.[11,12] There indeed exists a group of sarcomas sharing the common property of divergent differentiation toward more than one single histogenetic type. Unsuspected lines of differention continue to be recognised in various sarcomas. Cases of multipotential neoplasms of bone have been well documented in the literature. The majority of them consist of multiple histologic elements including chondrosarcomatous, osteosarcomatous, lymphoid, vascular, adamantinomatous, squamous and adenocarcinomatous differentiation. The rare occurrence of ”epithelial-like” areas mimicking metastatic carcinoma within tumors otherwise classifiable as osteogenic sarcomas has also been described.

These cases are usually reported in younger patients, and this entity has been designated epithelioid osteosarcoma. There are reported cases of tumors containing areas resembling adenocarcinoma, admixed with squamous differentiation, including pearl formation,[13] and mixed with Ewing sarcoma and areas of osteogenic sarcoma. These patients with mixed cytologic findings were young and did not demonstrate evidence of a primary epithelial malignancy from another site. Our case also presented at young age with no significant previous history and whole body PET CT did not reveal any other primary focus.

Osteosarcomas with epithelial differentiation are relatively rare, and rarer still are those showing rosette-like, glandular or squamous differentiation.

A small number of osteosarcomas have been reported with glandular or rosette-like differentiation and/or high molecular weight cytokeratin expression.[4,14,15] Some of these osteosarcomas including our case have a chondroblastic morphology. Our case demonstrated distinctive glandular differentiation. This adds to the spectrum of epithelial differentiation reported in the literature and expands the potential differential diagnosis to include metastatic adenocarcinoma.

Primary bone neoplasms containing cellular component showing epithelial differentiation raise the differential diagnosis of metastatic carcinoma with reactive bone formation, osteosarcoma with focal epithelial differentiation, and a true carcinosarcoma of bone. Our case had high grade osteocartilageous sarcomatous areas with only a peripheral foci of definite glandular differentiation. The differential diagnosis of a metastatic carcinoma arises when the sarcomatous areas are of low grade mimicking a reactive bone. The reactive bone associated with epithelial metastases usually shows less nuclear atypia than is characteristic of osteosarcomas showing focal epithelial differentiation. Carcinomatous metastases to bone are most commonly associated with a clinically or radiographically demonstrable primary lesion elsewhere in the body. Our case had undergone whole PET scan and a single primary focus was seen in the fibula.

The pathogenesis of carcinosarcomas is still not completely understood. Two commonly cited theories are used to explain the origins of carcinosarcomas in many organs, the convergence (multiclonal hypothesis) and the divergence (monoclonal hypothesis).[16–19]

Molecular studies are now being used to elucidate the origins of these tumors and most recent studies support a monoclonal origin for these types of tumors.[19,20] This hypothesis postulates that carcinosarcoma may progress through multistep carcinogenesis with accumulation of genetic alterations, genetic instability, and generation of multiple subclones, followed by secondary transdifferentiation from an epithelial to a mesenchymal phenotype. The differentiating mesenchymal cells can acquire an epithelial cell morphology and express epithelial antigenic markers. This stem cell is then acted on by a combination of the microenvironment and genetic alterations to produce different histologic expressions of cell types.

Our case is an example of the extremely rare occurrence of this type of rare differentiation arising primarily in bone.

Recent molecular analyses have demonstrated that the carcinomatous and sarcomatous components are of monoclonal origin in some organs, and carcinosarcoma may progress through multistep carcinogenesis. The hypothesis of multipotential (totipotent) stem cell is highly plausible in carcinosarcoma of the bone because no epithelial component is present in the bone.[4–6,21,22]

Sarcomas with significant heterogeneity would appear most likely candidates for the focal production of the epithelial phenotype. The known heterogeneity of osteogenetic sarcomas would make them likely candidates for polyphenotypic differentiation.

In summary our case illustrates the ability of osteosarcomas to show epithelial differentiation characterized both by cytokeratin expression and differentiation to adenocarcinomatous cells displaying distinct glandular differentiation.

4. Conflict of Interest

The authors declare no relevant conflicts of interest.

5. Source of Funding

None.

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Author biography

B Deepthi, Associate Professor https://orcid.org/0000-0003-3279-2383

B Soumia, Senior Resident

G Swyritha, Senior Resident

N Rukmangadha, Professor

Aruna K Prayaga, Senior Professor

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