Parosteal Osteosarcoma

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• Parosteal osteosarcoma is a rare malignant bone tumor arising from the bone cortical surface. It most commonly occurs in young women over the metaphyseal region, especially the long bones near the knee joint. Patients usually report a slow-growing mass for years. The tumor is characterized by its bland microscopic morphology, prone to be misdiagnosed as other benign tumors. In the absence of dedifferentiation, the prognosis is generally better than that of conventional osteosarcoma. Recent studies demonstrated distinctive cytogenetic abnormality resulting in amplification of the *CDK4* and *MDM2* genes, which may serve as markers for molecular diagnosis. In this article, we review the clinical, radiologic, and pathologic features of parosteal osteosarcoma and identify some diagnostic pitfalls, discuss the prognostic variables, and update recent molecular advances and their application in the diagnosis.

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According to the World Health Organization classification of tumors of soft tissue and bone,[1] osteosarcomas arising from the bone cortical surface are a spectrum of diseases and can be subdivided into parosteal, periosteal, and high-grade surface osteosarcoma. This distinction is based on the clinical presentation, histologic grade, and prognosis. Among the subdivisions, parosteal osteosarcoma represents the well-differentiated end. It is an uncommon malignant bone tumor, comprising 4% of all osteosarcomas.[2] This entity was first characterized by Geschickter and Copeland[3] in 1951 as "parosteal osteoma." By definition, the tumor arises from a juxtacortical location and is histologically low grade. In this article, we review the clinical, radiologic, and pathologic features of parosteal osteosarcoma, with a special highlight on the differential diagnosis and the recent advances in molecular biology and their application.

CLINICAL FEATURES

Compared with conventional osteosarcoma, parosteal osteosarcoma differs in prevalence with regard to sex and age. It has a slight female predominance and most frequently occurs in the third decade of life,[2] which is a decade older than the peak age of the conventional counterpart. The tumor is usually located at the posterior aspect of the distal femur in about 70% of cases, followed by the proximal tibia and proximal humerus. Rare locations, including cranial, mandible, rib, clavicle, and tarsal bone, have also been reported.[2,4–7] Patients usually report a painless mass lasting for years, with decreased range of movement of the adjacent joint. Dull pain and local tenderness are the second most common symptoms. The protracted clinical behavior is an important feature distinguishing parosteal osteosarcoma from other diseases of similar locations such as myositis ossificans and high-grade surface osteosarcoma, which usually have a more rapid onset.

RADIOLOGIC FEATURES

On the traditional plain radiograph, the tumor often manifests as a lobulated, mushroomlike mass protruding from the underlying cortex with a broad base attachment (Figure 1, A). It has an irregular pattern of mineralization, and the periphery of the tumor is generally less radiodense than the center. Most of the tumors involve the metaphyseal region of the long bones. Diaphyseal involvement has rarely been documented. The association of the tumor with the bone cortex and medullary cavity is better demonstrated by cross-sectional imaging such as computed tomography and magnetic resonance imaging. The former is superior for evaluating the cortical integrity, and the latter is better for assessing the bone marrow involvement.[8] A characteristic cleavage plane between the tumor and the underlying cortex, representing partially preserved periosteum, can be seen in up to 65% of cases.[9] The underlying bone cortex may be thickened or partially eroded, and the periosteal reaction is generally minimal. Medullary extension of parosteal osteosarcoma has been seen in 22% to 58% of patients, and this finding itself is not considered significant in the prognosis.[2,9,10] The presence of an ill-defined soft-tissue mass within or adjacent to the ossified tumor correlates with an area of dedifferentiation.[9] Contrast-enhanced images are valuable to demonstrate this area and further guide biopsy.[8] Rarely, parosteal osteosarcoma may show continuity with the adjacent cortex and medullary cavity, which mimics osteochondroma radiographically.[11]

GROSS AND MICROSCOPIC FINDINGS

Grossly, parosteal osteosarcomas are hard ossified masses arising from the cortical surface. About one-fourth of cases are initially seen with a cartilage cap on the outer surface of

