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(CASE REPORT)

Chondroblastoma of the proximal femur: Case report with a diagnostic challenge and brief literature review

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Abstract

Chondroblastoma is a rare benign cartilaginous neoplasm accounting for fewer than 1% of all primary bone tumors, with a well-established predilection for the epiphyses of long bones in skeletally immature patients. Its occurrence in a skeletally mature adult, combined with a large lesion size and metaphyseal extension, poses a distinct diagnostic and surgical challenge.

We report the case of a 28-year-old male who presented with several months of progressive right hip and groin pain. Imaging demonstrated a well-defined eccentric lytic lesion of the proximal femoral epiphysis measuring approximately 5.5 cm, with extension into the femoral neck and metaphysis. Following multidisciplinary tumor board review, CT-guided core needle biopsy was performed. Histopathological examination and immunohistochemistry (IHC) studies confirmed chondroblastoma. Molecular analysis identified the defining H3F3B K36M hotspot mutation, confirming the diagnosis and excluding principal mimickers.

The patient underwent extended intralesional curettage with high-speed burring, chemical adjuvant therapy, and reconstruction with bone graft and calcium sulfate pellets. Local recurrence was detected at 18 months, requiring a second curettage. The patient ultimately achieved full functional recovery without further evidence of disease.

This case illustrates the diagnostic complexity of chondroblastoma in an adult, underscores the indispensable role of molecular confirmation, and highlights the known risk of local recurrence at the proximal femur, a site recognized as particularly challenging for surgical access and local control.

Keywords: Chondroblastoma; Femur; Curettage; H3.3 K36M mutation; Chicken-wire pattern

1. Introduction

Chondroblastoma is a rare, benign bone tumor originating from cartilage-forming cells, most commonly affecting the epiphysis of long bones in adolescents and young adults. [1,2] Although classified as benign, chondroblastoma may exhibit locally aggressive behavior and can result in significant joint-related morbidity. Patients are commonly present with gradual, activity-related pain localized to the affected joint, often accompanied by stiffness, reduced range of

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motion, and a limp or difficulty with ambulation in weight-bearing joints. [1,3] These nonspecific symptoms are often misattributed to more common musculoskeletal conditions, which may delay diagnosis.

Radiographic assessment typically demonstrates a well-defined lytic lesion centered in epiphysis. However, these imaging features are not pathognomonic and may overlap with other entities, such as giant cell tumors and clear cell chondrosarcoma. Therefore, histopathologic confirmation remains essential. Recent advances in molecular pathology, particularly the identification of the H3.3 K36M mutation, have enhanced diagnostic accuracy and facilitated distinction between chondroblastoma and similar lesions [3,4]

Given the potential for local recurrence and the complexity of managing lesions in weight-bearing joints such as the proximal femur, timely recognition is critical. We report this case to highlight the diagnostic challenges and recurrence risk of chondroblastoma in a surgically challenging location.

2. Case Presentation

2.1. Clinical presentation and initial laboratory workup

A 28-year-old male presented to the orthopedic oncology clinic with a several-month history of progressive right hip and groin pain that had gradually worsened with weight-bearing activity. He described the pain as deep, aching, and poorly localized, occasionally radiating to the anteromedial thigh. He denied constitutional symptoms such as fever, night sweats, or unintentional weight loss, and had no prior history of malignancy or significant musculoskeletal disease. His past medical and family histories were otherwise unremarkable.

On physical examination, the patient was a well-appearing young man in no acute distress. There was a mildly antalgic gait favoring the right lower extremity. The right hip had a restricted range of motion and was painful, particularly with internal rotation and abduction. There were no palpable soft tissue masses and no regional lymphadenopathy. Neurovascular status of the extremity was intact.

Initial laboratory workup, including a complete blood count, comprehensive metabolic panel, lactate dehydrogenase, alkaline phosphatase, and erythrocyte sedimentation rate, returned within normal limits.

