GSC Advanced Research and Reviews
eISSN: 2582-4597 CODEN (USA): GARRC2
Cross Ref DOI: 10.30574/gscarr
Journal homepage: https://gsconlinepress.com/journals/gscarr/

(CASE REPORT)

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Dedifferentiated low-grade central osteosarcoma of the proximal tibia: Case report and a brief review of the literature

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GSC Advanced Research and Reviews, 2026, 27(01), 038-044

Publication history: Received on 24 February 2026; revised on 02 April 2026; accepted on 04 April 2026

Article DOI: https://doi.org/10.30574/gscarr.2026.27.1.0083

Abstract

Dedifferentiated low-grade central osteosarcoma (LGCOS) is an exceptionally rare, biphasic bone neoplasm characterized by the abrupt transition of a low-grade fibroblastic proliferation into a high-grade sarcoma. While conventional LGCOS has a favorable prognosis, dedifferentiation drastically alters the clinical course, presenting significant diagnostic and therapeutic challenges.

We report the case of a 29-year-old male who presented with progressive pain and swelling in the proximal left tibia. Initial radiographs demonstrated an ill-defined lytic lesion, but magnetic resonance imaging revealed a biphasic intramedullary mass with cortical breakthrough. A targeted core needle biopsy confirmed dedifferentiated LGCOS. The patient underwent neoadjuvant chemotherapy, achieving a suboptimal histological response (65% necrosis), followed by wide surgical resection and endoprosthetic reconstruction. Molecular analysis confirmed amplification of MDM2 and CDK4 in both tumor components. Despite adjuvant chemotherapy, the patient developed local recurrence and pulmonary metastases 18 months post-treatment, necessitating revision surgery and metastasectomy. He remains disease-free for three years following salvage therapy.

This case underscores the critical importance of advanced imaging and targeted biopsy in identifying dedifferentiated LGCOS. Furthermore, it highlights the relative chemoresistance of the high-grade component, emphasizing the need for rigorous long-term surveillance and the potential future role of targeted molecular therapies.

Keywords: Low-grade central osteosarcoma; High-grade osteosarcoma; MDM2 and CDK4 amplification; Immunohistochemical; Limb salvage surgery; Chemoresistance

1. Introduction

Osteosarcoma is a primary malignant bone tumor characterized by the production of osteoid matrix by malignant mesenchymal cells, most commonly affecting adolescents and young adults in the metaphyseal regions of long bones, particularly around the knee. [1,2] As described by Ritter et al, conventional high-grade osteosarcoma typically presents with aggressive clinical and radiographic features; however, rare subtypes such as LGCOS) pose a significant diagnostic challenge due to their indolent course and resemblance to benign fibro-osseous lesions. [1,3]

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LGCOS accounts for approximately 1–2% of all osteosarcomas and is characterized by a slow-growing intramedullary lesion composed of well-differentiated spindle cells producing osteoid. [4] Bertoni eta al demonstrated that LGCOS frequently mimics benign entities such as fibrous dysplasia, often resulting in delayed diagnosis or misclassification. [5] Despite its relatively favorable prognosis when treated with wide surgical resection [6], LGCOS carries a risk of dedifferentiation into high-grade osteosarcoma, which is associated with worse clinical outcomes, including increased metastatic potential and mortality. [6,7]

Radiographic findings are often subtle and may include cortical thickening, intramedullary sclerosis, and ill-defined margins, features that can overlap with those of benign processes. Andresen et al. highlighted that advanced imaging modalities, such as magnetic resonance imaging (MRI), may demonstrate marrow involvement and soft-tissue extension, increasing suspicion for malignancy; however, definitive diagnosis often requires histopathological evaluation, supported by molecular markers such as MDM2 and CDK4 amplification. [5,15] As emphasized by Dujardin et al, maintaining a high index of suspicion is essential when evaluating persistent or atypical bone lesions, particularly in young patients, to prevent delays in diagnosis and management. [15]

We report a case of dedifferentiated low-grade central osteosarcoma in the proximal tibia of a young adult, initially showing mild symptoms and subtle imaging, which later developed aggressive pathology. This case highlights the diagnostic challenges and underscores the importance of early recognition to prevent adverse outcomes associated with dedifferentiation.

