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(CASE REPORT)

Primary retroperitoneal extra-skeletal osteosarcoma with synchronous pulmonary metastases: A case report and literature review

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Abstract

Extraskeletal osteosarcoma (ESOS) is a rare high-grade malignant mesenchymal neoplasm characterized by the production of osteoid, bone, or chondroid matrix by malignant cells without direct attachment to bone or periosteum.

We report a 54-year-old man who presented with two months of progressive abdominal pain, early satiety, abdominal fullness, and weight loss. Cross-sectional imaging revealed a 12-cm necrotic retroperitoneal mass invading the left psoas muscle and multiple bilateral pulmonary nodules. Core biopsy showed pleomorphic spindle cells with marked atypia, brisk mitotic activity, and malignant osteoid. SATB2 and osteocalcin positivity supported osteoblastic differentiation, while the negative epithelial, neural, and MDM2 immunophenotype helped narrow the differential diagnosis; biopsy of a pulmonary nodule confirmed metastatic ESOS. Sequencing identified a complex karyotype without a therapeutically actionable alteration.

After multidisciplinary review, the patient received neoadjuvant doxorubicin, cisplatin, and high-dose methotrexate, with a 30% reduction in the primary mass. He subsequently underwent negative-margin en-bloc resection requiring partial nephrectomy and psoas resection, followed by adjuvant therapy. Progressive pulmonary disease, followed by hepatic and osseous metastases, developed despite metastasectomy and second-line treatment; he died 14 months after diagnosis.

This case illustrates the diagnostic complexity, limited durability of response, and aggressive metastatic biology of retroperitoneal ESOS despite intensive multimodal treatment.

Keywords: Extraskeletal Osteosarcoma; Retroperitoneum; Malignant Osteoid; Synchronous Pulmonary Metastases; Metastatectomy; Neoadjuvant Chemotherapy

1. Introduction

Extraskeletal osteosarcoma (ESOS) is a malignant soft-tissue neoplasm defined by tumor-cell production of osteoid or bone in the absence of direct skeletal or periosteal attachment. [1] It represents fewer than 1% of soft-tissue sarcomas and approximately 2–4% of osteosarcomas. [1,2] In contrast with conventional osteosarcoma of bone, ESOS generally affects adults in the fifth to seventh decades and most often arises in deep soft tissues of the extremities; the abdomen and retroperitoneum are less common but well-recognized sites. [2,3]

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Retroperitoneal disease is especially challenging because the capacious anatomic space permits substantial tumor growth before symptoms such as pain, early satiety, abdominal fullness, or weight loss prompt investigation. [4] Imaging may demonstrate a heterogeneous, necrotic, or mineralized mass, but these features are not diagnostic. [1,5] Definitive classification requires demonstration of malignant osteoid produced by neoplastic cells, exclusion of a primary osseous tumor, and careful assessment for mimics.

In the retroperitoneum, the most consequential pitfall is dedifferentiated liposarcoma with osteosarcomatous differentiation, which may require targeted MDM2/CDK4 assessment and extensive sampling. [1,4] Complete resection is central when feasible; however, evidence for chemotherapy, radiation, and metastasectomy remains limited to heterogeneous retrospective studies. [2,6] We report this case to highlight the diagnostic and therapeutic challenges posed by high-grade retroperitoneal ESOS with synchronous pulmonary metastases.

2. Case Presentation

2.1. Clinical Presentation

A 54-year-old male presented with a two-month history of progressive, dull, non-radiating abdominal pain, early satiety, and a subjective sensation of abdominal fullness. He reported an unintentional weight loss of approximately 10 pounds over the same period. Initial management by his primary care physician included a trial of proton pump inhibitors for presumed dyspepsia, which provided no relief. He also underwent an abdominal ultrasound that revealed a large, indeterminate retroperitoneal mass, prompting his referral to our tertiary care center for further evaluation.