2.2. Radiographic findings

Plain radiographs of the right hip demonstrated a well-defined, eccentric, lytic lesion occupying the epiphysis of the proximal right femur, measuring approximately 5.5 cm, with subtle intralesional calcifications and a sclerotic rim. There was an extension into the femoral neck and metaphysis without cortical breakthrough. MRI confirmed the extent of the lesion, revealing heterogeneous T2 signal with surrounding marrow edema, a characteristic feature that could initially be misleading toward an infectious or inflammatory etiology. No soft tissue extension or joint effusion was identified. A CT scan further delineated the cortical integrity and the presence of stippled chondroid calcifications within the lesion. (**Figure 1 A, B**)

The differential diagnosis at this stage was carefully considered and included giant cell tumor of bone, given the epiphyseal location in a skeletally mature individual; clear cell chondrosarcoma, which shares the epiphyseal predilection and could not be excluded on imaging alone; aneurysmal bone cyst; subchondral insufficiency fracture; and; Langerhans cell histiocytosis; intraosseous ganglion; and chondroblastoma (Favored). Infection, particularly tuberculous osteomyelitis, was also entertained, given the surrounding marrow edema on MRI.

2.3. Multidisciplinary tumor board discussion and management

The case was brought before the multidisciplinary tumor board, where the central discussion focused on the tissue sampling strategy, recognizing that the radiographic and clinical features were strongly suggestive of chondroblastoma but insufficient to guide definitive management without histopathologic confirmation. Image-guided core needle biopsy was performed under CT guidance with careful planning of the biopsy tract to permit its excision during any future surgical intervention. The biopsy yielded adequate tissue and was reviewed by a specialized musculoskeletal pathologist.

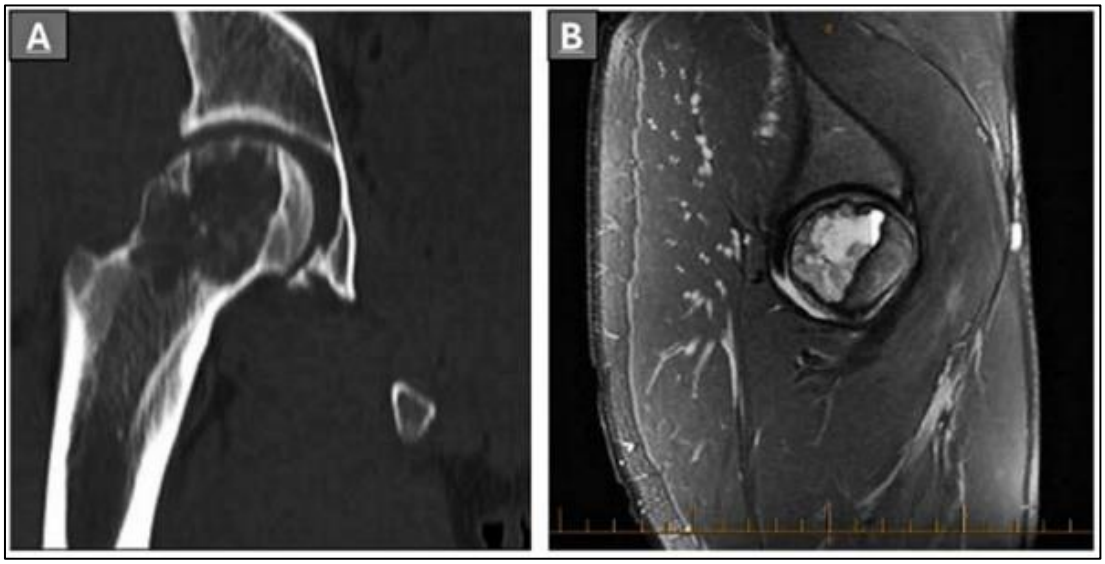
Histopathologic examination revealed a cellular tumor composed of mononuclear chondroblasts with well-defined cell borders, often showing a "chicken-wire" pattern of calcification surrounding individual cells, a hallmark of chondroblastoma. Scattered osteoclast-type giant cells were present throughout the background. Mitotic figures were identified, but none were atypical. (**Figure 2 A, B, C, D**) IHC analysis demonstrated strong and diffuse nuclear positivity

for S-100 protein, consistent with chondroid differentiation, and nuclear positivity for DOG1. Tumor cells were also positive for SOX9 and negative for desmin. Critically, molecular analysis identified a K36M hotspot mutation in the H3.3 gene (H3-3B), specifically the lysine-to-methionine substitution at lysine 36. This mutation is now recognized as a defining molecular alteration in chondroblastoma and serves to distinguish it from mimickers, particularly giant cell tumor and clear cell chondrosarcoma. The Ki-67 proliferative index was low (6%), supporting the tumor's benign but locally aggressive nature.