2. Case Presentation

2.1. Clinical Presentation, History, Physical Examination, Initial Laboratory Studies & Clinical Impression

A 29-year-old male presented to the orthopedic oncology clinic with a several-month history of progressive pain and swelling in the proximal left leg. He described the pain as dull and aching, initially intermittent and activity-related, but gradually evolving into a persistent discomfort present even at rest. He denied any preceding trauma. Over the preceding six to eight weeks, he had noticed a firm, enlarging soft-tissue swelling at the proximal left tibia, prompting him to seek medical attention. He reported no constitutional symptoms such as fever, night sweats, or significant unintentional weight loss. His past medical history was unremarkable, and he was not on any chronic medications. A detailed family history revealed no known hereditary bone tumors, no Li-Fraumeni syndrome, no retinoblastoma, and no familial cancer syndromes of note.

On physical examination, the patient appeared well-nourished and in no acute distress. Vital signs were within normal limits. Musculoskeletal examination of the left lower extremity revealed a firm, non-pulsatile, mildly tender mass at the metaphysis of the proximal left tibia, measuring approximately 6 to 7 centimeters in greatest dimension on palpation. The overlying skin was intact without erythema, warmth, or dilated superficial veins. The range of motion of the left knee was mildly restricted secondary to pain. The neurovascular status of the left lower extremity was intact distally.

Initial laboratory studies included a complete blood count, which was within normal limits, and a comprehensive metabolic panel, which showed no hepatic or renal abnormalities. Serum alkaline phosphatase was mildly elevated at 180 U/L. Lactate dehydrogenase was within normal range. Erythrocyte sedimentation rate and C-reactive protein were only minimally elevated. Serum calcium and phosphorus levels were unremarkable.

At this stage, the clinical impression was a primary bone lesion of the proximal left tibia in a young adult male. Due to the patient's age, metaphyseal lesion, gradual pain with swelling, and slightly elevated alkaline phosphatase, a primary bone sarcoma was the main consideration and prompted urgent imaging.

2.2. Radiographic Studies, Additional Testing & Differential Diagnosis

Plain radiographs of the left knee and proximal tibia were obtained as the initial imaging study. These revealed an ill-defined, lytic intramedullary lesion centered at the metaphysis of the proximal left tibia, with a permeative pattern of bone destruction and cortical thickening. A subtle, poorly marginated zone of sclerosis was also appreciated at the periphery, without a well-defined geographic margin. There was no evidence of a soft-tissue mass on plain film. No classic Codman's triangle or aggressive periosteal reaction was identified, which was somewhat atypical and lent initial consideration to a low-grade process; however, given the clinical picture, advanced imaging was promptly obtained.

MRI of the left tibia, with and without gadolinium contrast, demonstrated an intramedullary lesion with heterogeneous signal intensity on T1- and T2-weighted sequences, involving the proximal tibial metaphysis and extending into the

diaphysis. The lesion displayed mixed enhancement. The MRI identified areas of markedly different signal characteristics within the lesion, with a region exhibiting low-grade fibrous morphology coexisting with a separate, more aggressive-appearing component featuring cortical breakthrough and a small associated soft-tissue mass. This pattern raised suspicion of a biphasic or dedifferentiated lesion. The tumor measured approximately 9 centimeters in its long axis. A technetium-99m bone scan demonstrated intense radiotracer uptake at the proximal left tibia, with no definite evidence of additional skeletal lesions at that time. Chest CT showed no pulmonary nodules or metastatic disease. Staging was therefore consistent with localized disease.

The differential diagnosis formulated at this juncture included dedifferentiated low-grade central osteosarcoma, conventional high-grade osteosarcoma, fibrosarcoma of bone, malignant fibrous histiocytoma of bone (undifferentiated pleomorphic sarcoma of bone), desmoplastic fibroma, and, given the geographic low-grade component, the possibility of a fibrous dysplasia undergoing malignant transformation was briefly entertained but was considered unlikely in the absence of ground-glass matrix and given the lesion's location, the patient's age and presentation.