His past medical history was significant only for well-controlled hypertension, and he had no significant surgical history. He was a former smoker with a 20-pack-year history, having quit 15 years prior. His family history was non-contributory for malignancies, and he had no known history of prior radiation exposure or chronic lymphedema.

2.2. Diagnostic Workup, Imaging, and Differential Diagnosis

Physical examination revealed a firm, non-tender, deep-seated mass in the left upper quadrant, extending to the midline. There was no palpable lymphadenopathy or hepatosplenomegaly. Laboratory studies were largely unremarkable, with normal complete blood count and comprehensive metabolic panel; serum lactate dehydrogenase (LDH) and alkaline phosphatase were within normal limits.

Contrast-enhanced computed tomography (CT) of the abdomen and pelvis demonstrated a large, heterogeneously enhancing, centrally necrotic retroperitoneal mass measuring 12 cm in greatest dimension, with evidence of invasion into the left psoas muscle. The mass did not appear to be contiguous with the adjacent vertebral bodies or the pelvic bone. A CT of the chest identified several small, bilateral pulmonary nodules, highly suspicious for metastatic disease. Magnetic resonance imaging (MRI) of the abdomen delineated the mass's relationship to surrounding structures. It showed features of malignancy, including areas of hemorrhage and necrosis.

The clinical and radiological differential diagnosis was broad. It included soft tissue sarcomas (such as undifferentiated pleomorphic sarcoma, leiomyosarcoma, or liposarcoma), a gastrointestinal stromal tumor (GIST), an aggressive desmoid tumor, or a metastatic carcinoma.

2.3. Pathology and Diagnosis

A CT-guided core needle biopsy from the retroperitoneal mass was performed. Histological examination revealed a malignant neoplasm composed of pleomorphic spindle cells with marked atypia and a high mitotic rate. The definitive diagnosis was established by the presence of a malignant osteoid matrix, a dense, eosinophilic, amorphous material intimately associated with the neoplastic cells. The morphological features were mixed fibroblastic and osteoblastic. (Figure 1A, B). Immunohistochemistry (IHC) demonstrated strong positivity for SATB2 and osteocalcin, confirming the osteoblastic differentiation. The tumor cells were negative for cytokeratins, S100, and MDM2, effectively excluding carcinoma, melanoma, and well-differentiated liposarcoma, respectively. The presence of a large, rapidly growing retroperitoneal mass with pulmonary lesions in the absence of a primary bone tumor made the diagnosis of primary retroperitoneal osteosarcoma with metastatic spread to the lung.

Molecular studies, including next-generation sequencing (NGS), identified a complex karyotype with multiple chromosomal gains and losses, a hallmark of these high-grade sarcomas. Notably, no specific targetable mutations, such as those in the IDH1/2 or MDM2 genes, were identified, which further supported the diagnosis of a high-grade

conventional ESOS, distinct from its bone-based counterpart. The findings were consistent with a diagnosis of a high-grade extraskeletal osteosarcoma.

A core needle biopsy from one of the lung lesions displayed identical features to the primary retroperitoneal tumor, indicating metastatic ESOS to the lung. (Figure 2 A, B)

