Low-Grade Central Osteosarcoma of the Second Metatarsal in a 72 Year Old Male

R Parsa, M Marcus, R Orlando, C Parsa

Citation

R Parsa, M Marcus, R Orlando, C Parsa. *Low-Grade Central Osteosarcoma of the Second Metatarsal in a 72 Year Old Male*. The Internet Journal of Orthopedic Surgery. 2013 Volume 21 Number 2.

Abstract

Osteosarcoma is a primary bone neoplasm that classically affects metaphyseal long bones in adolescents and children. Involvement of short tubular bones, such as those in the hands or feet, is extremely rare. Most common site in the foot is the calcaneus with the mean age of 36 years and male to female ratio of 2.0:1. Central osteosarcoma is a rare intramedullary variant, constituting 1.2% of all osteosarcomas, known to cause diagnostic difficulties. We report a case of a 72 year-old male, to our knowledge the oldest patient with this metatarsal neoplasm, whose chief complaint was pain and swelling of the right foot. After surgical excision, histologic evaluation of the lesion revealed a low-grade intramedullary (central) osteosarcoma. Based on the findings in this case and following review of the literature, inclusion of osteosarcoma is warranted as a differential diagnostic consideration in elderly patients presenting with pain and swelling of toes, especially when associated with radiographic findings of a metatarsal mass. Delay in appropriate diagnosis and management may result in recurrences and transformation to a high-grade osteosarcoma. As in our patient who had a four year uneventful follow-up, the prognosis can, however, be excellent with appropriate early diagnosis and complete excision of the tumor. We discuss the clinicopathologic features and possible pathogenesis of this unique, unusual, and enigmatic neoplasm.

INTRODUCTION

Osteosarcoma is the most common primary malignant bone producing tumor of children and adolescents, usually affecting the metaphyseal regions of long bones, most commonly around the knee18. Wide range of histologic appearances has been described for this mesenchymal tumor. Based on cytoarchitectural and clinical characteristics, however, osteosarcomas may be classified into five distinct categories as follows: conventional (chondroblastic, fibroblastic, and osteoblastic), fibrohistiocytic, telangiectatic, small cell, anaplastic, and low-grade central7, 14, 26. The latter, also referred to as well-differentiated (low-grade) intramedullary (intraosseous/central) osteosarcoma, is microscopically so bland that it is often under-diagnosed as a benign lesion, particularly fibrous dysplasia26,32. Most patients in this category of osteosarcomas are adults (usually in the second and third decade), the femur and tibia being the most commonly involved sites. Exceptionally, the small phalangeal bones are affected30,26.

Most osteosarcomas arise de novo. Several predisposing conditions have, however, been described including: young children (rapid bone growth), Paget disease, radiation exposure, chemotherapy, foreign bodies, trauma, and certain genetic mutations and hereditary disorders 25, 30. Although significant advances have been made in understanding the molecular pathogenesis of osteosarcomas, so far no specific gene or gene products have been identified or considered definitively involved in all cases of low-grade osteosarcomas3, 16, 19, 21, 24. Comparative genomic hybridization reveals a low number of chromosomal imbalances in these tumors, which contrasts with the complex aberrations seen in conventional high-grade osteosarcomas26.

Recurrences are common with low-grade osteosarcomas, but metastases are very rare (unless the tumor converts in the recurrence into a conventional high-grade osteosarcoma), i.e., undergoes ‘dedifferentiation’26. We present a case of low-grade intramedullary osteosarcoma involving the second metatarsal in the right foot of a 72 year-old male who presented with the chief complaint of progressive right foot pain of approximately one-year duration. To our knowledge this represents the oldest patient with osteosarcoma of the metatarsal. With an appropriate diagnosis and early excision of the tumor, four year follow-up of the patient showed no evidence of recurrence or metastasis. Complete resection of the tumor as a single piece including a cuff of normal bone is

essential to promote the cited excellent prognostic outcome.

CASE REPORT

A 72 year-old male presented to the clinic with the chief complaint of progressive right foot pain of approximately one-year duration. At the time of initial evaluation, the patient stated his pain had been dull, constant and associated with swelling. He also noted exacerbation of his symptoms with weight bearing and ambulation. His history was negative for any trauma or prior surgery to that area of his foot. He denied any radiation of pain, numbness, tingling or any signs of infection such as skin lesions, drainage or fever.