2.3. Multidisciplinary Tumor Board Discussion, Biopsy & Diagnosis

The case was presented at the multidisciplinary musculoskeletal tumor board, attended by orthopedic oncology, medical oncology, radiation oncology, musculoskeletal radiology, and pathology. The board reviewed the imaging findings in detail, noting the radiographic and MRI evidence of a biphasic intramedullary lesion with distinct low-grade and high-grade components. Discussion centered on several critical issues: the need for tissue diagnosis before any definitive treatment, the optimal biopsy approach, the role of neoadjuvant chemotherapy given the suspected high-grade component, and the feasibility of limb-salvage surgery. The board unanimously recommended a CT-guided core needle biopsy of the proximal left tibia, with sampling directed at both radiographically distinct components of the lesion to ensure adequate tissue for histological, immunohistochemical (IHC), and molecular analysis.

The biopsy was performed without complication. Histopathologic examination of the core needle biopsy specimens revealed a biphasic neoplasm: one component demonstrated a low-grade spindle cell proliferation with mild cytologic atypia arranged in fascicles with a collagenous stroma, consistent with low-grade central osteosarcoma, while an adjacent and histologically distinct component showed a high-grade pleomorphic sarcoma with overtly malignant osteoid production, consistent with high-grade osteosarcoma. The pathologic diagnosis rendered was dedifferentiated central low-grade osteosarcoma (LGCOS).

2.4. Management, Pathology, IHC, Molecular Studies, Final Diagnosis & Initial Follow-Up

Following the tumor board's recommendations and the biopsy-proven diagnosis of dedifferentiated LGCOS, the multidisciplinary team initiated neoadjuvant chemotherapy prior to definitive surgical resection. The patient received three cycles of a standard high-grade osteosarcoma protocol consisting of cisplatin, doxorubicin, and high-dose methotrexate with leucovorin rescue. He tolerated the regimen with manageable toxicity, including grade 2 mucositis and transient myelosuppression, both of which resolved with supportive care. Repeat MRI following neoadjuvant therapy demonstrated a modest reduction in the soft-tissue component, with no new osseous lesions identified.

The patient subsequently underwent limb salvage surgery with wide resection of the proximal left tibia and reconstruction with a modular endoprosthetic replacement of the proximal tibia, including reconstruction of the extensor mechanism. Surgical margins were confirmed to be wide and negative on intraoperative frozen section analysis.