2.4. Multidisciplinary Tumor Board Discussion

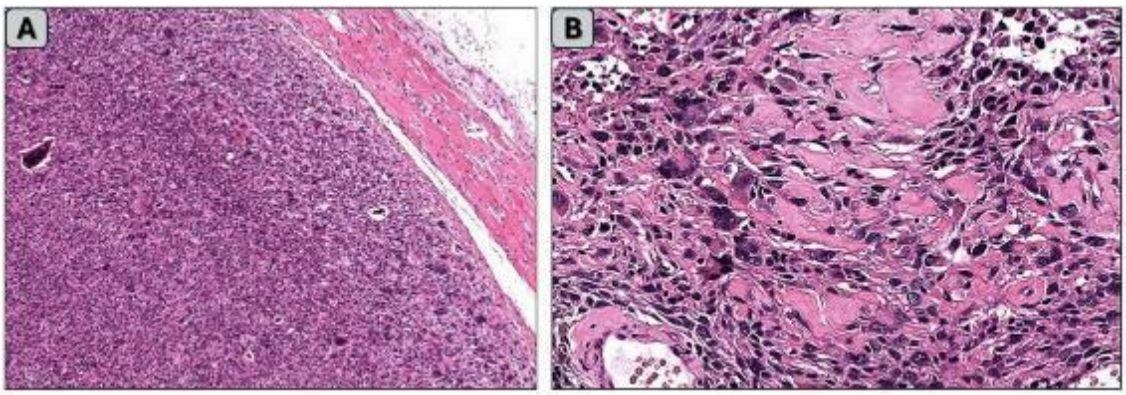
The case was presented at the multidisciplinary tumor board, attended by medical, surgical, and radiation oncologists, as well as radiologists and pathologists. The central discussion focused on the diagnostic confirmation from the biopsy, which revealed extraskeletal osteosarcoma, and the therapeutic implications of this aggressive histology in the context of synchronous limited pulmonary metastases. The team deliberated on the optimal sequence of therapy, recognizing that upfront surgery for the primary tumor would be morbid and unlikely to achieve negative margins given its size and local invasion, and would delay systemic treatment for the metastatic disease.

Given the aggressive nature of ESOS and its known chemosensitivity, especially to platinum-based agents, consensus was reached to pursue a neoadjuvant approach. The recommendation was to initiate aggressive multi-agent chemotherapy to achieve a significant response in both the primary and metastatic sites, thereby improving the likelihood of a complete surgical resection of the primary tumor and allowing for a subsequent metastasectomy. The patient was deemed a suitable candidate for this intensive regimen after a thorough performance status evaluation.

2.5. Treatment, Outcome, and Follow-up

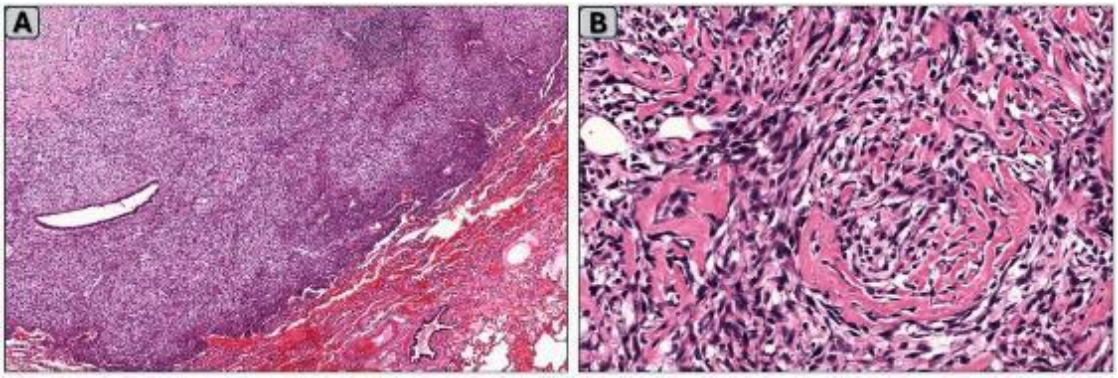
The patient commenced an aggressive neoadjuvant chemotherapy regimen consisting of doxorubicin, cisplatin, and high-dose methotrexate. Following three cycles, restaging imaging revealed a partial response, with a 30% reduction in the size of the primary retroperitoneal mass and stability of the pulmonary nodules. He subsequently underwent a complex en-bloc surgical resection of the primary tumor, which required a partial nephrectomy and segmental resection of the left psoas muscle to achieve negative margins.