On physical examination, a tender, firm, fixed mass was palpated on the dorsal aspect of the second metatarsal in the right foot. The mass spanned approximately 3 x 1 centimeters and had obvious surrounding soft tissue edema. The skin was intact, without erythema or fluctuant. Examination of the left extremity was unremarkable and bilateral lower extremities were neurovascularly intact.

An x-ray examination of the right foot revealed an expansile, intramedullary lesion and associated periosteal reaction consistent with a bone tumor involving the second metatarsal head (Figure 1). A computerized tomography scan of the right foot was subsequently performed (Figure 2) and interpreted as possible osteosarcoma versus chondrosarcoma affecting the second metatarsal with a presumptive pathologic stress fracture of the third metatarsal.

Figure 1

X-ray of the foot exhibiting a bone tumor involving the second metatarsal head

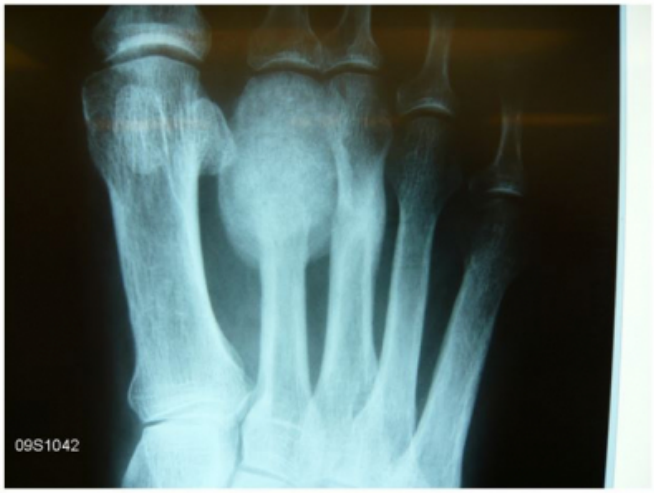
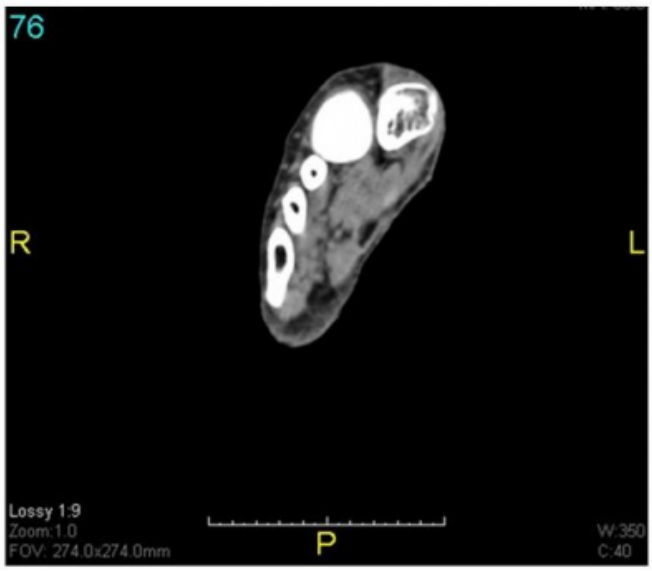


Figure 2

Computerized tomography scan showing a mass affecting the second metatarsal head, interpreted as “possible osteosarcoma versus chondrosarcoma”.



Pertinent studies, including metastatic workup, blood cell count, serum tumor markers, liver and renal function tests, serum alkaline phosphatase, and chest x-ray, were within normal limits. No lymphadenopathy was palpated in the ipsilateral extremity.

This isolated lesion resulted in a painful deformity of the right second ray, hindering the patient’s ability to ambulate. Operative recommendations were thoroughly discussed with the patient and a metatarsectomy with excision of the bony tumor was decided to be the best option as it would be diagnostic, therapeutic, and potentially curative.