Following tumor board consensus, the patient underwent surgical management with extended intralesional curettage, high-speed burring, adjuvant treatment of the cavity walls with phenol and hydrogen peroxide, and reconstruction with bone graft and calcium sulfate pellets. The articular cartilage was carefully preserved. He tolerated the procedure well and was mobilized with partial weight-bearing restrictions postoperatively.

2.4. Outcome and follow-up

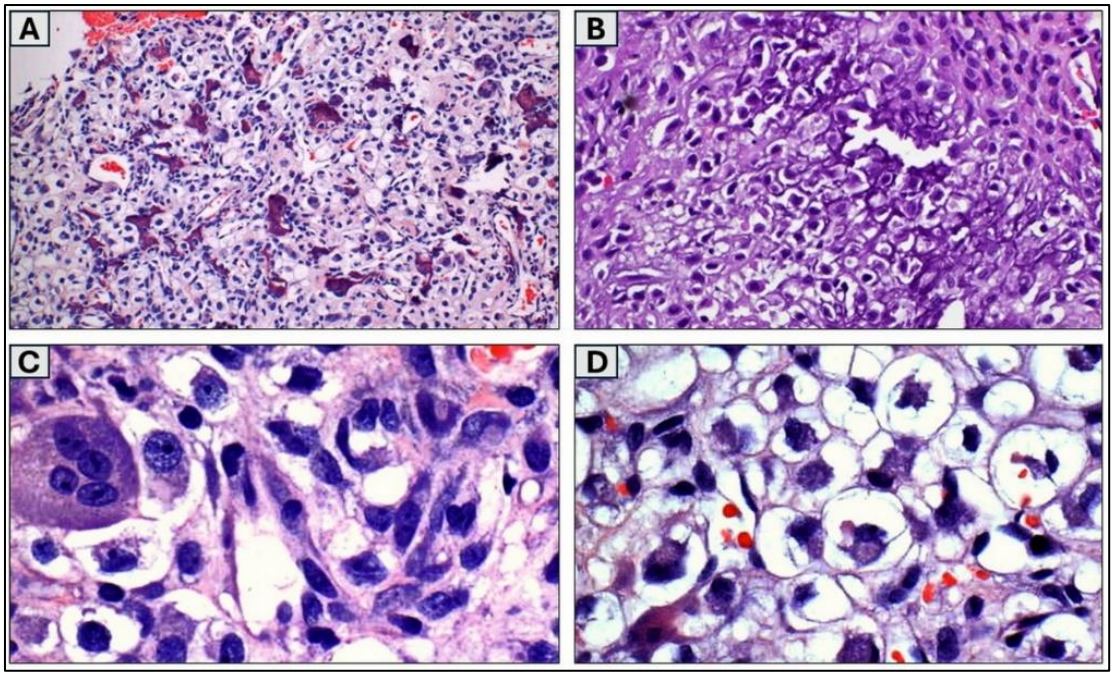
At approximately 18 months following the initial curettage, surveillance imaging demonstrated local recurrence within the femoral head and neck, without new lesions elsewhere. The patient was referred to the tumor board, and a second intralesional curettage was recommended with more aggressive local adjuvant therapy. He underwent repeat surgery, which confirmed viable chondroblastoma on permanent sections consistent with local recurrence. Postoperative recovery was uneventful. Long-term follow-up with serial radiographs and periodic MRI was established, with particular attention to joint integrity given the lesion's proximity to the articular surface. The patient remained disease-free at subsequent follow-up visits and returned to full functional activity without evidence of further recurrence or malignant transformation, a rare but reported phenomenon in chondroblastoma, particularly following radiation therapy, which was accordingly avoided in his management.



1A**:** Coronal CT showing a well-defined, eccentric, lytic lesion centered in the epiphysis with significant expansion. It extends into metaphysis and down to proximal diaphysis. The superior and lateral cortex of the femoral head and neck appears thinned (ballooning), but it looks largely intact. Focal punctate calcifications are also noted.

1B: Axial T2-Weighted MRI showing a heterogeneously high signal, which may indicate areas of cystic change or significant cartilaginous components. The joint space appears relatively preserved, though the lesion is near the subchondral bone plate.

