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(CASE REPORT)

Periosteal Osteosarcoma: A case report of a rare tumor and a brief review of the literature

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Abstract

Periosteal osteosarcoma (PerOS) is a rare intermediate-grade surface osteosarcoma (OS), accounting for fewer than 2% of all OSs. Its unique topographic characteristics and prominent chondroblastic element frequently make diagnosis very challenging, and it should be distinguished from other morphologic pretenders, such as periosteal chondrosarcoma, parosteal osteosarcoma, and high-grade surface osteosarcoma. Timely, accurate diagnosis and treatment require a multidisciplinary approach that considers the combination of clinical, radiological, and pathological features, including immunohistochemistry (IHC) and, if indicated, molecular studies. The presence of malignant osteoid and the absence of MDM2 amplification distinguish PerOS from its closest mimicker, parosteal OS.

Here, we report the case of a 42-year-old male with an insidious onset of mass and pain in the right knee. After discussion at the multidisciplinary tumor board, the patient was successfully diagnosed and treated with a wide excision and limb-sparing reconstruction. The presented case highlights the importance of a multidisciplinary diagnostic and therapeutic approach to achieve appropriate patient outcomes in this rare bone neoplasm.

Keywords: Osteosarcoma; Surface; Periosteal; Parosteal; Cartilage; Osteoid; Low-grade

1. Introduction

PerOS is an uncommon, intermediate-grade malignant neoplasm of the bone that arises on the surface of long bones. It most often arises along the shaft of the femur or tibia in teenagers and young adults (1). Histologically, it displays atypical chondroblastic tissue with varying degrees of malignant osteoid formation (2) (3). PerOS must be distinguished from other surface OSs and the usual intramedullary OS (4).

On X-ray, periosteal OS appears as a large soft-tissue mass attached to a thickened bone surface. It frequently exhibits a perpendicular, "hair-on-end" periosteal reaction that extends into adjacent soft tissues, along with evidence of cortical bone erosion or scalloping. (3) The imaging characteristics, cartilaginous component, and negativity to MDM2 play a key role in differentiating it from other surface bone OSs.

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In large institutional and multicenter series, PerOS has been shown to have a better prognosis than typical high-grade osteosarcoma, with long-term survival rates above 80% (1) (5). Wide surgical excision remains the mainstay of treatment, as the usefulness of chemotherapy is still debatable. The requirement for tailored decision-making based on tumor grade, extent, and presenting characteristics is highlighted by the several trials that have failed to show a significant survival benefit with adjuvant therapy in this subtype (1) (5).

This case adds to the existing literature on the diagnosis and treatment of PerOS, aiming to raise clinicians' and pathologists' awareness of its inclusion in the differential diagnosis of a surface bone mass.

2. Case Presentation

2.1. Clinical case presentation

A 42-year-old man presented to the orthopedic clinic with a history of four months of pain and a swelling that was growing in the lower part of the right knee. The patient stated that the pain started as mild in the knee 18 months prior to presentation. In the next year, the pain slowly deteriorated to be more persistent and activity-based. The pain slowly increased and influenced his walking and disturbed his sleep. The patient attempted to manage the symptoms using over-the-counter pain medication and changing his activity level, and assumed that it was a sports-related problem. However, there was no improvement in the symptoms. He was free of constitutional symptoms (Fever, weight loss, and night sweats).

2.2. Medical history and physical examination

The patient reported no history of previous radiotherapy, chemotherapy, bone malignancy, or any other tumors. There was no documented history of Paget disease, bone infarct, or fibrous dysplasia. The patient was an athlete, a non-smoker, and an occasional alcohol drinker. There was no family history of bone tumors, retinoblastoma, or hereditary cancer syndromes. The patient's parents were also healthy, and both siblings were alive and healthy without malignancies. In addition, no significant history was reported of the grandparents.

On physical examination, the patient was an alert and healthy appearing male with no acute distress. No remarkable changes in vital signs were observed. A hard, approximately incompressible 7x5 cm mass was detected along the anteroposterior aspect of the knee. There was no change in the overlying skin, such as erythema or extra warmth, just mild tenderness. Mild lack of mobility to 115 degrees of flexion (due mainly to mass effect and pain) in the right knee. There was no lymphadenopathy of the popliteal or inguinal areas. There were palpable distal pulses, normal capillary refill, and good sensory function in all dermatomes. Motor function was 5/5 in all extremities, but the patient guarded on exam due to pain.