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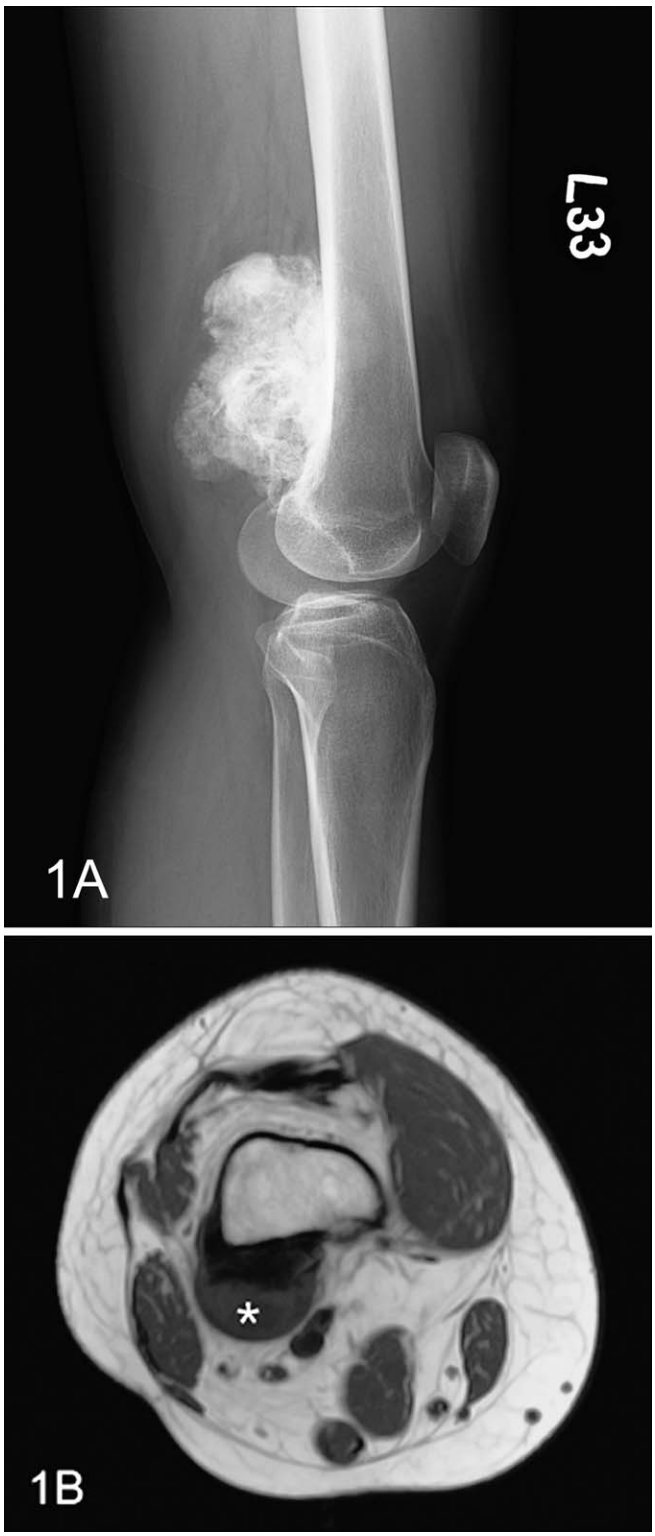

Figure 1. *A, Lateral radiograph of the left knee of a 33-year-old woman shows a radiodense, lobulated mass over the posterior distal femur. The tumor has an irregular mineralized pattern and attaches to the underlying cortex with a broad base. The periphery of the tumor is less radiodense than the center. B, Magnetic resonance axial scan of a T1-weighted image of the right distal femur from a 39-year-old woman reveals a protruding mass arising from the posterior cortex of the distal femur with low signal intensity. It is covered by a cartilage cap (asterisk). The medullary cavity is not involved.*

the tumor (Figure 1, B), simulating an osteochondroma. The dedifferentiated area appears to be a soft mass, in contrast to the bony tumor. Focal necrosis and hemorrhage may be seen.

Microscopically, parosteal osteosarcomas have a biphasic appearance composed of mature trabecular bone and fibroblastic spindle cell stroma. The trabecular bone is woven in nature, and irregular cement lines are sometimes observed. Osteoblastic rimming and osteoclastic giant cells, if present, are usually limited in focal areas. The stromal spindle cells have moderate cellularity and a varied collagenized background. The nuclei are oval shaped with tapered ends and 1 to 2 inconspicuous nucleoli (Figure 2, A). The chromatin is sparse, and the mitotic activity is low. By definition, the histologic grade of neoplastic stromal cells is low grade. The presence of any high-grade component warrants the diagnosis of dedifferentiated parosteal osteosarcoma (Figure 2, B). This issue will be further discussed in the Prognosis and Treatment section.