Figure 1 Radiographic images of the right proximal femur chondroblastoma



1A**:** Low power view showing diffuse, cellular sheets of polygonal mononuclear cells (Chondroblasts) and scattered coarse and focal amorphous deposits (H&E X20); 1B: Intermediate power view showing cellular tumor composed of mononuclear chondroblasts with well-defined cell borders, showing a "chicken-wire" pattern of calcification surrounding individual cells (H&E X40); 1C**:** High power view showing scattered osteoclast-type giant cells, which was present throughout the background, intermixed with oval, spindle, to polygonal chondroblasts (H&E X60); 1D: High power view showing chondroblasts with cell borders ranging from well demarcated to ill defined. Nuclei vary in size and configuration, with numerous multilobed forms. Cytoplasmic vacuolation was prominent in this case. (H&E X60).

Figure 2 Microscopic features of the curetted chondroblastoma

3. Discussion

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

Chondroblastoma was first described in 1942 by Jaffe and Lichtenstein as “benign chondroblastoma of bone”. It was previously misclassified as a variant of giant cell tumor before being recognized as a separate entity. Jaffe highlighted the tumor origin from immature cartilage-forming cells (Chondroblasts), in contrast to giant cell tumors, which arise from mesenchymal stromal cells. [5] Chondroblastoma affects the epiphyseal sites of long bones such as the proximal humerus, proximal tibia, and proximal femur. Less common locations include the hands and feet. [2,6]

The majority of these cases arise during adolescence and early adulthood, with rare presentations found in patients younger than 10 or older than 30 years old. [7] Genetic or environmental risk factors are not well-known; however, the tumor is strongly associated with skeletal immaturity and open growth plates. Males are more susceptible than females, with a male-to-female ratio of 2:1. [6,7] Although generally benign, the World Health Organization (WHO) classifies chondroblastomas as benign (But rarely metastasizing) tumor with the potential to be locally aggressive. [20]

3.2. Pathogenesis, Pathophysiology

Chondroblastoma can harbor both balanced and unbalanced rearrangements of chromosomes 5 and 8. In addition, IDH mutations are typically absent in chondroblastoma, a feature that helps distinguish it from other cartilaginous tumors such as enchondroma and chondrosarcoma. [8] Mutations in the H3F3B gene provide further insight into tumorigenesis. H3F3A and H3F3B both encode the histone variant H3.3, which is incorporated into chromatin independently of DNA replication and is enriched by promoters and enhancers of transcriptionally active genes. This distribution supports its proposed role in regulating chromatin accessibility and transcription. [9]

In chondroblastoma, the K36M mutation is exclusively seen. A study showed that 85 chondroblastomas and 10 clear cell chondrosarcomas had a K36M mutation in the H3F3A and H3F3B genes, with 93% having an H3F3B mutation and 7% having an H3F3A mutation. Furthermore, among almost 1800 other tumors sampled, none had mutations at this position, indicating a high level of specificity of this mutation in chondroblastoma. [2]

This is such a distinguishing mutation that researchers have used mutation-specific antibodies to identify chondroblastoma. Researchers showed that this mutation inhibits histone methyltransferases because the mutated methionine binds tyrosine residues more readily than the native lysine residue. [9] This was confirmed by solving the crystal structure of SETD2-H3K36M and doing various assays. [10] This change leads to hypomethylation across the genome and increased transcription of various pathways. Some examples are changes in BMP2 and RUNX2, which are associated with bone and cartilaginous differentiation. [9,10] The authors state that while current therapies targeting H3 interactions are lacking, the opportunities in this space are very real.

3.3. Comparative Analysis of Our Case with Existing Literature. (Clinical, radiology, pathology, Lab, diagnosis, management, and outcome)

The present case shares several features with previously reported series and case reports of chondroblastoma, while also demonstrating characteristics that set it apart. In terms of demographics, the typical patient profile described in the literature favors adolescents and young adults in the second decade of life, with a slight male predominance. [11,12] Our patient, at 28 years of age, falls to the older boundary of the conventional age range, consistent with reports noting that chondroblastoma can present in the third decade, particularly when arising in the proximal femur. [13]

The lesion size in this case, approximately 5.5 cm, exceeds the smaller lesions more commonly described in pediatric series, and the extension into the femoral neck and metaphysis adds a layer of surgical complexity, a factor specifically noted as a risk factor for local recurrence at this anatomical site. Serrano et al. identified the proximal femur among the locations most consistently associated with higher recurrence rates [14], a finding also emphasized by other investigators. [7,13,15,16]

