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Wolf in sheep's clothing: metatarsal osteosarcoma

Metatarsal bones are an unusual subsite for small bone involvement in osteosarcomas. This subgroup is often misdiagnosed and hence associated with significant treatment delays. The standard treatment of metatarsal osteosarcomas remains the same as for those treated at other sites, namely neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy. Limb salvage surgery or metatarsectomy in the foot is often a challenge owing to the poor compartmentalization of the disease. We hereby describe the case of a young girl with a metatarsal osteosarcoma who was managed with neoadjuvant chemotherapy and limb salvage surgery.

INTRODUCTION

Osteosarcomas are the most common primary malignant bone tumor in children and adolescents. Although predominantly occurring in pediatric and adolescent age groups, bimodal distribution (with a second incidence peak occurring in the sixth and seventh decades) is not uncommon.[1] Osteosarcomas of the foot and small bones represent a rare and distinct clinical entity. This must have been a well-known observation for years that led to Watson-Jones stating, "Sarcoma of this [metatarsal] bone has not yet been reported in thousands of years in any country."[2] The incidence of osteosarcomas of the foot is estimated to be from 0.2% to 2%.[3]

These tumors, owing to their rarity, often lead to diagnostic dilemmas and hence treatment delays.[4] They are usually mistaken for inflammatory conditions and often treated with—but not limited to—curettages and drainage procedures.[5] The following case of osteosarcoma of the metatarsal bone in a young girl highlights the importance of having a high index of clinical suspicion prior to treatment.

CASE PRESENTATION AND SUMMARY

A 10-year-old girl visited our outpatient clinic with a painful progressive swelling on the dorsum of the left foot of 2 months' duration. There was no history of antecedent trauma or fever. Physical examination revealed a bony hard swelling measuring around 5 x 6 cm on the dorsum of the left foot around the region of the second metatarsal. There was no regional lymphadenopathy or distal neurovascular deficit. She was evaluated with a plain radiograph that demonstrated a lytic lesion in the left second metatarsal associated with cortical destruction and periosteal reaction (**FIGURE 1**). A subsequent magnetic resonance image (MRI) revealed a bony lesion destroying part of the left second metatarsal with cortical destruction and marrow involvement and affecting the soft tissue around the adjacent third metatarsal (**FIGURE 2**). Needle biopsy showed chondroblastic osteosarcoma. Computed tomography (CT) of the thorax and bone scan were both negative for distant metastases.

She received 3 cycles of a MAP (high-dose methotrexate, doxorubicin, and cisplatin) regimen as neoadjuvant chemotherapy. Response assessment scans showed partial response (**FIGURES 3A** and **B**). We performed a wide excision of the second and third metatarsal with reconstruction using a segment of non-vascularized fibular graft as rigid fixation (**FIGURE 4**). The postoperative period was uneventful. She was able to begin partial

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DISCLOSURES

The authors report no conflicts of interest concerning the materials or methods used in this study or the findings specified in this paper.

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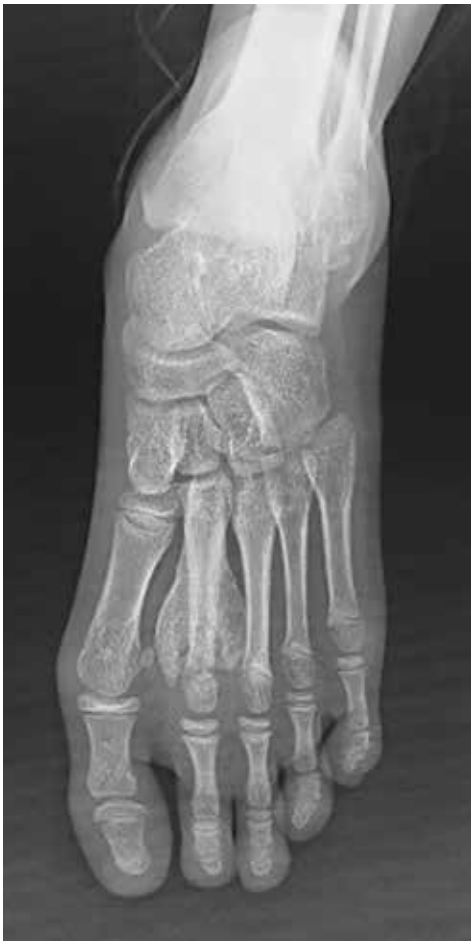


FIGURE 1. Radiograph showing lytic lesion of left second metatarsal with periosteal reaction.