During the surgical procedure, an enlarged lobular metatarsal mass was identified, grossly consistent with a neoplasm (Figure 3). Portions of the surrounding soft tissue closest to the tumor, submitted for frozen section evaluation, showed no evidence of malignancy. The tumor was then resected, including a one centimeter proximal segment of grossly uninvolved metatarsal bone and submitted in formalin for definitive diagnostic evaluation (Figure 4). Pathologic examination revealed a metatarsal bone with a conspicuously enlarged segment involving predominantly the epiphyseal and metaphyseal regions, measuring 4.0 x 3.0 x 2.5 cm in greatest dimensions. The specimen was decalcified prior to sectioning. On section, the cut surface of the mass was solid and homogeneous with sharp lines of demarcation from the uninvolved medullary metatarsal diaphyseal segment (Figure 5).

Figure 3

The identified bone mass after initial surgical dissection.

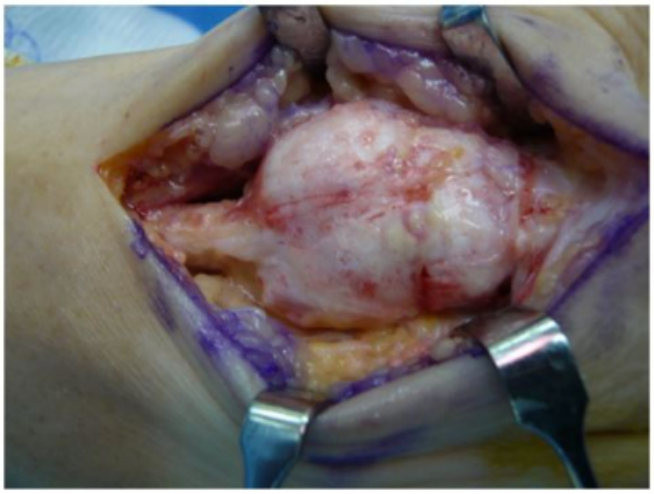


Figure 4

The excised metatarsal bone with a conspicuous osseous mass.

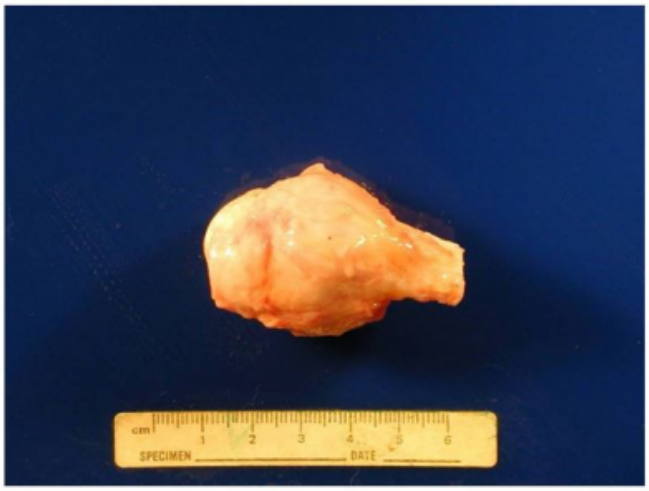
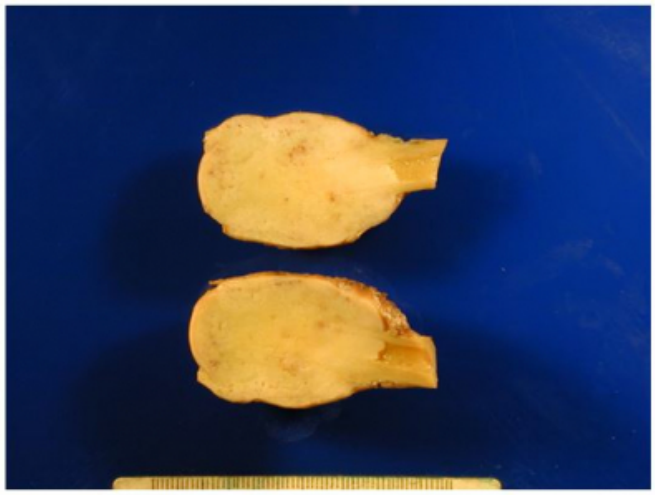


Figure 5

The cut surface of the lesion consists of a homogeneous solid tan mass.