Regarding molecular diagnostics, the H3F3B K36M mutation identified in this case is consistent with the landmark findings of Behjati et al. and subsequently validated by Amary et al., who demonstrated that this mutation is present in approximately 95% of chondroblastomas and detectable by IHC with high sensitivity and specificity. [10,17] The concurrent S-100, DOG1, and SOX9 positivity further aligns with the IHC profile described in the literature. [18]

The local recurrence at 18 months in this case is consistent with reported recurrence intervals, which range from less than 1 year to more than 4 years post-surgery. [14] Published recurrence rates following intralesional curettage range broadly from 8.3% to 38%, with the proximal femur and hip region consistently identified as high-risk sites. [15,19] The decision to avoid radiation therapy in managing the recurrence reflects the well-documented risk of malignant transformation following radiotherapy, a complication reported in both case series and the broader chondroblastoma literature. [11,13]

4. What Have We Learned from This Case?

This case reinforces several practical clinical lessons for clinicians encountering epiphyseal bone lesions in young adults. The first concerns the diagnostic trap posed by the MRI appearance of chondroblastoma. The prominent surrounding marrow edema in this patient initially suggested an infectious or inflammatory process, a pitfall well recognized in the literature. Clinicians should be aware that extensive perilesional edema is a characteristic, and sometimes misleading, feature of chondroblastoma, not a reliable indicator of malignancy or infection. When a young adult presents with hip pain, a well-defined epiphyseal lytic lesion with sclerotic margins and intralesional calcifications on plain radiography should prompt strong clinical suspicion for chondroblastoma, regardless of the MRI edema pattern or patient's age.

The second lesson concerns the indispensable role of molecular confirmation. Classic histopathology, while often sufficient, may be inconclusive in cases with overlapping features with giant cell tumor or clear cell chondrosarcoma. The H3F3B K36M mutation, as demonstrated in this case, serves as a definitive molecular anchor that resolves these diagnostic ambiguities with high sensitivity and specificity. Its routine incorporation into the workup of epiphyseal bone tumors in this demographic should be considered standard practice.

From a management standpoint, this case reinforces that the proximal femur is a high-risk site for local recurrence and that patients should be counseled accordingly. Surveillance with serial imaging, including periodic MRI, is essential, particularly during the first 2 years following surgery. The deliberate avoidance of radiation therapy in this patient was clinically sound, given the recognized risk of malignant transformation associated with radiotherapy in chondroblastoma. Finally, this case affirms that recurrence, while frustrating, does not preclude an excellent long-term outcome when managed with repeat surgery in a dedicated tumor center.

5. Conclusion

Chondroblastoma of the proximal femur in a skeletally mature adult presents a convergence of diagnostic and surgical challenges, as this case illustrates. The atypical patient age, large lesion size, metaphyseal extension, and misleading MRI edema pattern each contributed to a broad differential diagnosis that could not be resolved on imaging alone. The definitive diagnosis required the full integration of histopathology, IHC, and molecular analysis, specifically, the identification of the H3F3B K36M hotspot mutation, underscoring the critical role of specialized musculoskeletal pathology in the management of these tumors.

We present this case to highlight several clinical points of relevance. Chondroblastoma should remain in the differential diagnosis of epiphyseal lytic lesions in adults beyond the second decade of life, particularly at the proximal femur. The H3F3B K36M mutation analysis should be considered an essential component of the diagnostic workup when histopathological features are ambiguous or when the differential includes clear cell chondrosarcoma or giant cell tumor. Surgical management with extended intralesional curettage and adjuvant therapy remains the standard of care. However, the proximal femoral location demands meticulous technique and a clear long-term surveillance plan, given the elevated recurrence risk at this site. The favorable outcome achieved in this patient, including full functional recovery following two surgical interventions and no evidence of malignant transformation, reinforces the value of multidisciplinary management and structured follow-up in achieving durable disease control.

Compliance with ethical standards

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All authors make the following declarations:

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- 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 informed consent

The patient was lost to follow-up, and all attempts to reach the patient were unsuccessful. Therefore, the paper has been sufficiently anonymized to maintain patient confidentiality.

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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