The most well-recognized histologic pattern of parosteal osteosarcoma is the presence of paralleled trabecular bone with intervening spindle cell stroma, the so-called streamer pattern (Figure 2, C). Other less common histologic patterns include fibrous dysplasia–like pattern and desmoplastic fibroma–like pattern. The former is characterized by irregular arrangement of trabecular bone resembling Chinese calligraphy (Figure 2, D). The latter features a predominance of spindle cell stroma with abundant collagen bundles. It usually appears in the periphery of the tumor and has a slightly infiltrative margin with adjacent soft tissue (Figure 2, E). On small biopsy, these patterns may be deceptive, and correlation with clinical and radiologic findings is needed for the correct diagnosis.

Cartilage differentiation is encountered in parosteal osteosarcoma in up to 55% of cases.[2] The chondrocytes are usually irregularly arranged with mild to moderate pleomorphism and sometimes binucleation (Figure 2, F). A rare histologic variant with a combined well-differentiated liposarcomatous element has been recently reported.[12]

MOLECULAR ADVANCES AND ANCILLARY STUDIES

Early studies[13,14] demonstrated characteristic cytogenetic change with supernumerary ring chromosomes or giant marker chromosomes carrying amplified DNA materials from the 12q13–15 region in parosteal osteosarcoma. Subsequent analysis[15] identified the amplified genes, including *CDK4* and *MDM2*, which are important in cell cycle regulation. The protein products of these genes show coordinate overexpression in most cases.[16,17] These findings have been also noted in low-grade central osteosarcoma but rarely occur in other benign and malignant bone tumors.[14–18,31] In 2010 and 2011, two groups from Japan[16] and France[17] demonstrated that by coupling of immunohistochemical stains for CDK4 and MDM2 nuclear reactivity for at least 1 marker was noted in 87% to 100% cases of parosteal and low-grade central osteosarcoma, while other benign mimickers were rarely positive for either one, representing a valuable tool in diagnosis. However, because bone tumor specimens are usually treated for acid decalcification during tissue processing, the staining areas may be focal, and weak and negative staining does not preclude the diagnosis of parosteal osteosarcoma. In this setting, other modalities such as quantitative polymerase chain reaction or fluorescence in situ hybridization to demonstrate amplifi-