Microscopic sections of the lesion consisted of neoplastic spindle cells exhibiting an osseous matrix arising from the adjacent medullary bone and circumscribed by a delicate fibrous psuedocapsule. There was predominance of broad osseous trabeculae associated with a moderately cellular, cytologically bland, fibrous background (Figures 6 and 7). Portions of the specimen were associated with formation of immature cartilaginous tissue. There was no evidence of tumor extension into the surrounding soft tissues. A diagnosis of "low-grade intramedullary osteosarcoma" was made in consultation with the Armed Forces Institute of Pathology (Dr. Daniel Strum and his orthopedic pathology staff). The neoplasm was considered stage IA according to the TNM staging system for bone tumors27.

Figure 6

Histopathologic sections reveal predominance of broad osseous trabeculae associated with a moderately cellular, cytologically bland, fibrous background.

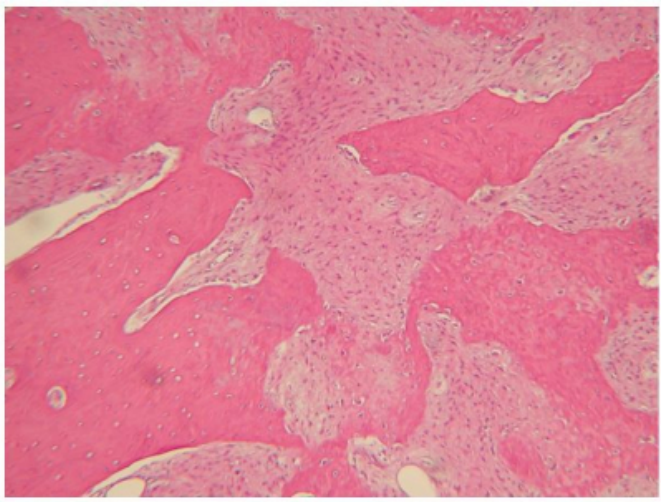
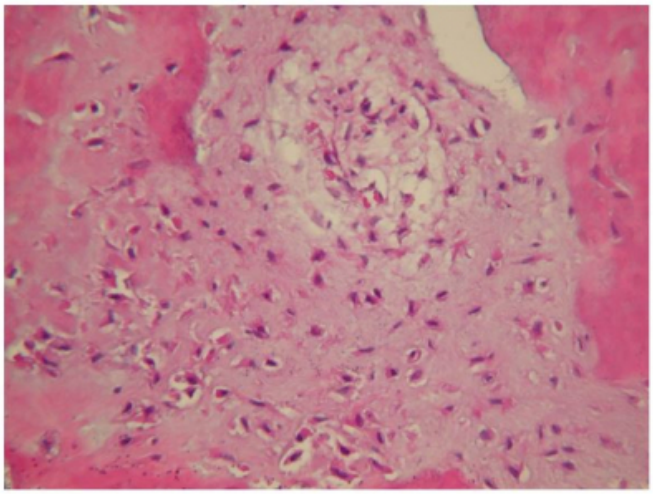


Figure 7

Higher magnification of the neoplasm shows neoplastic spindle cells exhibiting an osseous matrix arising from the adjacent medullary.



In consideration of the low-grade and limited solitary presentation of the tumor showing a thin rim of fibrous pseudo-encapsulation, no adjuvant therapy was recommended by the medical team in the postoperative course. However, the patient had frequent outpatient clinic follow-up evaluations to monitor for any evidence of local recurrence. There were no complications except for a minor contracture affecting the metatarsophalangeal joint secondary to the substantial resection of the metatarsal. This contracture developed seven weeks postoperatively and was treated conservatively in a small digit splint. At the four-year status post-resection, the patient denied any recurrence of symptoms or limitations in gait. Follow up x-rays and clinical evaluation confirmed no evidence of recurrence (Figures 8 and 9).

Figure 8

Four-year follow-up x-ray of the foot showing no evidence of a mass lesion.

