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Multicentric osteosarcoma

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ABSTRACT Multicentric osteosarcoma is a rare type of osteosarcoma with a poor prognosis. It is usually described as the occurrence of tumorous lesions in more than one bone, but without pulmonary metastasis. It may be of a synchronous or metachronous variety. We report the case of a 12-year-old boy with a synchronous variety of multicentric osteosarcoma, although he did not have any risk factors for the disease. We also discuss the current debate on whether multicentric osteosarcoma represents multiple primary tumours or metastatic disease.

Keywords: metachronous, multicentric osteosarcoma, osteosarcoma, synchronous
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INTRODUCTION

Multicentric osteosarcoma, first described by Silverman, is characterised by the presence of tumorous lesions in multiple osseous sites in the absence of pulmonary metastasis.[1] It is categorised into synchronous and metachronous types. Although the aetiogenesis of osteosarcoma has been attributed to chemicals, viruses, trauma, radiation, alteration of retinoblastoma and the *p53* gene, several unanswered questions about this cancer remain.[2,3] We report the case of an adolescent boy with synchronous multicentric osteosarcoma who presented with only vague pain without any swelling or constitutional symptoms, despite the multifocal involvement. The purpose of this report is to describe the features of this rare clinical entity and to review the possible theories, natural history and differential diagnosis of the disease.

CASE REPORT

A 12-year-old boy presented with mild pain over the lower end of both thighs and the upper part of the left leg for two weeks. The pain was nontraumatic in origin and present even at rest. There was no associated swelling or constitutional symptoms. He did not have any features of viral infection involving the urogenital, oropharyngeal or cutaneous areas. There was no history of Paget's disease, metabolic bone disorder, bone tumour or any other malignancies in the family. His general examination was normal. On local examination, mild warmth and minimal tenderness were noted on the medial aspect of the right distal femur and the lateral aspect of the proximal tibia without any swelling or redness. The ranges of movement of the hip, knee and ankle were normal. Elevation in serum levels of alkaline phosphatase (2,377 IU), phosphorus (5.2 MEq/L) and erythrocyte sedimentation rate (ESR) (28 mm/hr), with normal levels of vitamin D3 and parathyroid hormone, were noted. The enzyme-linked immunosorbent assay test for human immunodeficiency virus (HIV) was negative.

Radiographs showed dense sclerotic lesions involving the distal metaphysis of the left femur, the proximal metaphysis of both the tibiae and the right humerus, as well as mixed sclerotic and lytic lesions involving the distal half of the diaphysis and metaphysis of the right femur with periosteal reaction (Figs. 1 & 2). Technetium-99 bone imaging showed increased uptake over the skull, upper end of the right humerus, D3, D6, D8, L1, L3 and L5 vertebrae, multiple ribs, head of the right femur, both femoral shafts and upper end of the left tibia (Fig. 3).

Magnetic resonance imaging showed lesions with altered signal intensity in the bilateral femora and tibia with periosteal reaction, suggesting the possibility of osteoblastic metastasis, multicentric osteosarcoma or metabolic bone disease such as hyperphosphatasia (Fig. 4). Computed tomography imaging of the lungs showed no evidence of metastasis.

Incisional biopsy was taken from both the distal femur and left proximal tibia. Microscopic examination showed highly cellular tumour tissue made up of large masses, sheets and groups of pleomorphic neoplastic cells that have hyperchromatic and pleomorphic nuclei, moderate to severe degree of nuclear atypia, many atypical mitotic figures, small irregular clumps of osteoid-like material, masses of chondroid matrix, areas of necrosis and foci of haemorrhage (Figs. 5 & 6). The histopathological report was suggestive of multicentric osteosarcoma. A second opinion was sought in view of the rarity of this condition. The slides were sent to a higher oncopathology centre, which confirmed the diagnosis of multicentric high grade osteosarcoma. Cytogenetic analysis was not carried out to identify the possible aetiological factors. Considering the multicentricity and young age at presentation, our patient was diagnosed to have the Amstutz type I variety of synchronous multicentric osteosarcoma. Surgical option was abandoned when the multicentric origin of the neoplasia became clear, and chemotherapy with cisplatin, ifosphamide and adriamycin was started. Although the patient was planned for six cycles of chemotherapy, the treatment was discontinued after