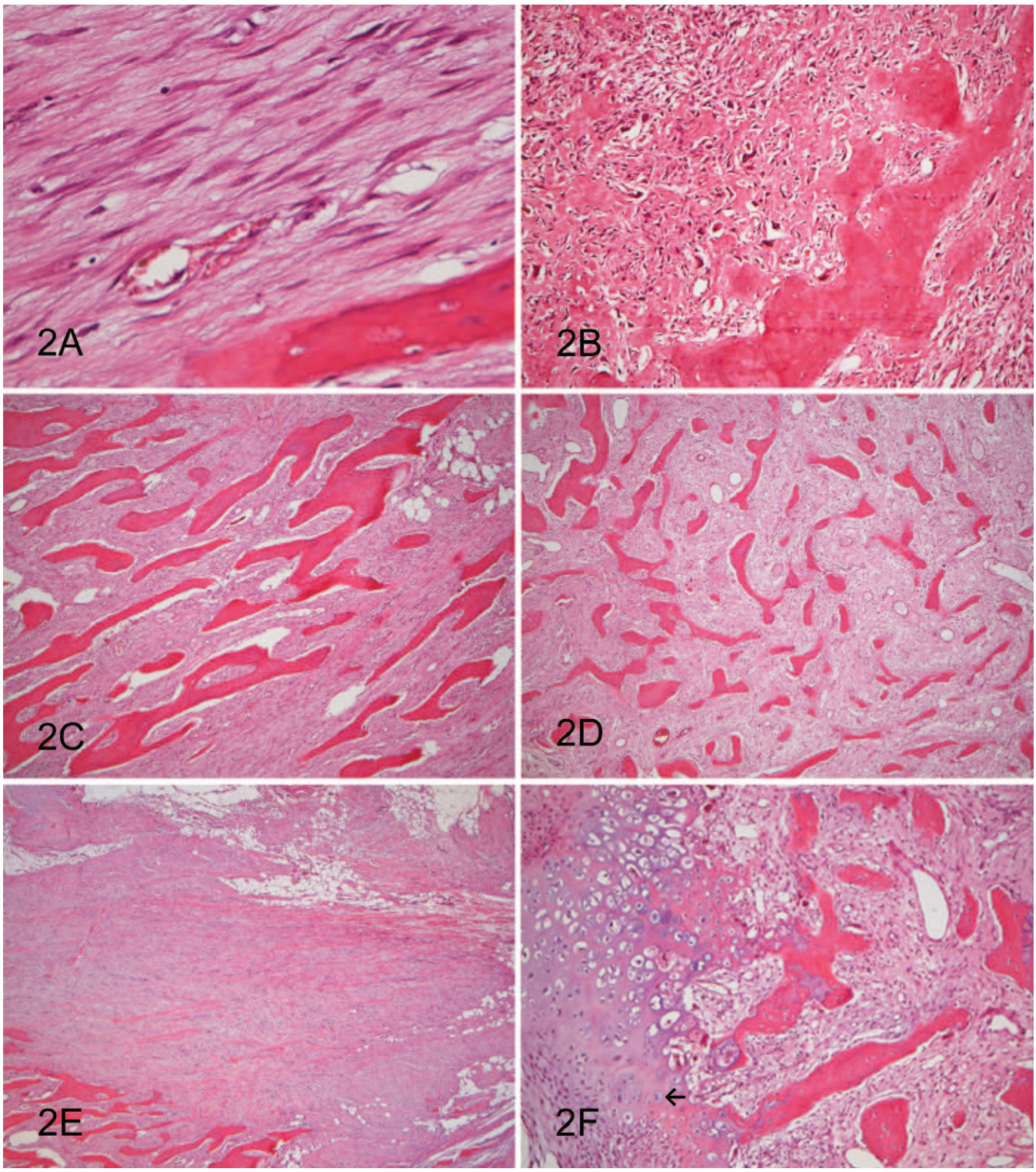

Figure 2. *A, Microscopic image of a parosteal osteosarcoma shows bland neoplastic stromal cells with taper-ended nuclei, sparse chromatin, and 1 to 2 inconspicuous nucleoli. B, In contrast, dedifferentiated parosteal osteosarcoma is characterized by high-grade tumor cells with marked pleomorphism. Lacelike immature osteoid formation is evident. C, Low-power field of parosteal osteosarcoma demonstrates streamers of trabecular bone with intervening neoplastic spindle cell stroma, the so-called streamer pattern. D, The fibrous dysplasia–like pattern consists of irregular-shaped trabecular bone resembling Chinese calligraphy. E, A spindle cell stroma–predominant area with dense collagen deposition can sometimes be seen at the periphery of the tumor, simulating desmoplastic fibroma. F, Cartilage differentiation of a parosteal osteosarcoma reveals irregularly arranged chondrocytes with mild to moderate pleomorphism and occasional binucleation (arrow). Enchondral ossification of trabecular bone is evident (hematoxylin-eosin, original magnifications ×20 [E], ×40 [C and D], ×100 [B and F], and ×400 [A]).*

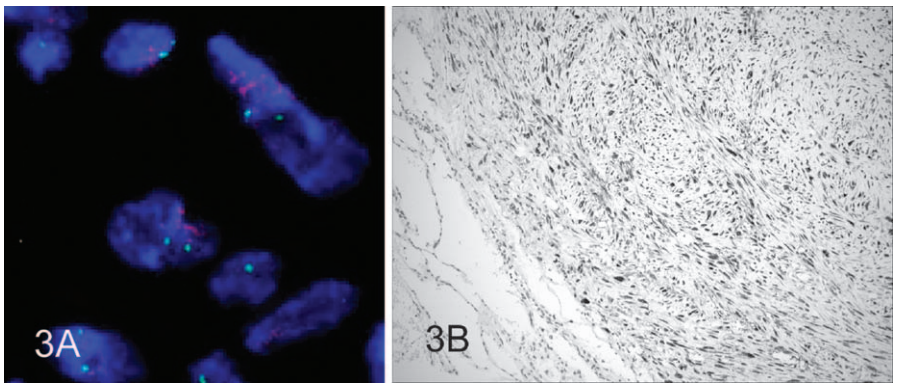

Figure 3. *A, Fluorescence in situ hybridization (FISH) demonstrates amplification of the* MDM2 *gene in a recurrent parosteal osteosarcoma from a 28-year-old woman. She was initially diagnosed as having osteochondroma 14 years previously (orange indicates* MDM2*; green, Chromosome Enumeration Probes 12; Vysis* MDM2*/CEP 12 FISH Probe Kit [Abbott, Abbott Park, Illinois]) (original magnification ×1000). B, Immunohistochemical stain for CDK4 shows positive nuclear staining in a metastatic dedifferentiated parosteal osteosarcoma of the lung. Note the marked nuclear pleomorphism (original magnification ×200).*

cation of these genes may also have a role (Figure 3, A).[18,19] A recent study[20] showed the same genetic changes in extraskeletal low-grade osteosarcoma, suggesting that the 2 entities share a common pathway of tumorigenesis and may be the same disease in different locations.