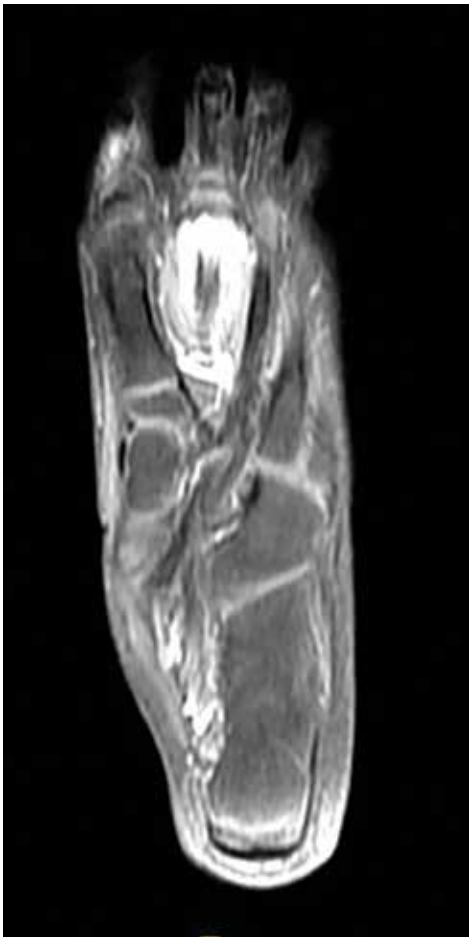


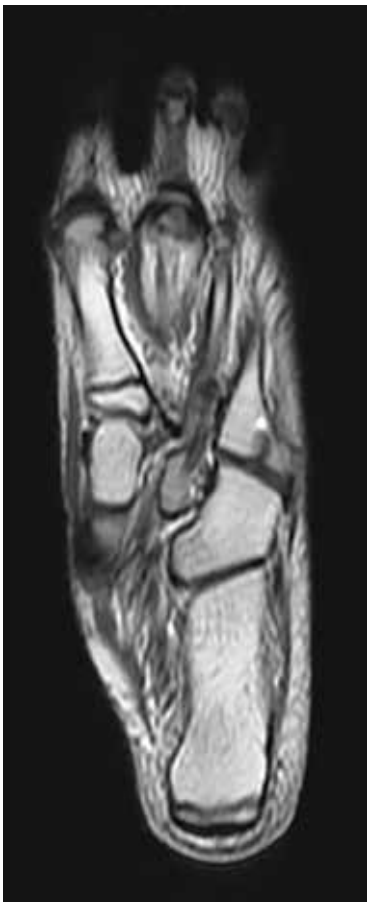
FIGURE 2. T2w MRI (plantar aspect) indicating marrow involvement of the left second metatarsal, with soft tissue component showing high signal intensity and involvement of adjacent metatarsal bone.

weight bearing on the fourth postoperative day and her sutures were removed on the twelfth postoperative day. She received adjuvant chemotherapy following surgery. The final histopathology report showed residual disease with Huvos grade III response (>90% necrosis) with all margins negative for malignancy (**FIGURE 5**). At present, the child is disease-free at 5 months of treatment completion and is undergoing regular follow-up visits.

DISCUSSION

Metatarsal involvement amongst small-bone osteosarcomas is uncommon.[3] There are about 32 cases of osteosarcomas reported in the literature from 1940 to 2018 involving the metatarsal bones (**TABLE 1**). According to a review article from the Mayo Clinic, the most common bone of the foot involved is the calcaneum.[6] While the incidence of osteosarcomas of the foot as a whole is around 0.2% to 2%,[3] metatarsal involvement is documented in 0.5% of these patients.[7] However, a recent study depicted metatarsal involvement in 33% of all osteosarcomas of the foot.[8]

Osteosarcomas at conventional sites tend to have a bimodal age distribution with respect to disease affliction.[9] Metatarsal osteosarcomas, however, are more common in an older age group.[4,10] Our patient is probably the second youngest reported case of metatarsal osteosarcoma in the literature.[11]



FIGURES 3A and 3B. Post chemotherapy CT images (plantar view on left) showing tumor with persisting soft tissue component.

