Multifocal Osteosarcoma is a rare aggressive disease often mistaken for metabolic bone disease or metastasis and early accurate diagnosis of this unusual entity can help in proper management.

Learning Point of the Article:
Multifocal Osteosarcoma: Multiple Primaries or Metastases? A Report of Rare Case and Review of Literature
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Introduction:
Multifocal osteosarcoma (MFOS) is characterized by multicentricity of osseous osteosarcomas, either synchronous or metachronous, without visceral involvement. They account for about 1.5% of all osteosarcomas. Most synchronous MFOS has one dominant lesion with one to four and very rarely five or more secondary lesions. The distal femur followed by the proximal tibia is the most common site of dominant lesions. Its prognosis remains extremely poor even with combined chemotherapy and surgery.

Case Report:
We describe a rare case of MFOS in a 10-year-old boy who presented with a short history of severe aching pain in the right lower limb following a trivial fall. Initial workup and relevant investigations revealed a synchronous multicentric osteosarcoma with extensive involvement of appendicular and axial skeletal system. The dominant lesion was at the lower end of the right femur with multiple secondary lesions in the right tibia, left femur, bilateral humeri, pelvis, cervical and dorsolumbar spine, ribs, and sternum. The patient received one cycle of doxorubicin and cisplatin-based chemotherapy but unfortunately succumbed to progressive disease, a month after initiation of chemotherapy.

Conclusion:
MFOS is a very rare presentation of osseous osteosarcoma. The non-specific clinical manifestation, despite the presence of generalized skeletal involvement, presents a diagnostic difficulty for both the clinician and the radiologist. Only biopsy and histopathological examination can confirm the diagnosis of this highly malignant disease and help in proper management.

Keywords: Multifocal osteosarcoma, synchronous multifocal osteosarcoma, multicentric osteosarcoma.
Radiograph of the right knee (Fig. 1a) showed a sclerotic lesion involving the lower metadiaphyseal region of the right femur with a wide zone of transition, a mild spiculated type of periosteal reaction, and cortical breach along the medial epicondyle with a soft-tissue component showing calcific foci within. Another sclerotic lesion with a wide zone of transition was noted involving the upper metadiaphyseal region of the tibia with the cortical breach at diaphysis (Fig. 1b). X-rays of the pelvis with visualized bilateral femori (c), dorsolumbar spines (d), cervical spines (e), and ribs (f) show similar radiological features.

Chest X-ray (Fig. 2a) and computed tomography scan of the lungs showed no evidence of metastasis; bone window images were suggestive of diffuse sclerotic lesions involving cervical, thoracic, and visualized lumbar vertebrae, sternum, ribs, and bilateral humeri (Fig. 2b, c). Bone scan with Technetium-99m showed abnormally increased radiotracer uptake at multiple sites (Fig. 3).

Biopsy from the lower end of the femur showed pleomorphic neoplastic cells in cords and nests with tumor osteoid composed of acellular coarse lace-like unmineralized bone rimmed by neoplastic cells having vesicular nuclei with prominent nucleoli (Fig. 4a, b). Bone marrow biopsy from the posterosuperior iliac spine showed intertrabecular spaces replaced by an infiltrating neoplasm displaying similar morphology (Fig. 4c). Histomorphology was suggestive of osteosarcoma; however, immunohistochemistry was done in view of the unusual presentation of this case and to exclude other clinical/radiological differential diagnoses such as lymphoma and histiocytic neoplasm. However, the neoplastic cells were immunonegative for LCA, CD1a, and CD68 with high Ki67 (50–60%) (Fig. 4d). The final diagnosis of MFOS was rendered as the child had multiple bony lesions at presentation.

The case was discussed at the institutional tumor board meeting and multidrug chemotherapy was planned with doxorubicin and cisplatin. The patient received one cycle of chemotherapy.
but unfortunately succumbed due to progressive disease.