DIFFERENTIAL DIAGNOSIS

Parosteal osteosarcoma is one of the most frequently misdiagnosed entities in bone and soft-tissue tumors.[21] It must be differentiated from other bone-forming tumors arising from the cortical surface. The most challenging differentiation is from osteochondroma because both tumors share some common clinical and morphologic features. They have similar prevalences in location and age group. Grossly, osteochondroma is a pedunculated or sessile mass covered by a thin cartilage cap. Microscopically, the chondrocytes are arranged in perpendicular columns and show polarity, forming clusters of lacunae superficially and small immature chondrocytes at the base. The underlying trabecular bone reveals enchondral ossification. Between trabecular bone, there is usually adipose or occasionally marrow tissue. As aforementioned, a portion of parosteal osteosarcoma forms a cartilage cap. In contrast to osteochondroma, the chondrocytes of parosteal osteosarcoma show more pleomorphism and occasional binucleation and a lack of the regular columnar arrangement and polarity. Approximately 15% of parosteal osteosarcomas have focal fatty components between trabecular bone,[2] but a high proportion of spindle cell stroma should always be present.

High-grade surface osteosarcoma may be grossly similar to parosteal osteosarcoma; however, the discrimination is readily observed microscopically. In high-grade surface osteosarcoma, the tumor spindle cells show marked nuclear atypia. Lacelike osteoid production, as seen in conventional osteosarcoma, is usually evident. For periosteal osteosarcoma, the radiological features differ from those of parosteal osteosarcoma by the finding of a fusiform growth pattern and the presence of Codman triangles. Histologically, periosteal osteosarcoma has the appearance of chondroblastic osteosarcoma of intermediate grade. Characteristic comblike new bone formation at the adjacent cortex is not present in parosteal osteosarcoma.

Histologically, parosteal osteosarcoma resembles other benign fibroosseous or fibrous diseases of soft tissue and bone. When involving the periosteum, myositis ossificans can mimic parosteal osteosarcoma radiologically and microscopically. The spindle cell component of the former usually shows reactive myofibroblasts with abundant cytoplasm and frequent mitotic figures. Another feature that is not seen in parosteal osteosarcoma is the zoning phenomenon from plump spindle cells in the center via immature osteoid production to mature trabecular bone at the periphery of the lesion. Fibrous dysplasia sometimes manifests as an exophytic mass (fibrous dysplasia protuberans) and may be morphologically indistinguishable from parosteal osteosarcoma.[22] Skull, jaw, and rib are the typical locations for fibrous dysplasia, and there is always an intramedullary component. On small biopsy, desmoplastic fibroma may be included in the differential diagnosis if the collagenized spindle stroma is predominant. Correlation with radiologic findings is important because desmoplastic fibroma is not osteogenic; therefore, the lesion should not be a radiodense mass. In response to trauma, reactive processes such as fracture callus and ossifying hematoma can also simulate mature bone tumors, and acknowledgement of the clinical history can avoid misdiagnosis.

As in most bone pathology, the importance of clinical, radiologic, and pathologic correlation cannot be overemphasized in diagnosing parosteal osteosarcoma. A simple diagnostic algorithm is proposed for the histologic discrimination of osteogenic lesions arising from the bone cortical surface (Figure 4). In difficult cases, immunohistochemical stains for CDK4 and MDM2 are helpful because lesions other than parosteal and central low-grade osteosarcoma are rarely positive for these markers.

PROGNOSIS AND TREATMENT

Various terms are used to describe the phenomenon of a histologically high-grade tumor arising from a low-grade counterpart, including *high-grade transformation*, *anaplastic change*, and *dedifferentiation*. The latter is the preferred term by the World Health Organization classification,[1] and this concept is well accepted, especially in the chondrosarcoma category. Dedifferentiation of parosteal osteosarcoma has been reported in 16% to 43% of cases, either concurrently or metachronously in recurrent tumor.[2,23,24] The dedifferentiated area can be conventional high-grade osteosarcoma with various subtypes (osteoblastic, fibroblastic, chondroblastic, giant cell rich, and telangiectatic) or pleomorphic spindle cell sarcoma.[2,23,25] Evidence shows that dedifferentiated parosteal osteosarcoma has the same distinct amplification of the *CDK4* and *MDM2* genes (Figure 3, B).[26] This finding is uncommon in conventional high-grade osteosarcoma; when present, it is associated with older age, female sex, and frequent surface location. The aforementioned features overlap with those of parosteal osteosarcoma.[18,26] In