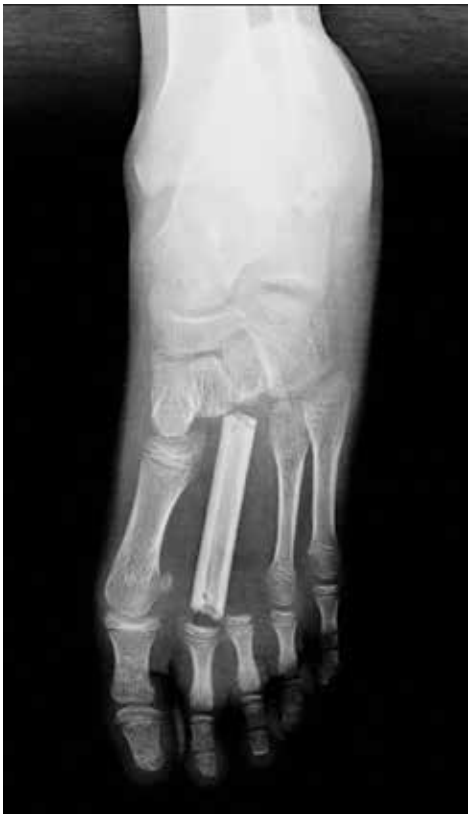


FIGURE 4. Post limb salvage radiograph showing reconstruction by non-vascularized fibular graft.

Biscaglia et al propounded that osteosarcomas of the metatarsal were a distinct subgroup due to the rarity of occurrence, anatomical location, and prognosis.[4] This often led to misdiagnosis and subsequent inadequate or inappropriate surgery. In six out of the ten cases (60%) described in Table 1, an incorrect pretreatment diagnosis was made that led to treatment delay. None, except one patient, received neoadjuvant chemotherapy, which is currently the standard of care. The average duration from symptom onset to diagnosis was found to be 2 years.[4] However, in our case, the duration of symptoms was approximately 2 months.

Surgery for metatarsal osteosarcomas can be challenging, as the compartments of the foot are narrow spaces with poor demarcation. Limb salvage surgery in the form of metatarsectomy needs proper preoperative planning and execution.

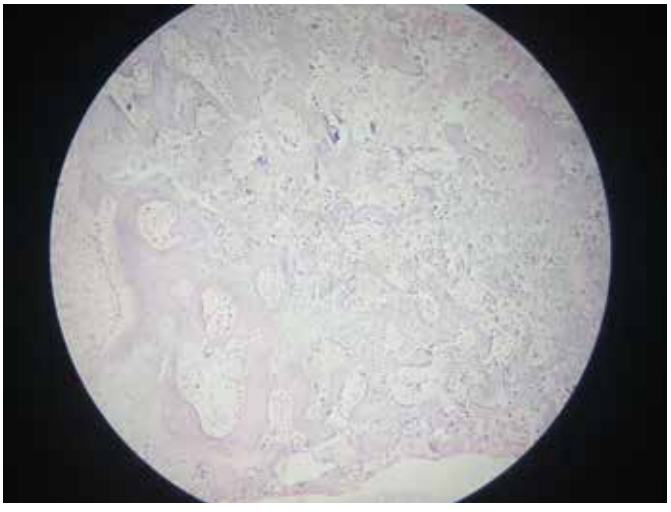


FIGURE 5. Photomicrograph showing immature bony trabeculae and immature cartilage seen amidst tumor cells.

Neoadjuvant chemotherapy will serve to downstage the tumor within the fascial barriers of the metatarsal compartment.

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TABLE 1. Various studies on metatarsal osteosarcoma: treatment and outcomes

Author/year	Age/sex	Initial diagnosis	Initial treatment	Final treatment	Histology	Outcomes
Biscaglia R[4]/ 1998	28 M	not known	NA	disarticulation	chondroblastic osteosarcoma	NED at 168 mo
	20 M	not known	NA	resection	osteoblastic osteosarcoma	NED at 120 mo
Fukuda K[14]/ 1999	18 F	not known	NA	NACT f/b BKA	osteoblastic osteosarcoma	NED at 55 mo
Lee EY[16]/ 2000	25 F	enchondroma	curettage	ray resection	high-grade osteosarcoma	NED at 9 mo
Choong PFM[6]/ 1999	27 M	osteosarcoma	NA	ray amputation radiotherapy	osteosarcoma grade II	DOD at 19 mo
Sneppen O[7]/ 1978	22 M	benign osteochondroma	Non-radical excision	BKA	osteosarcoma	DOD at 13 mo
Padhy D[17]/ 2010	17 M	osteosarcoma	NA	ray amputation f/b adjuvant chemotherapy	high-grade osteosarcoma	NED at 26 mo
Mohammadi A[18]/2011	33 F	osteosarcoma	NA	radical excision	chondroblastic osteosarcoma	NED at 9 mo
Nishio J[19]/ 2012	16 M	fibrous dysplasia/ giant cell reparative granuloma	curettage	wide excision + free vascular scapular graft	low-grade osteosarcoma	NED at 18 mo
Parsa R[15]/ 2013	72 M	osteosarcoma	NA	metatarsectomy	low-grade osteosarcoma	NED at 48 mo
Aycan OE[11]/ 2015	10 M	aneurysmal bone cyst/giant cell tumor	NA	resection	chondroblas-toma-like osteosarcoma	NED at 6 mo
PRESENT CASE	10 F	chondroblastic	NA	NACT f/b metatarsectomy	chondroblastic osteosarcoma	NED at 3 mo