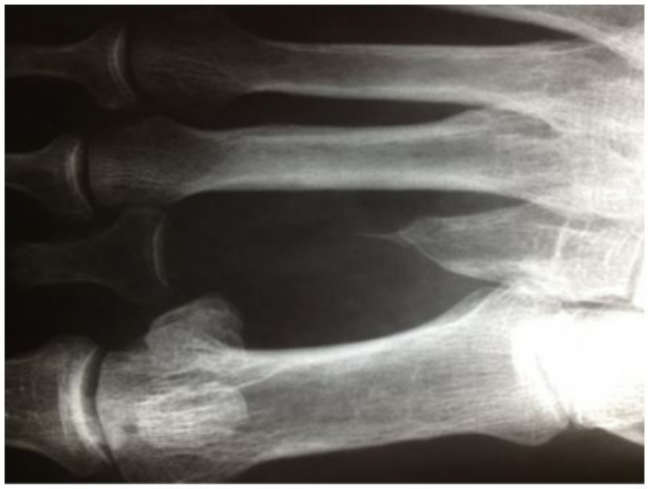
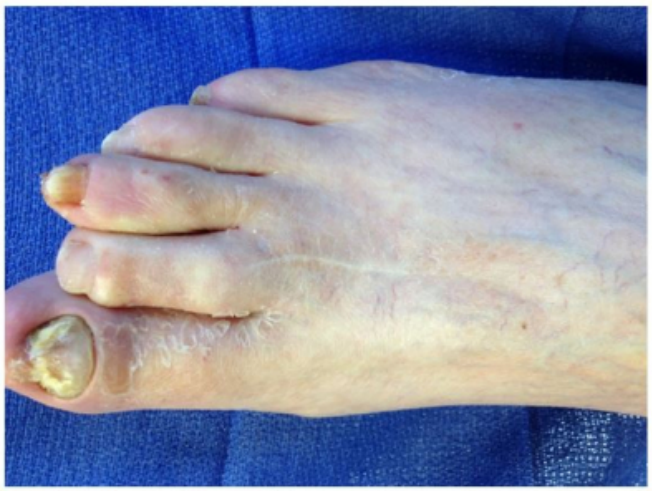


Figure 9

Four-year follow up clinical presentation of the foot showing no evidence of a mass lesion.



DISCUSSION

Osteosarcoma is the most frequent primary bone neoplasm that classically affects the metaphyseal long bones in adolescents and children1,2,9,11,13,15,17. Only ten percent of these tumors occur in people over the age of sixty13 . Moreover, it is extremely rare for osteosarcoma to affect short tubular bones, including metatarsals1, 8, 10, 12,15,20,23,28,29,31. Merely one percent of these tumors occur in the foot. In one recent study from United Kingdom

only 18 of 1,540 patients with osteosarcoma had the low-grade central variant, constituting a 1.2% subset of osteosarcomas21; with the exception of one that occurred in the calcaneum, all involved the long bones of the leg. It is uncommon in the hands and feet and only exceptionally occurs as an intramedullary low-grade sarcoma of the metatarsal in the elderly. These patients typically present around the third to fourth decade. To our knowledge, our case represents the oldest patient with such as tumor in the short tubular bones of the foot. The usual presenting symptoms are persistent foot pain localized over one of the metatarsals. The duration of symptoms prior to presentation may vary from several months to a year. In a recent largest cohort study of 40 patients with osteosarcoma of hands and feet, no patient died of low-grade osteosarcoma2. Statistically, there was no significant difference between patients receiving and those not receiving chemotherapy in that study.

Due to significant advances in our understanding of the molecular basis of osteosarcoma, multiple factors have been implicated in the pathogenesis of, or as risk factors for, this neoplasm and its clinical properties4. The most commonly cited examples include: bone growth (e.g., predilection for developing in the rapidly growing bones of children); environmental factors (e.g. ionizing radiation and certain chemical agents); chromosomal abnormalities (e.g. amplifications of chromosomes 6p21, 8q24, and 12q14, as well as loss of heterozygosity of 10q21.1); tumor suppressor gene dysfunction (e.g., mutations in p53

and retinoblastoma genes); growth factors [e.g., dysregulated expression of growth factors such as transforming growth factor (TGF), insulin-like growth factor (IGF),and connective tissue growth factor (CTGF)], resistance to apoptosis (specifically disruption of anoikis pathway); tumor angiogenesis (down regulation of the anti-angiogenic proteins); cell adhesion and migration (overexpression of ezrin protein involved in cell to cell interaction and binding to extracellular matrix associated with increased metastatic potential); inverse relationship between urokinase plasminogen activator and survival time; and invasive properties related to interactions between the bone matrix, osteosarcoma cells, osteoblasts, and osteoclasts.