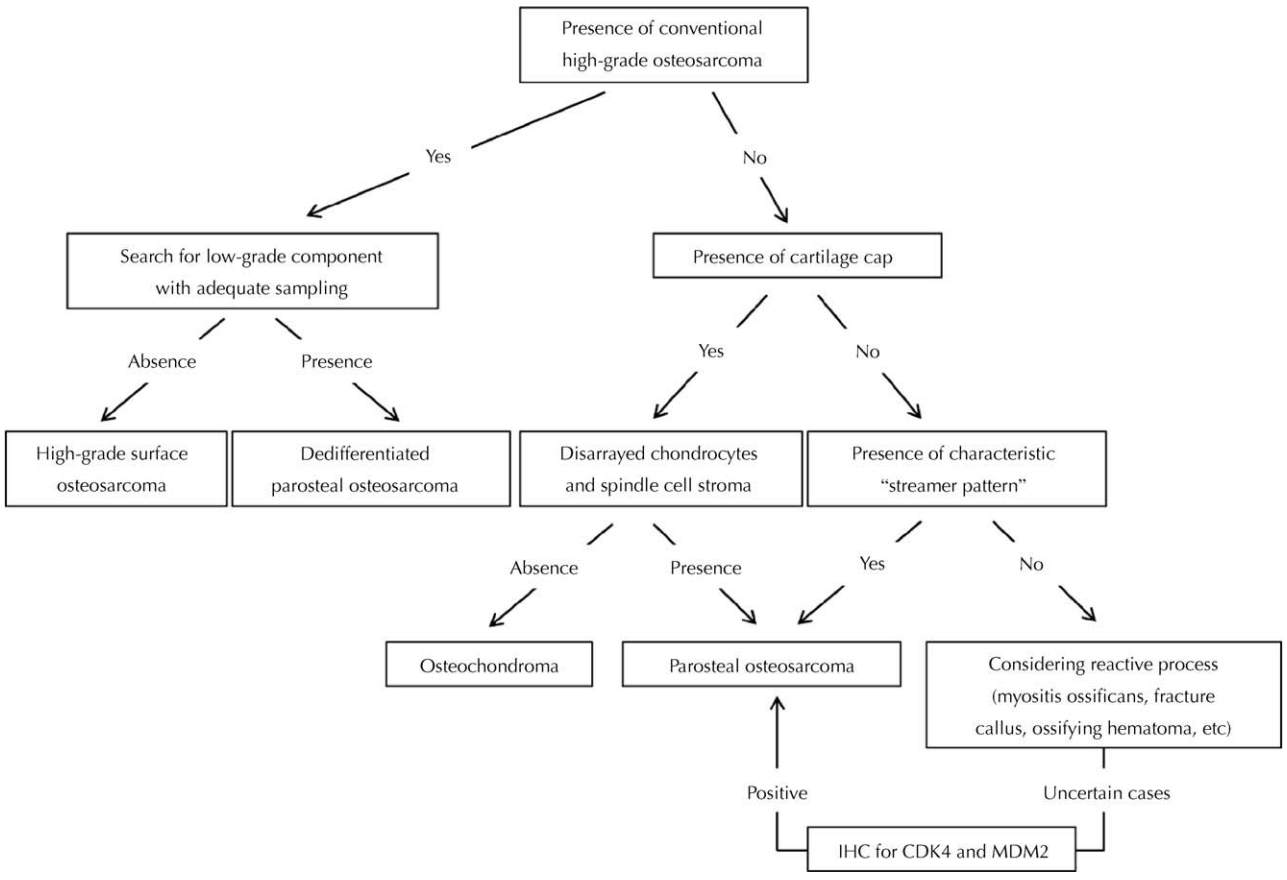

Figure 4. *Proposed algorithm for histologic diagnosis of osteogenic lesions arising from the bone cortical surface. Abbreviation: IHC, immunohistochemistry.*

a recent study, Yoshida and colleagues[26] tested 107 high-grade osteosarcomas with CDK4 and MDM2 immunohistochemically, and coexpression was seen in 7 cases. Further histologic review of these cases revealed focal low-grade elements in 6. Therefore, it has been proposed that expression of these markers may discriminate dedifferentiated low-grade osteosarcoma from conventional high-grade osteosarcoma, and it may be helpful to identify dedifferentiated tumor with a predominant high-grade component and a minor low-grade area.