2.3. Radiographic features

Anteroposterior and lateral plain radiographs of the right knee showed a surface lesion in the cortex of the proximal tibial metaphysis. The lesion displayed a typical sunburst periosteal reaction showing spiculated bone perpendicular to the cortical surface. The tibial cortex was thickened, with saucer-like erosion and scooping on the external cortical surface. A Codman's triangle at the margins of the lesional tissue was noted. There was no medullary cavity involvement, distinguishing it from central osteosarcoma.

CT revealed a subcutaneous 7.2 × 5.1 × 4.8 cm mass with chondroid matrix mineralization in an arc- and ring-configuration. The medulla was not involved, and the cortex was minimally eroded, but with extension into the surrounding soft tissue. The T1-weighted MRI imaging of the mass revealed a lobulated contour and intermediate signal intensity. T2-weighted imaging showed a bright cartilage signal. There was inhomogeneous enhancement within the lesion and perilesional soft tissue oedema. No intramedullary extensions or other lesions were identified.

Radiologic differential diagnosis for the underlying pathology in this case was predominantly PerOS (most likely), periosteal chondrosarcoma (absence of osteoid production), high-grade surface OS (more aggressive morphologic appearance), parosteal OS (usually lower-grade, more organized bone), juxtacortical chondroma and reactive bone formation, osteochondroma with atypical features, and chronic osteomyelitis. PerOS was the preferred imaging diagnosis due to its topographical localization, chondroid matrix, perpendicular periosteal reaction, and intermediate-grade radiographic features. [4] [6] [8] **[Table-1]**

Table 1 Differential Diagnosis of Surface Periosteal Osteosarcoma (PerOS)

Condition	Key Features	Distinguishing Points
Periosteal Osteosarcoma (PerOS)	Low-grade surface osteosarcoma. Osteoid formation	Presence of osteoid, negative for MDM2
Periosteal Chondrosarcoma	Cartilage-producing tumor on the bone surface; lobulated mass.	Typically, lower grade; more chondroid matrix vs. PerOS.
Parosteal Osteosarcoma	Low-grade surface osteosarcoma; dense ossified mass.	More mature bone formation; lacks significant osteoid seen in PerOS. Positive for MDM2.
High-grade Surface Osteosarcoma	Aggressive surface tumor with high-grade histology.	More aggressive appearance; higher degree of atypia.
Chronic Osteomyelitis	Bone inflammation with sclerosis, possible sequestra.	Presence of infection signs; irregular periosteal reaction.
Stress Fracture with Periosteal Reaction	Linear fracture line; callus formation.	History of repetitive stress; lacks tumoral matrix.
Periosteal Reaction from Trauma	Reactive bone formation after injury.	Clinical trauma history; smooth periosteal thickening.
Periosteal Chondrosarcoma	Cartilage-producing malignant tumor on the bone surface; lobulated chondroid matrix.	Usually lower grade; more uniform chondroid matrix than PerOS.
Juxtacortical Chondroblastoma	Rare surface variant; chondroblasts with 'chicken-wire' calcification.	Younger patients; characteristic calcification pattern and less aggressive periosteal reaction.
Osteochondroma with Atypical Features	Surface exophytic lesion with cartilage cap; may show irregular growth.	Cortex and medulla continuity with native bone; lacks malignant osteoid.

*Compiled from [4] [6] [8]

2.4. Biopsy and diagnosis

Several core fragments were obtained from the superficial soft tissue component of the mass. Pathological microscopic examination displayed malignant cartilage, hypercellularity, nuclear atypia, and pleomorphic binucleated cells. Chondroid matrix was focally observed, with areas of malignant osteoid deposited by malignant cells, a feature of osteosarcoma. The cartilaginous element was predominant, consistent with a cartilage-rich OS. (**Figure 1 A, B, C**)

These features, in conjunction with the site and radiological appearance of the tumor, led to the diagnosis of a PerOS. This rare intermediate-grade surface OS represents less than 2% of all OSs. The presence of malignant osteoid distinguished it from periosteal chondroblastoma, and the more abundant subperiosteally located cartilaginous matrix along the surgical surface established the diagnosis of PerOS.