As indicated above, amongst the many factors implicated in the pathogenesis of osteosarcoma, an aberration of the normal bone growth and remodeling may be a contributing factor in the development of this malignancy. Although, there are some commonly cited genetic mutations such as RB-1, 17p12, MDM2, and CDK4, there has so far been no specific gene or gene products identified or considered definitively involved in all cases of low-grade osteosarcomas3, 16, 19, 21, 24. This may indicate that an initiating molecular event in any of the many points of regulation in the cell cycle may potentially give rise to such a tumor. An interesting finding in this patient is the lack of obvious past medical history regarding any of the cited risk factors that may have contributed to the development of this tumor.

It is however commonly understood that bones are not static structures, but are constantly remodeling and redistributing their matrix along lines of mechanical stress through the coordinated activity of osteoblasts and osteoclasts. An immature skeleton undergoes more frequent cycles of remodeling, and is therefore more predisposed to an anomaly in the pathway of its development. It is inferred that areas exposed to higher mechanical loads are also subject to more frequent cycles of remodeling ("Wolff's Law"). Mechanical stresses arising from ambulation can be placed on various aspects of the foot either secondary to the differences in individual foot anatomy or gait pattern.

After examination of the patient's left foot x-rays, it was noted that his second ray was greater in length than all the other digits, including the great toe. Discrepancy in metatarsal length has been cited as a causative factor in primary metatarsalgia and most commonly attributed to a long second metatarsal6. Increased length may lead to additional pressure during locomotion, and therefore, an increased risk of incurring repeated stress fractures to that metatarsal. It is therefore plausible that long-standing subclinical reparative and remodeling of the patient's long second metatarsal bone may have been a contributing factor to the development of neoplasm in this case.

Because of its bland histomorphologic appearance and rare incidence, low-grade central osteosarcoma is a well-established difficult diagnostic challenge. MDM2 and CDK4 immunostains as well as other ancillary studies including cytogenetic analysis for ring chromosomes have been recommended by some investigators, as markers that can reliably distinguish low-grade osteosarcomas from high-grade osteosarcomas and their benign histological mimics5, 33. Cytogenetic studies, electron microscopy, or molecular analysis may serve as a useful adjunct in the difficult differential diagnostic situations, particularly in cases with atypical radio-clinical presentation and/or limited biopsy samples5. Adequate sample such as an open incisional or

excisional biopsy should however always be submitted for conventional light microscopic evaluation before tissue is taken for such ancillary studies27.

Radiographic findings are essential in the initial diagnostic evaluation of these lesions9,13,27. The pathologic features can be deceptively benign, and when associated with a fracture, can lead to a false diagnosis of exuberant callus or normal reactive and reparative response to injury. Other benign and malignant osseous lesions such as fibrous dysplasia, parosteal osteosarcoma, non-ossifying fibroma, giant cell tumor, and aneurysmal bone cyst may be included in the differential diagnostic consideration. Imaging studies are usually extremely helpful in excluding most of these lesions22. Because of its potential for recurrence and transformation to a high-grade sarcoma, low-grade osteosarcoma should always be a lesion to be excluded in the list of differential diagnostic consideration.

In conclusion, osteosarcoma of the metatarsal in elderly patients is exceptionally rare. The findings in this case and review of the literature however warrant inclusion of this tumor as a differential diagnostic consideration in such patients complaining of foot pain associated with a slowly enlarging metatarsal mass. The neoplasm is commonly low-grade central type at presentation. It is often difficult to differentiate other benign and malignant neoplasms as well as reactive osseous lesions from a low-grade central osteosarcoma. Early and accurate diagnosis, in correlation with radiographic findings and possibly molecular studies, is imperative for the successful treatment of this neoplasm. Inadequate excision of this tumor is associated with high rate of recurrence and transformation to a high-grade sarcoma with poor prognostic implications due to its metastatic potential.