Early studies[2,10,23,27] demonstrated an association between histologic grade and prognosis in parosteal osteosarcoma. A 4-tier grading system is most commonly used, but the criteria are arbitrary. Nevertheless, most of these studies demonstrate a trend that the presence of high-grade (grade 3 and grade 4) components correlates with an increasing rate of distant metastasis and a poor clinical outcome. The survival data for dedifferentiated parosteal osteosarcoma are discordant in different series. Some studies[2,24] have demonstrated poor overall survival as found in conventional osteosarcoma, while other studies[23,28] have shown a better prognosis. Further investigations are needed to evaluate if there is prognostic and therapeutic significance in distinguishing the dedifferentiated subtype from conventional high-grade osteosarcomas. On a practical basis, it is more clinically relevant to discriminate pure low-grade parosteal osteosarcomas from other benign mimickers and to identify the dedifferentiated components in low-grade parosteal osteosarcomas.

Surgery remains the treatment of choice. Wide excision with more than a 1-cm surgical margin is considered adequate, while incomplete excision almost inevitably leads to local recurrence.[2,10,27] In cases of marginal excision, a positive microscopic surgical margin warrants a second operation.[29] For recurrent disease, re-excision or amputation may provide a possible cure in cases that lack tumor dedifferentiation.[30] To achieve complete excision, a preoperative diagnosis and radiological evaluation of the extent of disease are required. When areas of dedifferentiation are suspected and proven by biopsy, neoadjuvant chemotherapy may improve the clinical outcome.[24]

SUMMARY

Parosteal osteosarcoma is a slow-growing malignant bone tumor most commonly occurring in young women. It is usually found at the cortical surface of long bones in the metaphyseal region. Radiologically, it manifests as an ossified mass with irregular mineralization and is characterized by a cleavage plane with the underlying cortex. The bland and diverse histologic patterns need to be distinguished from other benign mimickers such as osteochondroma and myositis ossificans. Recent molecular investigations have demonstrated distinct amplification of the *CDK4* and *MDM2* genes, and immunohistochemical stains detecting the overexpressed protein are sensitive and specific for the diagnosis. The prognosis of parosteal osteosarcoma is more favorable than that of conventional

high-grade osteosarcoma. Poor prognostic factors include incomplete excision and the presence of tumor dedifferentiation, associated with local recurrence and distant metastasis, respectively.

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References

1. Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F, eds. *WHO Classification of Tumours of Soft Tissue and Bone*. 4th ed. Lyon, France: IARC Press; 2013.

2. Okada K, Frassica FJ, Sim FH, Beabout JW, Bond JR, Unni KK. Parosteal osteosarcoma: a clinicopathological study. *J Bone Joint Surg Am*. 1994;76(3):366–378.

3. Geschickter CF, Copeland MM. Parosteal osteoma of bone: a new entity. *Ann Surg*. 1951;133(6):790–807.

4. Kumar R, Moser RP Jr, Madewell JE, Edeiken J. Parosteal osteogenic sarcoma arising in cranial bones: clinical and radiologic features in eight patients. *AJR Am J Roentgenol*. 1990;155(1):113–117.

5. Banerjee SC. Juxtacortical osteosarcoma of mandible: review of literature and report of case. *J Oral Surg*. 1981;39(7):535–538.

6. Jatoi A, Garcia-Moliner ML, Daly BD. Parosteal osteosarcoma from a rib. *Ann Thorac Surg*. 1998;65(1):265–267.

7. Kumm DA, Rutt J, Hackenbroch MH. Parosteal osteosarcoma of the tarsus. *Arch Orthop Trauma Surg*. 1997;116(6–7):437–439.

8. Donmez FY, Tuzun U, Basaran C, Tunaci M, Bilgic B, Acunas G. MRI findings in parosteal osteosarcoma: correlation with histopathology. *Diagn Interv Radiol*. 2008;14(3):142–152.

9. Jelinek JS, Murphey MD, Kransdorf MJ, Shmookler BM, Malawer MM, Hur RC. Parosteal osteosarcoma: value of MR imaging and CT in the prediction of histologic grade. *Radiology*. 1996;201(3):837–842.

10. Campanacci M, Picci P, Gherlinzoni F, Guerra A, Bertoni F, Neff JR. Parosteal osteosarcoma. *J Bone Joint Surg Br*. 1984;66(3):313–321.

11. Papathanassiou ZG, Alberghini M, Thiesse P, et al. Parosteal osteosarcoma mimicking osteochondroma: a radio-histologic approach on two cases. *Clin Sarcoma Res*. 2011;1(1):2. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3372285/. Accessed June 27, 2013.

12. Larousserie F, Chen X, Ding Y, et al. Parosteal osteoliposarcoma: a new bone tumor (from imaging to immunophenotype) [published online ahead of print December 15, 2011]. *Eur J Radiol*. doi:http://dx.doi.org/10.1016/j.ejrad.2011.11.035.