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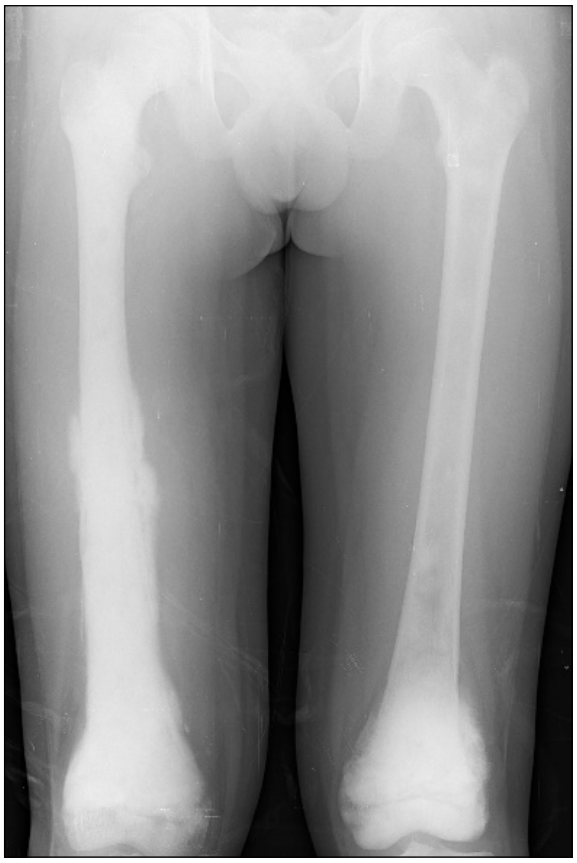

Fig. 1 Anteroposterior radiograph of the bilateral femur shows dense sclerotic lesions and periosteal reaction.

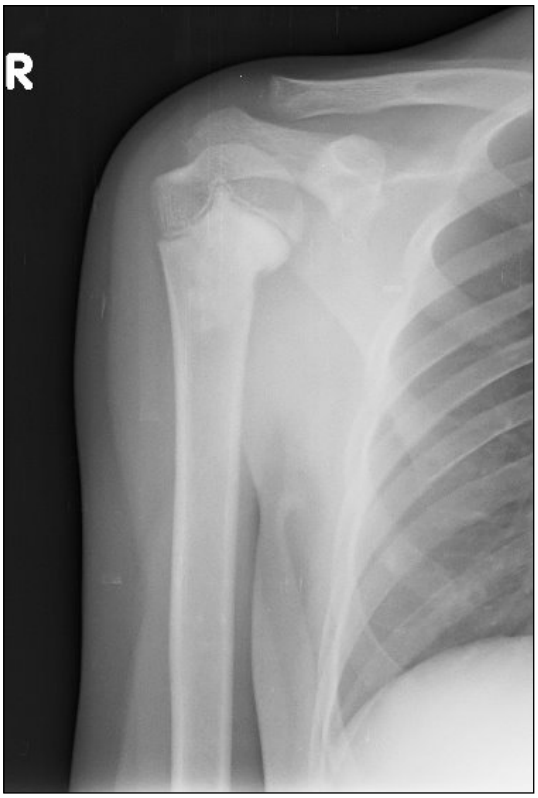

Fig. 2 Anteroposterior radiograph of the right humerus shows a sclerotic lesion in proximal metaphysis.