Open biopsy or lesional excision, if possible, is recommended since small biopsy samples can lead to under-diagnosis or incorrect diagnosis25 and may preclude their precise classification27. As immunohistochemical markers (e.g., MDM2 and CDK4) and cytogenetic analysis (e.g., ring chromosomes) become more widely available, however, less invasive procedures may be utilized, when appropriate, in the initial primary diagnostic evaluation of these patients as a guide for further definitive therapy5. Currently, radiographic and histopathologic studies are essential for confirmation of the diagnosis of osteosarcoma. Wide excision of the neoplasm is considered curative in most cases. Accurate early definitive diagnosis is imperative in order to institute proper management in these patients and hope for the cited excellent prognosis. Recurrences and transformation to a higher grade osteosarcoma have been reported in an inadequately excised low-grade osteosarcoma19. Histologic grade is the only significant variable related to survival2. In this location, osteosarcoma is usually low-grade with excellent prognosis, when the lesion is appropriately excised. The risk for metastasis is considered small and conservative therapy has been suggested1. However, close clinical follow-up is warranted for possible local recurrences23,28,.

References

1. Agarwal RP, Pathak KV, Dewedi SC, Agarwal AK. Osteosarcoma at the rare sites. J Indian Med Assoc. 1994 Jun;92(6):203-4.
2. Anninga, JK, et. al. Osteosarcoma of the hands and feet: a distinct clinico-pathological subgroup. Virchows Arch. 2013 Jan;462(1):109-20.
3. Berman SD, et al. Metastatic osteosarcoma induced by inactivation of Rb and p53 in the osteoblast lineage. Proc Natl Acad Sci U.S.A. 2008 Aug; 105(33):11851-6.
4. Broadhead ML, et. al. The Molecular Pathogenesis of Osteosarcoma: A Review. Sarcoma. Volume 2011.
5. Dujardin F, et. al. MDM2 and CDK4 immunohistochemistry is a valuable tool in the differential diagnosis of low-grade osteosarcomas and other primary fibro-osseous lesions of the bone. Mod. Pathol. 2011 May;24(5):624-37.
6. Espinosa N, Brodsky JW, Maceira E. Metatarsalgia. J Am Acad Orthop Surg. 2010; 18:474-485.
7. Fletcher CDM, Unni KK, Mertens F, eds. Pathology and Genetics of Tumours of Soft Tissue and Bone. Lyon, France: IARC Press; 2002. World Health Organization Classification of Tumours, Vol. 4
8. Fox C, Husain ZS, Shah MB, Lucas DR, Saleh HA. Chondroblastic osteosarcoma of the cuboid: a literature review and report of a rare case. J Foot Ankle Surg. 2009 May-June; 48(3):388-93.
9. Fukuda K, Ushigome S, Nikaidou T, Asanuma K, Masui F. Osteosarcoma of the metatarsal bone. Skeletal Radiol. 1999 May;28(5):294-7.
10. Gangadharan VP, Ramachandran K, Elizabath SK, Preetha S, Chithrathara K, Elizabath KA. Primary osteosarcoma of metatarsal bone. Am J Clin Oncol. 2000 Aug; 23(4):429-30.
11. Gorlick R, Bielack, et al. Osteosarcoma: Biology, diagnosis, treatment, and remaining challenges. Principles and Practice of Pediatric Oncology, 6th ed, Pizzo, PA, Poplack, DG (Eds), Lippincott, Williams and Wilkins, Philadelphia PA 2011. p.1015.
12 Jarkiewicz-Kochman E, Gołebiowski M, Swiatkowski J, Pacholec E, Rajewski R. Tumours of the metatarsus. Ortop Traumatol Rehabil. 2007 May-Jun;9(3):319-30.
13. Johnson K, Davies AM, Mangham DC, Grimer RJ. Parosteal osteosarcoma of a metatarsal with intramedullary invasion. Skeletal Radiol. 1999 Feb;28(2):111-5.
14. Klein MJ, Siegal GP: Osteosarcoma: anatomic and histologic variants. Am J Clin Pathol 2006; 125:555-581
15. Kliman ME, Fornasier VL, Hastings DE. Parosteal osteosarcoma of the fourth metatarsal bone. Foot Ankle. 1982 Jul-Aug;3(1):50-2.
16. Kuijer ML, et al. Identification of osteosarcoma driver genes by integrative analysis of copy number and gene expression data. Genes Chrom Cancer. 2012 Jul;