2.5. Discussion in tumor board and treatment decision

Imaging findings, pathology results, and clinical information were presented to the multidisciplinary tumor board. The surgical margin of PerOS was discussed due to its intermediate grade (G2) and superficial location. The discussion centered on two choices: wide excision with clean margins or marginal resection and adjuvant therapy. A wide excision was eventually decided as the therapeutic option of preference. Given the intermediate grade of the tumor, neoadjuvant chemotherapy was not suggested, as in conventional high-grade osteosarcoma. Limb-salvage was also to be incorporated into the plan, with reconstruction and local control, followed by chemotherapy if there were positive margins or dedifferentiated disease in the excised entire mass.

2.6. Treatment and outcome

The patient was treated with wide excision (limb-sparing) and en bloc resection of the mass with a cuff of grossly uninvolved adjacent soft tissue, along with partial sectioning of the proximal tibial cortex. Fixed plating and a structural

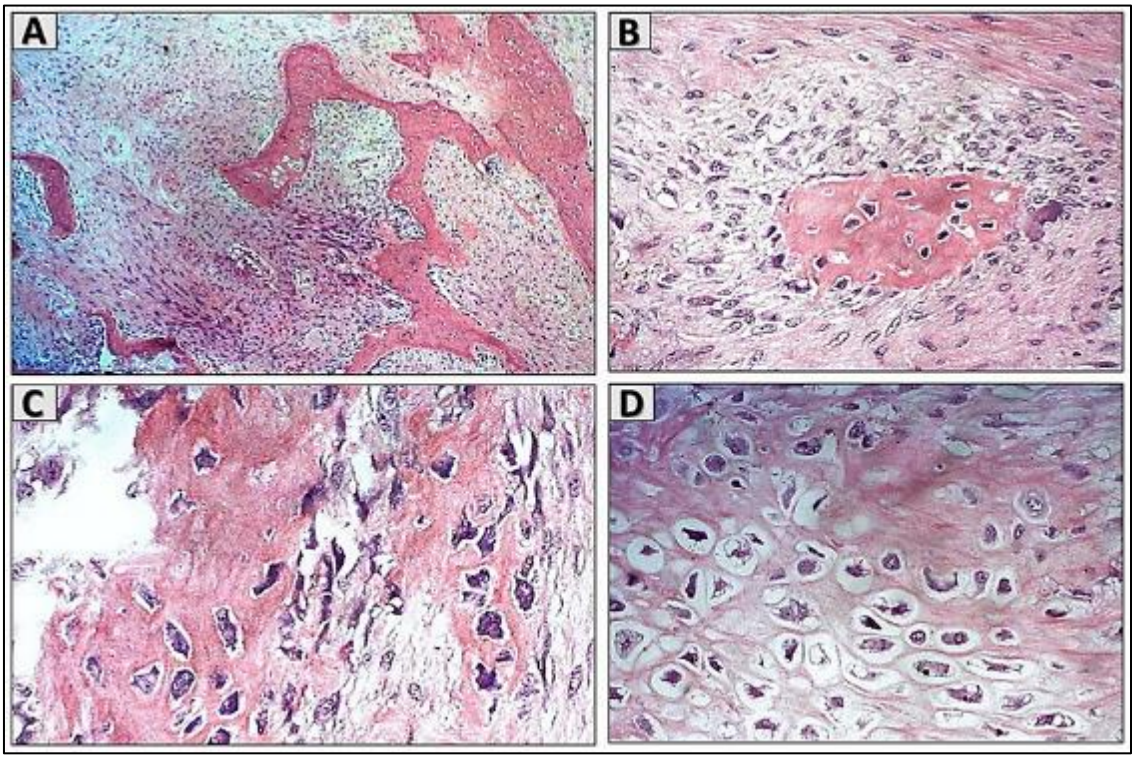
cortical allograft were used to reconstruct the defect. The resected specimen measured 9 × 6 × 5 cm and had a solid , lobulated, gray-white cut surface. The tumor manifested as a shallow cortical surface-based lesion with only slight endosteal erosion and no medullary involvement. Ossification was more advanced, and the cartilaginous portion was thicker. Histologically, there were areas with a chondroblastic predominant pattern, in which the malignant cartilage displayed moderate to marked cellular atypia, hypercellularity, and pleomorphism. Surgical excision confirmed the preoperative core biopsy diagnosis of PerOS, which was identified in about 30% of the tumor mass by the presence of malignant osteoid. The mitotic rate was 4-6 per 10 high-power fields, indicating an intermediate tumor grade. Surgical margins were free (>1 cm). Pathologic differential diagnosis included periosteal chondrosarcoma (ruled out by production of osteoid), parosteal OS (excluded by lack of more organized bone and lower grade), and dedifferentiated PerOS (excluded as it would be seen to have discrete high-grade areas)