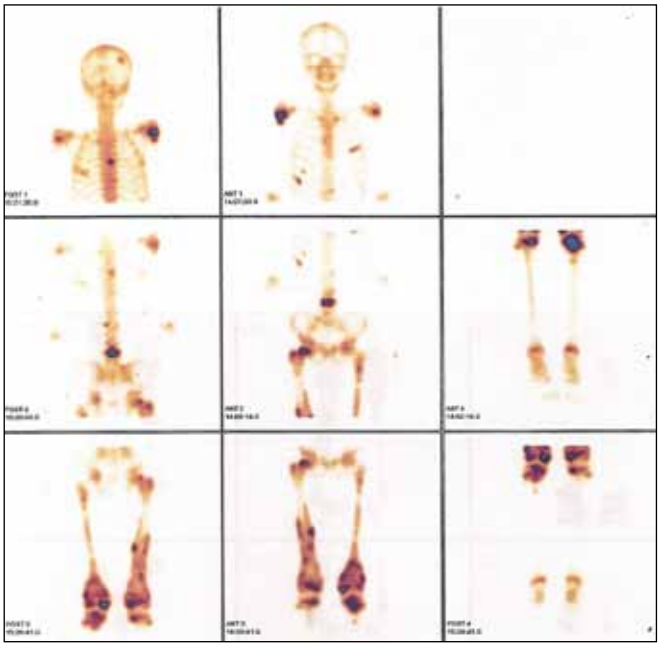

Fig. 3 Technetium bone image shows increased uptake at multiple sites.

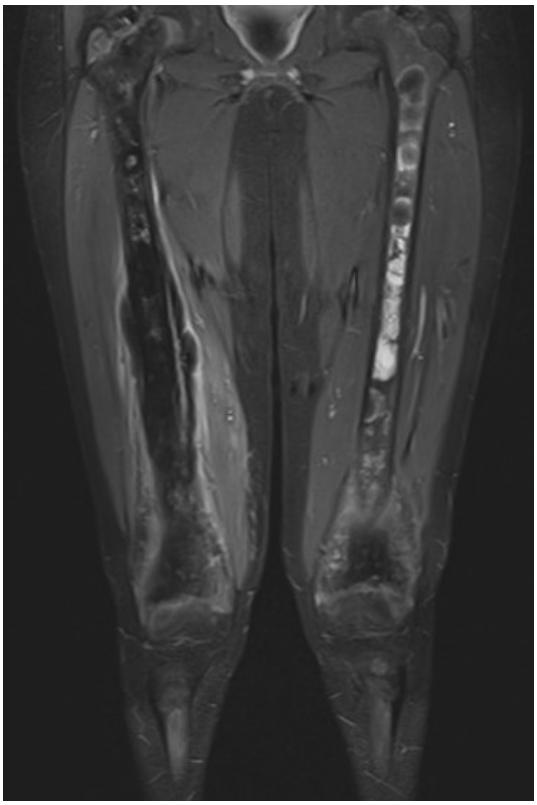

Fig. 4 MR image shows altered signal intensity of the lesions in the bilateral femora and tibia with periosteal reaction.

two cycles and the patient was discharged. He died six months after the onset of the initial symptoms.

DISCUSSION

Osteosarcoma is the most common skeletal malignancy in childhood and adolescence (20% of all primary malignant bone tumours); however, the multicentric variety is very rare (1%–2%).[4] Although there were isolated reports of osteogenic sarcoma with multiple skeletal foci in 1883[5] and later by White in 1922,[6] it was Silverman who postulated the multicentric origin and absence of pulmonary metastasis in 1936.[7] Multifocal or multicentric

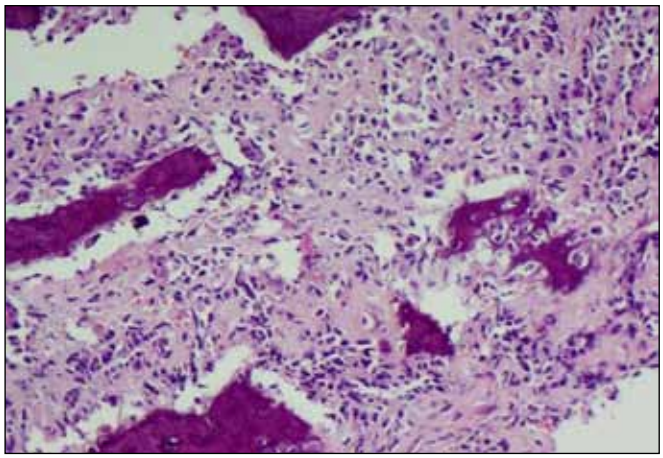

Fig. 5 Photomicrograph shows the invasive tumour composed of diffuse sheets and nests of malignant cells with slivers of osteoid in-between (Haematoxylin and eosion, × 10).