13. Sinovic JF, Bridge JA, Neff JR. Ring chromosome in parosteal osteosarcoma: clinical and diagnostic significance. *Cancer Genet Cytogenet*. 1992;62(1):50–52.

14. Szymanska J, Mandahl N, Mertens F, Tarkkanen M, Karaharju E, Knuutila S. Ring chromosomes in parosteal osteosarcoma contain sequences from 12q13-15: a combined cytogenetic and comparative genomic hybridization study. *Genes Chromosomes Cancer*. 1996;16(1):31–34.

15. Wunder JS, Eppert K, Burrow SR, Gokgoz N, Bell RS, Andrulis IL. Co-amplification and overexpression of CDK4, SAS and MDM2 occurs frequently in human parosteal osteosarcomas. *Oncogene*. 1999;18(3):783–788.

16. Yoshida A, Ushiku T, Motoi T, et al. Immunohistochemical analysis of MDM2 and CDK4 distinguishes low-grade osteosarcoma from benign mimics. *Mod Pathol*. 2010;23(9):1279–1288.

17. Dujardin F, Binh MB, Bouvier C, 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;24(5):624–637.

18. Mejia-Guerrero S, Quejada M, Gokgoz N, et al. Characterization of the 12q15 *MDM2* and 12q13-14 *CDK4* amplicons and clinical correlations in osteosarcoma. *Genes Chromosomes Cancer*. 2010;49(6):518–525.

19. Duhamel LA, Ye H, Halai D, et al. Frequency of mouse double minute 2 (*MDM2*) and mouse double minute 4 (*MDM4*) amplification in parosteal and conventional osteosarcoma subtypes. *Histopathology*. 2012;60(2):357–359.

20. Kyriazoglou AI, Vieira J, Dimitriadis E, Arnogiannaki N, Teixeira MR, Pandis N. 12q Amplification defines a subtype of extraskeletal osteosarcoma with good prognosis that is the soft tissue homologue of parosteal osteosarcoma. *Cancer Genet*. 2012;205(6):332–336.

21. Grimer RJ, Carter SR, Spooner D, Sneath RS. Diagnosing musculoskeletal tumours. *Sarcoma*. 2001;5(2):89–94.

22. Dorfman HD, Ishida T, Tsuneyoshi M. Exophytic variant of fibrous dysplasia (fibrous dysplasia protuberans). *Hum Pathol*. 1994;25(11):1234–1237.

23. Bertoni F, Bacchini P, Staals EL, Davidovitz P. Dedifferentiated parosteal osteosarcoma: the experience of the Rizzoli Institute. *Cancer*. 2005;103(11):2373–2382.

24. Sheth DS, Yasko AW, Raymond AK, et al. Conventional and dedifferentiated parosteal osteosarcoma: diagnosis, treatment, and outcome. *Cancer*. 1996;78(10):2136–2145.

25. Wines A, Bonar F, Lam P, McCarthy S, Stalley P. Telangiectatic dedifferentiation of a parosteal osteosarcoma. *Skeletal Radiol*. 2000;29(10):597–600.

26. Yoshida A, Ushiku T, Motoi T, et al. MDM2 and CDK4 immunohistochemical coexpression in high-grade osteosarcoma: correlation with a dedifferentiated subtype. *Am J Surg Pathol*. 2012;36(3):423–431.

27. Ahuja SC, Villacin AB, Smith J, Bullough PG, Huvos AG, Marcove RC. Juxtacortical (parosteal) osteogenic sarcoma: histological grading and prognosis. *J Bone Joint Surg Am*. 1977;59(5):632–647.

28. Schwab JH, Antonescu CR, Athanasian EA, Boland PJ, Healey JH, Morris CD. A comparison of intramedullary and juxtacortical low-grade osteogenic sarcoma. *Clin Orthop Relat Res*. 2008;466(6):1318–1322.

29. Han I, Oh JH, Na YG, Moon KC, Kim HS. Clinical outcome of parosteal osteosarcoma. *J Surg Oncol*. 2008;97(2):146–149.

30. Song WS, Jeon DG, Kong CB, Cho WH, Lee SY. Outcome of re-excision for intralesionally treated parosteal osteosarcoma. *J Surg Oncol*. 2011;103(3):264–268.

31. Tarkkanen M, Böhling T, Gamberi G, et al. Comparative genomic hybridization of low-grade central osteosarcoma. *Mod Pathol*. 1998;11(5):421–6.