On IHC, the tumor cells were immunoreactive for S100 protein (chondroid component) and focally for SATB2 (osteoblastic differentiation). The Ki-67 proliferative index was approximately 20%, consistent with an intermediate-grade tumor. MDM2 amplification was tested, and a negative result ruled out parosteal osteosarcoma with dedifferentiation. TP53 mutation testing was considered but was not required for diagnosis; therefore, it was not performed. Adjuvant chemotherapy was not recommended in view of clear, wide margins and an intermediate-grade histology as per historic practice, which reserves chemotherapy for high-grade or incompletely resected PerOSs.

2.7. Follow-up

The patient experienced an uneventful postoperative recovery with wound healing, though recovery was prolonged. Postoperative treatment used physiotherapy for range of motion and strengthening, achieving 120 degrees of active flexion at the knee at 3 months. The follow-up plan included clinical examination and plain radiographs every 3 months for the first year, then every 6 months thereafter, and an annual chest CT to assess for pulmonary metastasis.

The patient was disease-free and without any local recurrence or metastasis at 24-month follow-up. He had already gone back to recreational activities with very few restrictions. Serial imaging evidenced the stable incorporation of allografts with no recurrence.



1A: Low power view showing infiltrating tumor mass associated with malignant and reactive bone formation (H&E stain X20); **1B:** Intermediate power view showing malignant osteoid formed by malignant osteoblasts (H&E stain X40); **1C**: High power view showing pleomorphic malignant osteoblasts with large, irregular, hyperchromatic nuclei making malignant osteoid (H&E stain X60); **1D**: High power view showing Malignant osteoid surrounded by malignant chondroblasts with nuclear atypia, and binucleated cells (H&E stain X60)

Figure 1 Microscopic features of periosteal osteosarcoma in a bone biopsy of the mass

3. Discussion

3.1. Background (History, epidemiology, and WHO classification)

Malignant bone tumors most commonly develop from metastasis from other malignant tumors. It is estimated to occur in 5-8% of all cancer patients, or with an annual incidence of 18.8 per 100,000 in the US. [9] Bone is the third most common site of metastasis, behind the lung and the liver. [10] On the other hand, primary malignant bone tumors are much rarer, at approximately 0.2% of all cancers, with an incidence of 0.9 per 100,000 and a five-year survival rate of 67.9%. Age-specific incidence of primary bone tumors shows a bimodal distribution, with a typical onset peak in the second decade of life and a second peak in the sixth decade. [11] Primary bone tumors are further classified as benign, intermediate, or malignant. [6] Benign tumors are most common and are usually asymptomatic, though the actual incidence is unknown. Intermediate tumors are locally aggressive but rarely metastasize and include giant cell tumor, osteoblastoma, and desmoplastic fibroma. [6]

Primary bone tumors can be further classified based on histologic features and the products of proliferating cells. The most common group of primary bone malignancies is hematopoietic histologic types (myelomas, lymphomas, and leukemia), followed by chondrogenic tumors, then osteogenic tumors. There are several other types as well, such as fibrogenic tumors, histiocytic tumors, notochordal tumors, lipogenic tumors, neurogenic tumors, tumors of bone vasculature, and tumors of unknown origin (such as giant cell tumors). However, these are exceedingly rare. [7] [12] Typically, bones with the highest growth. Rates are usually affected. Approximately 20% of all OSs are associated with genetic predisposition [13]**.** Individuals who present with OS in the first or second decades of life are typically associated with other genetic variables/predispositions, such as Li-Fraumeni or Beckwith-Wiedemann syndrome, Paget's disease, fibrous dysplasia, or prior radiation exposure. OS can be further classified into central, surface, intracortical, gnathic, and extraskeletal subtypes, depending on histologic features and anatomic location. [4]