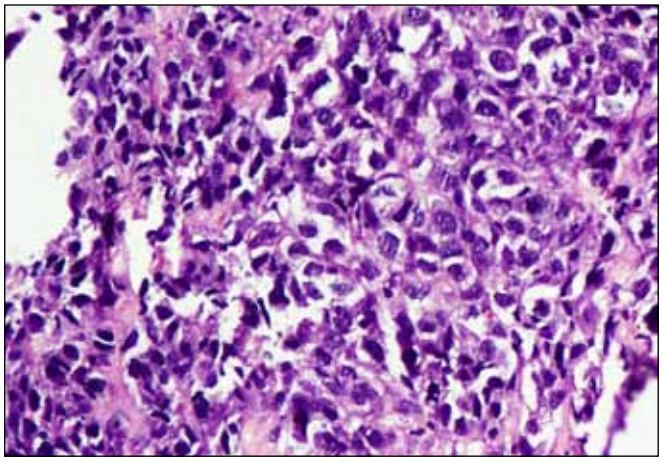

Fig. 6 Photomicrograph of tumour cells shows pleomorphic hyperchromatic to vesicular nuclei and brisk mitosis in a desmoplastic stroma (Haematoxylin and eosin, × 40).

osteosarcoma is usually defined as the occurrence of tumour at two or more sites in a patient without pulmonary metastases, and may be synchronous or metachronous.[8] When additional lesions are simultaneously present at diagnosis, the tumour is known as synchronous multifocal osteosarcoma.[9] The reported incidence of synchronous multifocal osteosarcoma is 1% to 3 %.[8] If smaller lesions appear at different intervals after treatment of the dominant lesion, it is termed metachronous multifocal osteosarcoma.[9] The following conditions are required to establish the multicentric origin of an osteosarcoma: (a) the absence of previous systemic bone pathology; (b) a negative history of exposure to radiation; (c) the simultaneous appearance of lesions in the affected bones; and (d) the absence of lung metastasis or metastasis in other organs when the multiple bone lesions are observed for the first time.[10]

The pathogenesis and aetiology of osteosarcoma still remains obscure. However, various aetiological agents have been identified and categorised into chemical agents (e.g. beryllium silicate, beryllium oxide and methylcholanthrene), viruses (e.g. murine sarcoma virus, Epstein Barr virus, human papilloma virus and HIV), radiation and miscellaneous (e.g. Paget's disease and electrical burn or trauma).[2] More recently,

Table I. Amstutz classification of multicentric osteosarcoma.

	Type 1	Type 2	Type 3*
Age group	Child/ adolescent	Adult	Adult
Variety of lesion	Synchronous	Synchronous	Metachronous
Site of lesion	Long bones	Long bones	Long and flat bones
Radiological appearance	Sclerotic	Sclerotic	Mixed sclerotic and lytic
Grade of tumour	High grade	Low grade	Usually low
Prognosis	Extremely poor	Poor	Average
Mean survival	About 6 mths	5 to 72 mths	2.5 yrs
Pulmonary metastasis	Early	Early	Late

*Further classified as early or late.

patients with hereditary diseases such as Rothmund-Thomson syndrome, Bloom syndrome and Li-Fraumeni syndrome were found to have an increased risk of having osteosarcoma.[2] Tumourigenesis has been attributed to loss of gene function of the retinoblastoma susceptibility locus (Rb1) and *p53* (normally tumour suppressor genes).[3] Transforming growth factor (beta 1 and beta 3) has also been implicated in the development and progression of osteosarcoma.[2] Normal vertebrate genome contains many potential cancer-causing genes and subsequent mutations convert them into oncogene.[2] However, our patient did not have syndromic features or exposure to radiation, was asymptomatic in the past and had no history of any type of malignancies in the family. Although in our case, as the exact aetiology was not known, a *de novo* mutation probably triggered by some unidentified virus might have caused the disease.