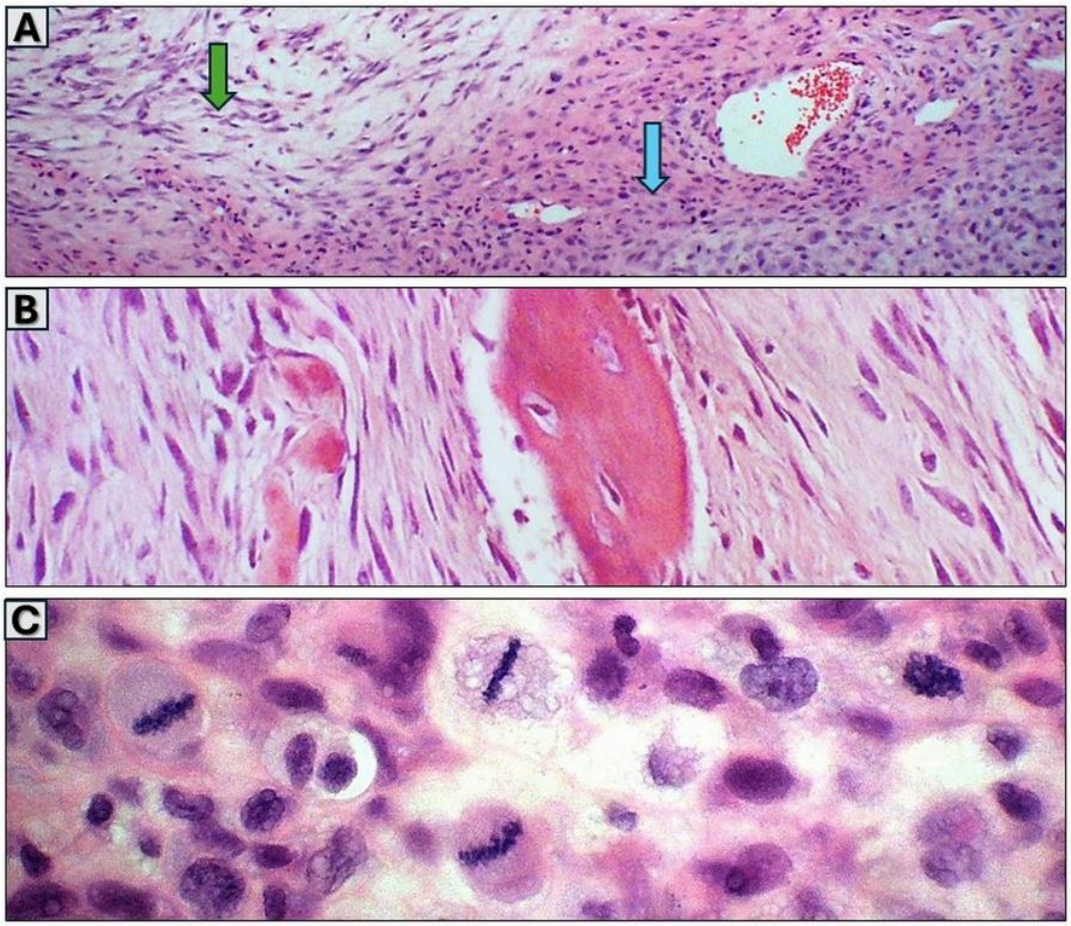
Definitive histopathologic examination of the resected specimen confirmed the presence of two morphologically distinct components. The low-grade component demonstrated hypocellular spindle cell proliferation arranged in a storiform-to-fascicular pattern within a collagenous stroma, with minimal nuclear pleomorphism and rare mitotic figures, consistent with low-grade central osteosarcoma. About 55% of the tumor consisted of highly atypical pleomorphic cells with frequent abnormal mitoses and irregular high-grade osteoid, indicating high-grade osteosarcoma arising from a low-grade precursor, a defining feature of dedifferentiation. (Figure 1 A, B, C) The percentage of tumor necrosis in the resected specimen following neoadjuvant therapy was assessed at approximately 65 percent, which was interpreted as a suboptimal but partial histological response.

IHC analysis demonstrated diffuse vimentin positivity and focal SATB2 expression in both components, supporting osteogenic differentiation. MDM2 protein overexpression was demonstrated by IHC in the low-grade component, correlating with gene amplification. CDK4 immunostaining was similarly positive. Fluorescence in situ hybridization (FISH) molecular studies confirmed amplification of the chromosomal region 12q13–15, encompassing both the CDK4 and MDM2 genes, molecular findings diagnostic of low-grade central osteosarcoma and definitively distinguishing this

entity from other low-grade bone lesions. The final integrated diagnosis was dedifferentiated LGCOS of the proximal left tibia, pT2bNxMx.

Postoperatively, the patient completed three additional cycles of adjuvant chemotherapy with cisplatin and doxorubicin. He was enrolled in a structured surveillance program consisting of clinical examinations, plain radiographs of the operative site, and chest CT at 3-month intervals for the first 2 years.

2.5. Outcome, Recurrence, Metastasis, Repeat Tumor Board, Treatment & Three-Year Status



1A: Low power view showing biphasic morphology, low-grade component (Green arrow), and high-grade component (blue arrow) (H&E X20).; 1B: High power view showing low-grade component with hypocellular spindle cell proliferation arranged in a storiform-to-fascicular pattern within a collagenous stroma, minimal nuclear pleomorphism, and rare mitotic figures—malignant bone formation in the center (H&E X40).; 1C: High power view showing morphological details of the high-grade component with highly atypical pleomorphic cells with frequent abnormal mitoses (H&E X60).

Figure 1 Microscopic examination of the excised dedifferentiated low-grade central osteosarcoma (LGCO)

Approximately eighteen months following completion of adjuvant chemotherapy, surveillance imaging identified a lytic lesion at the site of the proximal tibial endoprosthesis consistent with local recurrence, as well as two new pulmonary nodules on chest CT, the largest measuring 1.4 centimeters, highly suspicious for pulmonary metastases. CT-guided biopsy of the lung nodule confirmed metastatic high-grade osteosarcoma consistent with the prior dedifferentiated component. The case was re-presented to the multidisciplinary tumor board.