BKA: below knee amputation; DOD: dead of disease; F, female; f/b: followed by; M, male; mo, months; NA, not available; NACT, neoadjuvant chemotherapy; NED, no evidence of disease

It has also been postulated that osteosarcoma of the foot may have a better prognosis and survival compared to other osteosarcoma subsites.[10] This can be extrapolated from the fact that the majority are found to be low grade, and despite a long delay in treatment, there was no rapid increase in size and/or metastatic spread. However, tumor grade remains an important factor affecting survival—patients with higher grade tumors have worse survival.[8]

A number of differentials, including benign tumors, are to be kept in mind when diagnosing and treating such patients (**TABLE 2**). The most common benign tumors affecting the metatarsal are giant cell tumors (GCT) followed by chondromyxoid fibroma. Osteosarcomas and Ewing sarcomas constitute the malignant tumors.[12] Occasionally, infections like osteomyelitis of the small bones may mimic malignancy. The absence of an extensive soft tissue component and/or calcifications with the presence of bony changes (like sequestrum) favors a diagnosis of infection/osteomyelitis. In addition, clinical findings like fever, skin redness, and presence of a painful swelling (especially after onset of fever) point to an inflammatory pathology rather than malignancy. Stress fractures rarely simulate tumors. MRI showing marrow and soft tissue edema with a visible fracture line points to the diagnosis.

A plane radiograph showing corti-

TABLE 2. Important differential diagnosis of metatarsal swelling in a young patient

Differential diagnosis	Osteosarcoma	Chronic osteomyelitis	Ewing sarcoma	Eosinophilic granuloma
Age group	10 – 30 years	2 – 12 years	10 – 20 years	Less than 10 years
Male:female	1.43:1	3:1	1.5:1	2:1
Most common site	Lower limb distal femur	Lower limb and lumbar vertebrae	Femur	Skull, mandible, spine, ribs
Plain X-ray features	Eccentric cortical bone destruction. Soft tissue mass + tumor matrix calcification. Codman triangle periosteal reaction commonly seen.	Mildly expansile sclerotic lesion with cortical thickening (involucrum) and medullary sclerosis. Sequestrum may be seen as thickened sclerotic bone. Buttress type of periosteal reaction.	Moth-eaten appearance/ permeative–cortical destruction. Periosteal/ onion skin appearance –aggressive periostitis Calcification–Uncommon	Well-defined osteolytic lesion with a zone of sclerosis "button sequestrum." May appear aggressive with no sclerosis in early stages.
Imaging	MRI – On T1w – Bone marrow replaced by hypointense soft tissue mass. T2w – shows general hypointensity with thin marginal area of hyperintensity.	CT – best study to delineate sequestrum from another lesion (sequestrum does not enhance). MRI – sequestrum in cortical bone: hypointense and in cancellous bone sequestrum is hyperintense on T1, T2, and STIR sequences. Granulation tissue is hyperintense on T2.	CT – degree of bone destruction appreciated better. MRI – T1 – low signal. T2 – heterogeneously high signal. Shows high uptake on Ga67 and Tc99 bone scan.	CT – lytic lesion with periosteal reaction and cortical and medullary bone destruction. On spin-echo MRI, decreased SI on T1w and high on T2w. Lesion enhances on gadolinium.

CT, computed tomography; Ga, gadolinium; MRI, magnetic resonance imaging; SI, spin intensity; STIR, Short-TI Inversion Recovery; T1, T2, longitudinal relaxation time; T2w, longitudinal relaxation time-weighted images; Tc, technetium

cal bone destruction with a soft tissue component and calcification should be considered suspicious and must be thoroughly evaluated prior to surgical treatment.[13] In a young patient such as ours, the important differentials that need to be considered include Ewing sarcoma, chronic osteomyelitis, and eosinophilic granuloma, which can radiologically mimic osteosarcoma at this location.

CONCLUSIONS

Osteosarcoma of the metatarsal is rare. Our case remains unique as it reports the second youngest patient in the literature. Erroneous or delayed diagnosis resulting in inadequate tumor excision and limb loss (amputation) often occurs in a majority of the cases. Proper pretreatment radiological imaging becomes imperative, and when clinical suspicion is high, a needle biopsy must follow in those cases. Early diagnosis with administration of neoadjuvant chemotherapy may allow us to perform limb salvage surgery or wide excision in these cases. **TSJ**

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