After an uncomplicated recovery, the patient completed three additional cycles of adjuvant chemotherapy. Restaging scans then demonstrated a significant increase in the size and number of pulmonary metastases, indicating progressive disease. Given the oligoprogressive nature of his disease, a video-assisted thoracoscopic surgery (VATS) metastasectomy was performed to resect the most prominent nodules. However, he developed new hepatic and osseous metastases within three months. Second-line systemic therapy with gemcitabine and docetaxel was initiated but was poorly tolerated and offered only a transient response. His clinical condition deteriorated due to progressive disease and treatment-related toxicities. He was transitioned to hospice care and expired 14 months after his initial diagnosis.



1A: Low-power view showing a malignant neoplasm composed of solid sheets of pleomorphic spindle cells with marked atypia (H&E X20); 1B: High-power view showing the presence of a malignant osteoid matrix, a dense, eosinophilic, amorphous material intimately associated with the neoplastic cells, osteoblastic (H&E X40)

Figure 1 Microscopic features of Extraskeletal retroperitoneal osteosarcoma



1A: Low-power view showing similar findings to the tumor from the retroperitoneum with solid sheets of malignant osteoblasts (H&E X20); 1B: High-power view showing similar findings to the tumor from the retroperitoneum with malignant osteoid associated with malignant osteoblasts (H&E X40)

Figure 1 Microscopic features of lung metastasis from extraskeletal osteosarcoma

3. Discussion

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

Extraskeletal osteosarcoma (ESOS) was first described by Wilson in 1941, and it is now recognized as a distinct clinicopathological subtype of osteosarcoma. [3,8] It accounts for approximately 2–5% of all osteosarcomas and less than 1% of soft tissue sarcomas. [8,9] Unlike conventional skeletal osteosarcoma, which predominantly affects children and adolescents, ESOS typically occurs in adults between 50 and 70 years of age and demonstrates a slight male predominance. [9]

According to the current World Health Organization (WHO) classification, ESOS is classified as a malignant osteogenic (chondro-osseous) tumor of soft tissue with osteogenic differentiation. [10] Histologically, it is categorized into six subtypes based on the predominant morphologic pattern: osteoblastic, chondroblastic, fibroblastic, malignant fibrous histiocytic, small cell, and telangiectatic. [3] Although the lower extremities, particularly the thighs, are the most common sites of involvement, ESOS has been reported in nearly every anatomic soft-tissue location, including the retroperitoneum, trunk, abdomen, and chest wall. [3,9,11]

Most cases arise sporadically; however, prior radiation exposure, trauma, and hereditary cancer predisposition syndromes, including Li-Fraumeni syndrome, have been implicated as potential risk factors (8). Molecular studies indicate that ESOS lacks a single recurrent targetable driver mutation and is instead characterized by a complex genomic landscape with frequent alterations involving the TP53 and RB1 tumor suppressor pathways. [12]

Clinically, ESOS follows an aggressive course, with a high risk of local recurrence and early hematogenous dissemination. The lungs are the most common site of distant metastasis, followed by bone and lymph nodes. [7,9] Complete surgical excision with negative margins remains the cornerstone of treatment, while the role of perioperative chemotherapy remains controversial because the rarity of the disease limits prospective evidence.

3.2. Pathogenesis, Pathophysiology

The initiating event and precise cell of origin of ESOS remain unresolved. The tumor is thought to arise through malignant transformation of multipotent mesenchymal cells in soft tissue that acquire osteoblastic differentiation. Prior radiotherapy and antecedent trauma have been reported in a minority of cases, but most ESOSs arise de novo; these associations should not be interpreted as established causes. [1,3]