The board deliberated on several clinical challenges: the management of simultaneous local recurrence and distant metastatic disease, the extent of prior chemotherapy exposure, and the patient's performance status. Recommendations included surgical excision of the local recurrence, revision of the endoprosthesis to achieve negative margins, and systemic second-line chemotherapy. The patient underwent revision surgery with excision of the recurrent tumor and endoprosthetic revision, achieving negative margins confirmed on final pathology. Pulmonary metastasectomy was subsequently performed via video-assisted thoracoscopic surgery (VATS), with complete resection of both pulmonary nodules.

Systemic therapy was initiated with ifosfamide and etoposide, which the patient received for four cycles. He tolerated treatment with grade 3 hematologic toxicity requiring growth factor support. Following completion of chemotherapy, surveillance imaging demonstrated no evidence of residual or new metastatic disease.

Three years following treatment of recurrence and metastasis, the patient remained alive with no evidence of disease on the most recent imaging surveillance. Functional outcomes with the revised endoprosthesis were satisfactory, and the patient had returned to activities of daily living with moderate functional limitation.

3. Discussion

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

Low-grade central osteosarcoma (LGCOS) is a rare, malignant, bone-forming neoplasm that originates within the intramedullary cavity, accounting for only 1% to 2% of all osteosarcomas. [8] According to the 2020 World Health Organization (WHO) classification of bone tumors (5th edition), LGCOS is characterized as a fibroblastic bone-forming tumor with mild nuclear atypia and well-formed neoplastic trabeculae. [5,9] The disease predominantly affects young adults, with a peak incidence in the third decade of life and exhibits a slight female predilection. [8,10] It most frequently arises in the metaphysis or metadiaphysis of long bones, particularly the distal femur and proximal tibia. [8] While the exact etiology remains unknown, LGCOS is cytogenetically defined by supernumerary ring chromosomes harboring amplifications of the 12q13-15 region, which includes the MDM2 and CDK4 genes. [2,11] Clinically, patients typically present with an insidious onset of progressive pain and swelling that may persist for months or even years before diagnosis. [8] Although LGCOS is generally associated with an excellent prognosis with wide surgical resection, a critical subset of these tumors undergoes dedifferentiation, an abrupt transition into a high-grade sarcoma, which drastically alters the clinical course and necessitates a more aggressive, multidisciplinary therapeutic approach. [2,12]

3.2. Pathogenesis, Pathophysiology

The pathogenesis of LGCOS is fundamentally driven by the amplification of the 12q13-15 chromosomal region. This genetic hallmark distinguishes it from benign fibro-osseous mimics such as fibrous dysplasia. [2,13] This amplification leads to the marked overexpression of the MDM2 and CDK4 proteins. MDM2 functions as an E3 ubiquitin ligase that binds to and degrades the p53 tumor suppressor protein, thereby inhibiting apoptosis and promoting cellular survival. [2] CDK4 is a cyclin-dependent kinase that promotes cell cycle progression from the G1 phase to the S phase; its overexpression can lead to uncontrolled cellular proliferation. [2] Together, these molecular aberrations sustain the indolent growth of the low-grade spindle cell proliferation and neoplastic osteoid formation characteristic of LGCOS. [13] Dedifferentiation occurs when this low-grade precursor acquires additional, yet incompletely understood, genetic mutations, leading to an abrupt morphological and biological transformation into a high-grade, pleomorphic sarcoma. [2,12] This high-grade component exhibits aggressive local tissue destruction, cortical breakthrough, and a high propensity for hematogenous metastasis, most commonly to the lungs, thereby dictating the tumor's aggressive clinical behavior and poorer prognosis. [2,14]

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

The presented case of a 29-year-old male with dedifferentiated LGCOS of the proximal tibia aligns with the established epidemiological profile, as the tumor occurred in a young adult and involved a classic metaphyseal location. [8] Consistent with the literature, the initial radiographic presentation lacked aggressive features such as a Codman's triangle, which often leads to diagnostic delays or misinterpretation as a benign lesion. [8,13] However, the MRI findings of a biphasic lesion correctly raised suspicion for dedifferentiation, a phenomenon reported to occur synchronously in approximately 17% to 20% of LGCOS cases. [2,12] A key clinical red flag is the presence of cortical breakthrough or a soft-tissue component in an otherwise low-grade appearing lesion, which should raise suspicion for dedifferentiation.