PerOS was first recognized by James Ewing in 1939. Louis Lichtenstein described it as a unique entity in the 1950s, and was identified as a specific clinicopathological type different from central osteosarcoma by Unni, Dahlin, and Beaboutin in 1976. [21] The WHO classifies PerOS as an intermediate-grade, malignant, surface (juxtacortical) subtype of OS (6)**.** Other surface osteosarcomas include low-grade parosteal osteosarcoma, high-grade dedifferentiated parosteal osteosarcoma, and high-grade surface osteosarcoma (4). PerOS is much less common than the other surface subtypes. The genetic predisposition to PerOS is similar to that of other OSs. Genetic drivers, such as mutations in TP53 and RB1, are central to tumor development. Overexpression of Runx2, ALP, Wnt/β-catenin, BMP/TGFβ pathways also contributes to the manifestation of OS. [14] Surgical resection of the PerOS is the treatment of choice. For higher-grade variants, adjuvant chemotherapy may be considered after negative margins. However, it remains controversial in moderate-grade tumors, and more research is likely needed given the scarcity of cases. [14] Prognosis after treatment is excellent, with a 10-year survival rate of 97% and very low recurrence rates, particularly with wide-margin excision in more moderate grades. [4]

3.2. Pathogenesis, pathophysiology

It is believed that periosteal osteosarcoma develops as a result of the inner periosteum layer, where osteoprogenitor cells are located. PerOS is a purely superficial tumor, unlike the traditional high-grade osteosarcoma, which is believed to arise in the medullary cavity. [15] The pathophysiology of this disease is characterized by predominantly chondroblastic differentiation, i.e., the malignant cells are primarily capable of producing cartilaginous matrix. However, the necessary presence of malignant osteoid, which is the staple of osteosarcoma, is also present. [15] The tumor grows external to the bone surface, producing the typical radiographic appearance of a perpendicular, spiculated periosteal reaction and saucer-like erosion of the underlying cortex. The intermediate-grade nature of PerOS is also indicated by its cellular features, which are intermediate for hypercellularity and nuclear atypia. However, it has a reduced mitotic rate and less aggressive behavior than conventional osteosarcoma. [16] At the molecular level, the absence of MDM2 amplification, as observed in this case, contributes to distinguishing PerOS from parosteal osteosarcoma, suggesting a divergent, but infrequent, oncogenic pathway. [2]

3.3. Comparative analysis of our case with the existing literature. (Diagnosis, pathology, IHC, molecular findings, management, and outcomes)

The clinical presentation in the present case report (slowly enlarging, firm, superficial mass with gradually increasing pain around the knee, negative for constitutional symptoms) best fits the most prevalent PerOS series, which presents young to middle-aged subjects with localized pain/swelling but no systemic complaints. [2] [16] Radiographically, the juxtacortical metaphyseal-based lesion with a sunburst periosteal reaction, cortical thickening, saucerization of the outer cortex, and absence of medullary involvement in our patient is consistent with the classic radiographic description

of PerOS as a broad-based surface soft-tissue mass producing extrinsic cortical erosion along with an associated thickened diaphyseal cortex and perpendicular spiculated periosteal reaction extending into the soft tissues. [3] [15] CT showing a lobulated mass with predominance of chondroid ["arc-and-ring"] mineralization, and findings on MRI of intermediate T1 and high-T2 signal in the region corresponding to cartilaginous components can also be seen and serve to differentiate from parosteal osteosarcoma (more ossified, lower grade) and periosteal chondrosarcoma (absence of malignant osteoid). [15] [17] [18] Conventional laboratory findings in PerOS are frequently not unique, and the normal baseline studies found in this case are consistent with previous reports in which either inflammatory or tumor markers were not diagnostic. [8] [15]

Histologically, the tumor in this case had a predominantly chondroblastic pattern with hypercellularity, nuclear atypia, and focal formation of malignant osteoid by pleomorphic malignant cells outlining <30% of the total tumor volume, with an intermediate mitotic rate. This profile is the intermediate-grade PerOS category, which demonstrates greater cartilage malignancy but does not require a specific percentage of osteoid, thereby separating PerOS from periosteal chondrosarcoma. [15] [19] IHC studies can also be helpful, with S100 reactive at chondroid areas and SATB2 positive in osteoid areas. These patterns are correlated with the reported literature, although they are not specific, and interpretation should occur within context. [20] The negative result of MDM2 amplification in our case is consistent with the molecular findings that parosteal and low-grade central osteosarcomas characteristically have MDM2/CDK4 amplification.