The most commonly quoted classification is that by Amstutz. He classified multicentric osteosarcoma into three types. Type 1 involves children and adolescents and is characterised by high grade multiple synchronous lesions involving the metaphysis of long bones, and carries an extremely poor prognosis. In type 2, patients are usually adults and have low grade synchronous lesions in the axial skeleton.[4,5] The prognosis for synchronous multifocal osteosarcoma is poor, with a mean survival time of six months for type I and a slightly better range of 5 to 72 months for type II. In the synchronous variety, radiographic imaging most often reports sclerosing lesions.[8] In type III, patients are usually middle aged and have metachronous lesions (subdivided into IIIa and IIIb for early and late onset of new lesions, respectively). In this type, a solitary lesion in the long or flat bones is noted at presentation and new lesions in other bones develop in five months or later. The lesions are usually asymmetric and appear either as lytic or sclerotic. Patients have longer survival times (average 2.5 years) and pulmonary metastasis is very late (Table I).[7] Another classification is that by Mahoney et al, who categorised multicentric osteosarcoma into groups A and B. The main differences between patients in the two groups were the histological grade of the tumour (highly anaplastic and high grade in A; well differentiated

and low grade in B), location within the bone (long bone metaphysis in A; long bones, skull or vertebrae in B), and the age of onset (mean age of onset 10 years in A; 37 years in B) (Table II).[11]

Usually, patients with multicentric osteosarcoma present with pain and swelling in only one site, whereas tumours in other bone locations are asymptomatic and found only during initial investigation with bone scintigraphy. They may also present with polyarthralgia because of the metaphyseal distribution of the bony lesions,[4] anorexia and weight loss.[10,11] The very high serum alkaline phosphatase represents the strongest element for the diagnosis of osteosarcoma.[10] Our patient presented in a benign manner with mild pain at multiple sites without any swelling. General and local examinations were also insignificant, and the multiple affections were picked up only after radiography and bone imaging.

There is much debate in the literature on whether this tumour represents multiple primary tumours or metastatic disease. In the past, the diagnosis of multiple primary tumours was favoured, as the haematogenous route of spread was strongly considered and lung metastasis was absent. However, more recent reviews have concluded that it is most likely to be multiple metastases, based on these findings: (a) the usual presence of a large dominant lesion, which could be the primary route of spread via Batson's venous plexus or lymphatic spread, apart from the haematogenous route; and (b) the correlation demonstrated between the responses of the dominant lesion and other lesions to chemotherapy.[8]

The radiographic differential diagnosis of multicentric osteosarcoma includes metastatic carcinoma, multifocal chronic recurrent osteomyelitis and hyperphosphatasia. Metastatic carcinoma with blastic secondaries is uncommon in children. Radiographs of multifocal chronic recurrent osteomyelitis typically show multiple lytic, mixed or pure sclerotic lesions, and the disease may be associated with palmar and plantar pustulosis.[4] Sclerotic lesions are also seen in the axial and appendicular skeletons of patients with hyperphosphatasia, but the long bones are usually bowed. Affected children tend to be very short and have high alkaline phosphatase levels.

In synchronous multifocal osteosarcoma, the role of chemotherapy combined with surgery has not been investigated in large series. The results of Curral and Dixon[8] and Bacci et al[9] indicate that the prognosis for synchronous multifocal osteosarcoma remains extremely poor, even with combined chemotherapy and surgery.[9] Despite the poor prognosis, some authors have stressed the need for both systemic chemotherapy and wide excision of all involved bones.[7]

The debate still continues as to whether multicentric osteosarcoma should be considered a specific entity or multiple metastases from a major primary site. However, the prevailing opinion in the reviewed literature seems to indicate that synchronous multifocal osteosarcoma represents one extreme of a vast spectrum of metastatic osteosarcoma. The benign nature of its presentation and the absence of significant clinical findings despite the presence of generalised skeletal involvement would present diagnostic difficulty for an inexperienced orthopaedic surgeon, who tends to treat these cases as benign lesions. Only biopsy and histopathological examination can reveal the highly malignant nature of this disease and help to predict the prognosis. In view of the rarity of this condition, it is advisable to obtain a second opinion from a higher oncopathology centre and to rule out the rare possibility of metabolic disorders using appropriate investigations. Our case is a good example of a highly malignant tumour with a benign presentation, which can easily mislead both the radiologist as well as the orthopaedic surgeon.

Table II. Mahoney classification of multicentric osteosarcoma.

	Group A	Group B
Mean age of onset	10 yrs	37 yrs
Location of lesions	Metaphysis of long bones	Long bones, skull, vertebra
Histologic appearance	Highly anaplastic	Well-differentiated
Grade of tumour	High grade	Low grade

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