Molecularly, ESOS is characterized by genomic complexity rather than a single defining driver alteration. In a molecular series, tumors showed numerous copy-number gains and losses, with recurrent inactivation of cell-cycle and tumor-suppressor genes including CDKN2A, TP53, and RB1. [12] These alterations do not currently direct standard therapy. The present tumor's complex karyotype is concordant with this pattern. Osteoblastic differentiation produces the diagnostic malignant osteoid matrix; SATB2 and osteocalcin support this lineage but are not specific enough to establish ESOS on their own without the presence of malignant osteoid. [1] Hematogenous dissemination, particularly of the lungs, is common, but the mechanisms governing metastatic progression remain incompletely defined. [2,13]

3.3. Comparative Analysis of Our Case with Existing Literature

This patient's age, deep retroperitoneal primary, 12-cm size, high-grade morphology, and synchronous lung involvement fit the high-risk phenotype reported in the ESOS series. In Paludo et al.'s 43-patient cohort, 19% of tumors were retroperitoneal-visceral, and lung was the dominant metastatic site at presentation and first relapse. [2] The case also resembles the 2024 report by Jeo et al., in which an invasive abdominal ESOS required multivisceral resection and later recurred with pulmonary and peritoneal metastases. [8] It differs from the low-grade, nonmetastatic retroperitoneal ESOS reported by Jaipuria et al., whose patient was disease-free three years after surgery and cisplatin/doxorubicin, illustrating the prognostic importance of grade and stage. [13]

The partial primary-tumor response to doxorubicin, cisplatin, and high-dose methotrexate supported attempted resection, but subsequent rapid multiorgan progression showed that radiographic response did not predict durable disease control. Treatment evidence remains conflicting: Paludo et al. found an association between platinum-containing chemotherapy and improved outcomes, whereas Wang et al. and Liao et al. did not demonstrate a statistically significant survival benefit in their cohorts. Thus, this case supports the literature's central message: individualized multimodal treatment is reasonable for selected patients, but its ability to overcome the biology of metastatic ESOS remains uncertain.

Abbreviations

- Extraskeletal osteosarcoma (ESOS)
- Immunohistochemistry (IHC)
- Next-generation sequencing (NGS)
- Video-assisted thoracoscopic surgery (VATS)

4. Conclusion and What Have We Learned from This Case?

We report this case because it documents the full clinical trajectory of a high-grade primary retroperitoneal ESOS with biopsy-proven synchronous pulmonary metastases: initial systemic treatment and cytoreductive surgery were feasible, yet rapid multiorgan progression followed. It adds a clinically instructive example of how favorable local control and an initial radiographic response may coexist with early systemic failure in this rare disease.

The first practical lesson is diagnostic. In an older adult with a deep, enlarging abdominal or retroperitoneal mass, constitutional symptoms, and suspicious pulmonary nodules, clinicians should promptly consider high-grade sarcoma and obtain staging imaging plus a planned image-guided core biopsy before definitive surgery. Diagnosis should integrate radiology, morphology, and a focused IHC/molecular workup. Malignant osteoid and supportive osteoblastic markers must be interpreted alongside exclusion of bone origin and of retroperitoneal mimics, especially dedifferentiated liposarcoma with heterologous osteosarcomatous differentiation.

The second lesson concerns management and surveillance. Decisions regarding neoadjuvant therapy, resection, and pulmonary metastasectomy should be made in a sarcoma multidisciplinary team, balancing response, resectability, performance status, and the likelihood of occult systemic disease. The conflicting retrospective evidence for chemotherapy should be communicated candidly; an initial response should not be mistaken for proof of durable benefit.

Finally, the short interval to progression in this case reinforces the need for close cross-sectional surveillance of both the chest and abdomen after treatment. More importantly, it highlights the need for prospective registries and multi-institutional studies that can clarify treatment sequencing and identify biologically informed systemic therapies for metastatic ESOS.

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

This work did not involve any studies on human or animal subjects performed by the authors. It was a retrospective review of archival pathology material collected during routine clinical care, and all data were fully de-identified before analysis.

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

The patient expired, and all attempts to reach the family members were unsuccessful. Therefore, the paper has been sufficiently anonymized to maintain patient confidentiality.

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