Discussion

Osteosarcoma is the most common skeletal malignancy in childhood and adolescence; however, its multifocal variant is very rare, representing 1–2% of all osteosarcomas [1, 2]. Silverman in 1936 first described MFOS as multiple tumors occurring either synchronously or metachronously at two or more sites in a patient without pulmonary metastases [3]. The term synchronous is used when multiple lesions are present simultaneously at diagnosis, whereas metachronous lesions appear at different intervals usually after treatment of the dominant lesion, but always in the absence of any other visceral organ involvement representing spontaneous development of lesions in other parts of the skeleton [4]. In the study by Corradi et al., MFOS constituted only 1.5% (0.6% synchronous and 0.9% metachronous) of all osteosarcomas [1]. Fuchs et al. described multiple etiological factors for the development of osteosarcoma. MFOS can occur as part of hereditary syndromes (Rothmund-Thomson syndrome, Bloom syndrome, and Li-Fraumeni syndrome). Genetic events such as mutations of RB1 and p53 tumor suppressor genes or a de novo unidentified mutation may play a role in the pathogenesis of multicentric osteosarcoma [5, 6, 7]. The present case was not associated with any hereditary syndromes.

MFOS predominantly affects the young, with a mean age of 16 years (range 2–70 years) and a male predominance [1, 4]. Patients usually present with complaints of pain and swelling at the dominant site with other lesions identified incidentally on initial workup with radiological investigations such as skeletal survey or bone scintigraphy. The distal femur followed by the proximal tibia is the most common sites to show the dominant tumor with 1–4 (very rarely more than 5) synchronous additional bone lesions [1, 4]. In long bones, these lesions are located in metaphysis or metadiaphysis and show imaging features typical of a primary osteosarcoma of bone, that is, aggressive mixed lytic and sclerotic pattern of bone destruction with associated cortical destruction, soft-tissue extension, a wide zone of transition, and malignant periosteal new bone formation [1]. The clinical features and radiological findings in our case were similar to cases reported in the literature. However, extensive involvement of almost all bones of the body is an exceedingly rare presentation and has not been reported earlier.

In the study of 42 cases by Bacci et al., 88% and 61% of cases showed elevated serum alkaline phosphatase and LDH levels, respectively, which were also seen in the present case [4]. Histomorphological features of MFOS are the same as conventional osteosarcoma, and most of them show osteoblastic differentiation characterized by acellular lacy eosinophilic osteoid surrounded by neoplastic cells [1, 4].

There is much discussion in the literature as to whether MFOS represents multiple primary tumors or metastatic disease. Most studies conclude that synchronous MFOS represents one extreme of a vast spectrum of metastatic osteosarcoma [8, 9, 10], with one dominant lesion of a primary osteosarcoma, and the remaining lesions suggestive of metastases, typically manifesting as purely sclerotic and/or heavily mineralized lesions with a narrow transition zone and showing no evidence of cortical destruction, soft-tissue mass, or malignant periosteal new bone formation. Bone-to-bone metastases could occur through a similar mechanism to that of prostate cancer through Batson’s venous plexus or intraosseous embolization through marrow sinusoids [9, 11]. Hatori et al. demonstrated lymphatic invasion as a possible route of spread in MFOS [12]. In the present case, lower end of the femur is the likely primary site with multiple sclerotic metastases to other bones as described.

On the other hand, many studies have shown several features such as (1) absence of metastasis to the lung which rules out hematogenous spread, (2) genetic mutations of p53 and retinoblastoma gene, and (3) equal response of predominant and secondary tumors following chemotherapy – which favor multiple synchronous primary lesions [6, 7, 11].

Neoadjuvant chemotherapy followed by surgical resection of the predominant tumor with or without secondary lesions (based on their number) is the modality of treatment [4]. Resection of a maximum of 4 secondary lesions is documented in the literature, but only patients with 1–2 secondary lesions had remission in most studies [4]. Prognosis is extremely poor in synchronous MFOS. Bacci et al. reported the mean survival of 27 months and only one out of 42 patients was disease-free at 9 years [4]. Chemotherapy is the only treatment for extensive multifocal tumors like in the present case, which usually consists of a combination of doxorubicin and cisplatin.

Conclusion

MFOS is a very rare presentation of osseous osteosarcoma. The non-specific nature of its presentation and the absence of significant clinical findings despite the presence of generalized skeletal involvement presents a diagnostic difficulty for both the clinician and the radiologist, especially when there is no dominant lesion. Only histopathological examination can confirm the diagnosis of this highly malignant disease and helps in proper management which includes multiagent chemotherapy in most cases and surgery of the dominant lesion if necessary. The prognosis for synchronous MFOS remains extremely poor, even with combined chemotherapy and surgery.
Clinical Message

Multicentricity is a rare clinical manifestation of osteosarcoma. MFOS is often mistaken for metabolic bone disease unless there is a high index of suspicion. Early and accurate diagnosis of this aggressive sarcoma can assist the oncologist in making appropriate, timely treatment decisions.

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