In contrast, PerOS usually does not, further supporting the genetic separation. [16] [19] The wider literature on OS genomics documents highly prevalent alterations of TP53/RB1 pathways across subtypes; however, routine testing for these aberrations was not mandatory for the diagnosis of PerOS, and this was rightly not considered in this case. [16]

Wide excision with adequate margins of clearance is the gold standard of care for our patient, which was adopted in this instance and recommended in numerous case series and reviews. [8] [15] [19] [21] Our patient was treated with wide en bloc resection, structural cortical allograft reconstruction, and plate stabilization, as predicated by modern limb-salvage principles that aim to restore stability and function while preserving oncologic control. [8] [21] Adjuvant chemotherapy was not offered due to intermediate grade, absence of medullary involvement, and wide (negative) margins. This strategy is based on current evidence that the role of chemotherapy in classic PerOS remains unclear and can be justified only as second-line adjunct treatment, or, better yet, should be considered only in high-grade, medullary invasive, or dedifferentiated forms. Several series and narrative reviews have failed to demonstrate a clear survival benefit from adjuvant chemotherapy in typical PerOS. [19] [21] [22] Reported 5-year overall survival rates for PO are generally around 77–83% with improved results in patients without intramedullary extension and in those who have an adequate surgical margin. [19] [21] [22] Thus, the 24-month disease-free interval and excellent functional restoration in our patient are, however, consistent with the favorable prognosis and limb function described in the literature about appropriately resected, intermediate-grade, medullary-spared PerOS. [16] [19] [21] [22]

4. The future of diagnosis and management with the current technological revolution

The rapid development of molecular oncology, imaging, and computational technologies is changing the diagnostic and therapeutic landscape for PerOS, a relatively rare and difficult-to-diagnose surface OS. High-resolution imaging techniques, including photon-counting detectors for CT scanning, radiomics-based analysis of MRI data, and machine-learning pattern recognition algorithms, are projected to introduce a step-change in discrimination between PerOS and parosteal OS, periosteal OS, and high-grade surface OS by quantification of mineralization patterns, cortical interface characteristics, and tumor heterogeneity on a scale not achievable with traditional radiology. [23] [24] Molecular profiling is also prospective, especially as sequencing becomes faster and cheaper; recurrent changes in TP53, RB1, and osteogenic differentiation pathways might serve to refine risk stratification, early detection of dedifferentiation, and the development/ targeting of monoclonal therapy. [17] [18]

On the management side, patient–specific (3D–printed) cortical and metaphyseal blocks are increasingly used to reproduce complex surface bone anatomy following wide excision with functional limb retention. [25] In addition, ctDNA and liquid biopsy platforms show potential for detecting minimal residual disease and earlier recurrence than imaging alone. [26] Finally, the convergence of molecular diagnostics, AI-assisted imaging interpretation, and personalized reconstructive technologies has the potential to evolve PerOS care into a discipline that is more precise, biologically informed, and function-preserving.

5. What have we learned from this case?

The presented case raises several valuable issues regarding the diagnosis and treatment of rare surface OSs. First, it highlighted the diagnostic challenge of distinguishing PerOS from its morphological mimics, especially periosteal chondrosarcoma and parosteal OS. A clear finding of a malignant osteoid on biopsy, even at a focal level, was the decisive factor, which altered the diagnosis of a cartilaginous tumor to an OS. Second, the case confirmed the role of multidisciplinary tumor board discussion in achieving accurate diagnosis and customizing treatment. The decision to proceed to wide excision without neoadjuvant chemotherapy was not a rush decision, as it was made based on the intermediate grade of the tumor and the aim of achieving clear margins and sparing of the limb. Lastly, the current management paradigm for intermediate-grade PerOS can be justified by the favorable 24-month disease-free survival rate, which included aggressive local control with wide excision to achieve clear margins and systemic therapy in cases of high-grade or incompletely resected disease.

Abbreviation

Osteosarcoma (OS); Periosteal Osteosarcoma (PerOS); Immunohistochemistry (IHC)

6. Conclusion

In this case, we outlined a PerOS of the proximal tibia to demonstrate the complexity of diagnosis and the best management approach for this rare bone tumor. The case is also useful to the medical community, offering a clear example of the process of differentiating juxtacortical lesions, which should be based on a combination of clinical, radiological, and pathological information. In addition, it supports the existing evidence-based practice of extensive surgical excision of intermediate-grade PerOS to achieve local control and an excellent long-term prognosis.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors make the following declarations:

- Payment/services information: All authors have declared that they received no financial support from any organization for the submitted work.
- Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might be interested in the submitted work.

Statement of ethical approval

Ethical review and approval were not required for this study involving human participants. The paper has been sufficiently anonymized to maintain the patient's confidentiality.

Statement of informed consent

Informed Consent for the publication of this case was obtained from the patient.

Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

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