51(7):696-706.
17. Kumar NL, Rosenberg AE, Raskin KA. Osteoblastoma-like Osteosarcoma of the Cuboid: A Case Report. Journal of Orthopaedic Surgery and Research 2010, 5:52
18. Kumar V. Pathologic Basis of Disease. Saunders. 2013: 776-777.
19. Kurt AM, Unni KK, McLeod RA, and Pritchard DJ. Low-grade intraosseous osteosarcoma. Cancer. 1990; 65(6): 1418–1428.
20. Lee EY, Seeger LL, Nelson SD, Eckardt JJ. Primary osteosarcoma of a metatarsal bone. Skeletal Radiol. 2000 Aug;29(8):474-6.
21. Malhas AM, et al. Low-grade central osteosarcoma: a difficult condition to diagnose. Sarcoma. 2012;2012:764-796.
22. Miller, TT. Bone Tumors and Tumor-Like Conditions: Analysis with Conventional Radiography. Radiol; 2008: 246, 662-647.
23. Mirra JM, Kameda N, Rosen G, Eckardt J. Primary osteosarcoma of toe phalanx: first documented case: review of osteosarcoma of short tubular bones. Am J Surg Pathol 1988; 12:300-7.
24. Parker HR, Jung WW, Bertoni F, Bacchini P, Park JH, Kim YW, Park YK. Molecular analysis of p53, MDM2 and H-ras genes in low-grade central osteosarcoma. Pathol Res Pract. 2004; 200(6):439-45.
25. 20. Picci P. Osteosarcoma (Osteogenic Sarcoma) Orphanet J Rare Dis. 2007; 2:6.
26. Rosai J. Rosai and Ackerman's Surgical Pathology. 10th edition; Elsevier, Inc. 2013; 2024-2032
27. Rubin BP, et. al. CAP Protocol for Classification for the Examination of Specimens from Patients with Tumors of Bone. College of American Pathologists. June 2012.
28. Sneppen O, Dissing I, Heerfordt J, Schiödt T. Osteosarcoma of the metatarsal bones. Review of the literature and report of a case. Acta Orthop Scand. 1978 Apr;49(2):220-3.
29. Sugano I, Tajima Y, Ishida Y, et al. Phalangeal intraosseous well differentiated osteosarcoma of the hand. Virchows Arch 1997; 430:185-9.
30. Sugano I, Tajima Y, Ishida Y, Nagao K, Saga N, Ohno T, Miyakawa E: Phalangeal intraosseous well-differentiated osteosarcoma of the hand. Virchows Arch 1997; 430:185-189.
31. 8. Thomas IJ. Sarcoma of the metatarsal bones. Br J Surg. 1945 Oct;33:191-4.
32. 29. Uribe-Botero G, Russell WO, Sutow WW, Martin RG: primary osteosarcoma of bone. A clinicopathologic investigation of 243 cases, with necropsy studies in 54. Am J Clin Pathol 1977; 67:427-435
33. 22. Yoshida A, et. al. Immunohistochemical analysis of MDM2 and CDK4 distinguishes low-grade osteosarcoma from benign mimics. Mod. Pathol. 2010 Sep;23(9):1279-88.

Author Information

Ronna Parsa, D.O.
Midwestern University
Olympia Fields, IL
rparsa@westernu.edu

Michael Marcus, D.P.M, FACFAS
Beverly Hospital
Montebello, CA
michaeljmarcus@dpm.com

Robert Orlando, M.D., Ph.D., FCAP
Beverly Hospital
Montebello, CA
dromd@hotmail.com

Cyrus Parsa, D.O., FCAP, FASCP
Western University of Health Sciences
Pomona, CA
cparsa@westernu.edu