Histologically and molecularly, our case demonstrated the classic MDM2 and CDK4 amplifications in both the low-grade and high-grade components, confirming the clonal relationship between the two distinct morphologies. [2,13] Therapeutically, the management of dedifferentiated LGCOS remains challenging. While wide surgical resection is the definitive treatment for conventional LGCOS, the presence of a high-grade component typically prompts the use of neoadjuvant and adjuvant chemotherapy, mirroring protocols for conventional high-grade osteosarcoma. [2,14] In our case, the patient exhibited a suboptimal histological response (65% necrosis) to neoadjuvant chemotherapy. This reflects findings from recent systematic reviews and comparative studies, which indicate that dedifferentiated LGCOS often shows a poorer histological response to standard chemotherapy than conventional osteosarcoma, and that adding chemotherapy may not significantly improve overall survival in these patients. [2,12] Furthermore, the patient's

subsequent development of local recurrence and pulmonary metastases underscores the aggressive biological behavior of the dedifferentiated component, which dictates the ultimate prognosis. [2,14]

4. What Have We Learned from This Case?

This case highlights several critical clinical insights into the management of dedifferentiated LGCOS. Diagnostically, it highlighted the paramount importance of advanced imaging, particularly MRI, in identifying biphasic tumor components when plain radiographs suggest a low-grade or indeterminate process. A key diagnostic lesson was the necessity of targeted, image-guided core needle biopsies to ensure adequate sampling of both the low-grade and aggressive-appearing regions, preventing the misdiagnosis of a purely benign or low-grade lesion.

A significant red flag for clinicians is the presence of cortical breakthrough or an associated soft-tissue mass in a radiographically "low-grade" intramedullary lesion, which should immediately raise the suspicion of dedifferentiation. Regarding management, this case reinforced the literature indicating that the high-grade dedifferentiated component often exhibits relative chemoresistance, as evidenced by the suboptimal histological response to standard neoadjuvant therapy. [2,12] These challenges highlight the reliance on conventional osteosarcoma chemotherapy protocols and underscore the urgent need for novel, targeted therapeutic strategies, potentially utilizing MDM2 or CDK4 inhibitors. Finally, the occurrence of late local recurrence and pulmonary metastases emphasizes the absolute necessity of rigorous, long-term oncologic surveillance, as the dedifferentiated component dictates a high-risk clinical course that requires prompt, aggressive surgical salvage when recurrence occurs.

Abbreviations

- Low-grade central osteosarcoma (LGCOS),
- Immunohistochemical (IHC)

5. Conclusion

This case report detailed rare presentation of dedifferentiated low-grade central osteosarcoma of the proximal tibia, illustrating the complex clinical, radiographic, and histomolecular features of this biphasic neoplasm. We presented this case to emphasize the diagnostic pitfalls associated with LGCOS and to highlight the critical role of multidisciplinary evaluation, advanced imaging, and molecular pathology, specifically MDM2 and CDK4 amplification, in achieving an accurate diagnosis. Furthermore, this report added value to the medical community by documenting the tumor's relative resistance to standard neoadjuvant chemotherapy and its aggressive metastatic potential. By sharing these findings, we aim to reinforce the necessity for meticulous biopsy techniques, underscore the importance of prolonged postoperative surveillance, and stimulate further research into targeted therapies for patients harboring this challenging and aggressive variant of osteosarcoma.

Compliance with ethical standards

Acknowledgments

Special thanks to Nyla Lindo, Nadin Abboud, and Kayla Addai for their assistance in reviewing the final manuscript. Additionally, we appreciate the assistance of Grammarly's language editor and the Claude Sonnet 4.6 program, which provided valuable writing support by identifying and correcting errors in grammar, spelling, punctuation, and writing style, ultimately enhancing the manuscript.

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.

Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

Statement of informed consent

This study was conducted as a retrospective review of archival pathology material collected during routine clinical care. All data were fully de-identified prior to analysis. No patient contact or intervention was involved, and informed consent was not required in accordance with institutional policies.

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