

Primary Metastatic Pleural Ewing Sarcoma in a Young Adult: A Case Report and Literature Review.

Abstract

Background:

Ewing sarcoma (EWS) is a highly aggressive small round cell tumor that typically arises in bone or soft tissue. Primary pleural involvement is exceedingly rare, particularly in young adults, and its management remains challenging due to its non-specific presentation and rapid progression.

Case Presentation:

We report the case of a 20-year-old male presenting with a six-month history of progressive left laterothoracic swelling, intermittent pleuritic pain, dyspnea, and a 10 kg weight loss. Chest CT revealed a large pleural-based mass measuring 144 × 110 × 147 mm, with local chest wall invasion and multiple osteolytic metastases (ribs, D6, D8, D12, L3, sacrum, and ilium).

A CT-guided biopsy showed a small round cell tumor with diffuse CD99 expression, negative lymphoid markers, and a Ki-67 proliferation index of 60%, consistent with Ewing sarcoma.

The patient received three cycles of dose-dense VDC/IE chemotherapy with G-CSF support. Imaging showed a marked reduction in the primary pleural mass but progression of bone metastases. Despite this mixed response, treatment was continued.

During the fifth cycle, the patient developed clinical deterioration with desaturation, tachypnea, and massive pleural effusion. Ultrasound-guided thoracentesis yielded milky fluid. The patient was subsequently lost to follow-up and later died before a scheduled CT scan.

Conclusion:

Primary pleural Ewing sarcoma is an aggressive malignancy with a poor prognosis, especially when metastatic at diagnosis. This case highlights the therapeutic challenges in managing metastatic disease, with discordant response patterns and rapid clinical deterioration despite initial local control.

Keywords:

Ewing sarcoma; pleural sarcoma; primary pleural Ewing sarcoma; metastatic Ewing sarcoma; young adult; case report

30 Introduction

31 Ewing sarcoma (EWS) is the second most common primary bone malignancy in children and
32 young adults and is characterized by the pathognomonic translocation $t(11;22)(q24;q12)$,
33 resulting in the EWSR1-FLI1 fusion gene [1]. Extraskkeletal Ewing sarcoma (EES) accounts for
34 approximately 20–30% of all EWS cases and can arise in the soft tissues of the trunk,
35 extremities, retroperitoneum, and viscera [2]. Primary pleural involvement is exceptionally
36 rare, with fewer than 50 cases reported worldwide [3,4].

37 Pleural Ewing sarcoma presents a diagnostic challenge due to its non-specific clinical and
38 radiological features, often mimicking mesothelioma, lymphoma, or other small round cell
39 tumors [5]. The prognosis of metastatic EWS at diagnosis remains poor, with a 5-year overall
40 survival rate of less than 30% despite intensive multimodal therapy [6]. We report the case of
41 a 20-year-old male with primary pleural Ewing sarcoma and metastatic disease at
42 presentation, who exhibited a paradoxical response to dose-dense VDC/IE chemotherapy—
43 characterized by good local control but progression of bone metastases—and ultimately died
44 from pleural complications. We also compare our findings with previously reported cases in
45 the literature, particularly that described by Zou et al. [7].

46 Case Report

47 A 20-year-old male with no significant past medical history presented to the Medical
48 Oncology Department of Hassan II University Hospital, Fez, on April 17, 2023. His symptoms
49 had begun six months earlier following minor trauma to the left thoracic wall, after which he
50 noticed a progressively enlarging, painless laterothoracic mass. He subsequently developed
51 intermittent pleuritic chest pain, New York Heart Association (NYHA) class I dyspnea, and a 10
52 kg weight loss.

53 A chest X-ray revealed a left-sided opacity associated with lung compression. A thoracic CT
54 scan performed on February 11, 2023, demonstrated a large intrathoracic soft tissue mass of
55 pleural origin measuring $144 \times 110 \times 147$ mm (anteroposterior $\times$ transverse $\times$ craniocaudal
56 dimensions). The mass extended through the 8th and 9th left intercostal spaces into the
57 latissimus dorsi muscle. It was associated with a small left pleural effusion and a centimetric
58 midline subdiaphragmatic lymph node. Osteolytic lesions were identified in the middle arch of
59 the left 8th rib and in the vertebral bodies of D6 and D8.

60 A subsequent CT scan of the chest, abdomen, and pelvis performed on March 9, 2023,
61 revealed additional findings, including cervical lymphadenopathy (supraclavicular,
62 jugulocarotid, and submandibular), subdiaphragmatic lymph nodes, coeliac lymph nodes (up
63 to 12 mm), and further osteolytic lesions involving D12 and L3. The primary pleural mass
64 measured $149 \times 144 \times 147$ mm at this time (Figure1).

65 A CT-guided biopsy of the pleural mass was performed on February 25, 2023.
66 Histopathological examination showed an undifferentiated small round cell tumor infiltrating

the pleura. Immunohistochemistry was negative for CD20, CD3, CD30, CD45, TdT, CD10, p63, cytokeratin, and desmin, while INI1 expression was retained. Diffuse and strong membranous CD99 expression was observed, with a Ki-67 proliferation index of approximately 60%. These findings were highly suggestive of Ewing sarcoma/primitive neuroectodermal tumor (PNET). Molecular analysis by fluorescence in situ hybridization (FISH) for EWSR1 rearrangement was requested but was not available at the time of treatment initiation.

At initial clinical evaluation, the patient had an Eastern Cooperative Oncology Group (ECOG) performance status of 1 and was hemodynamically stable with no respiratory distress. Physical examination revealed a palpable swelling over the left lower posterior thoracic wall.

Given the aggressive nature of the disease, systemic treatment with dose-dense VDC/IE chemotherapy (vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide) was initiated, with granulocyte colony-stimulating factor (G-CSF) support. Treatment was generally well tolerated, with grade 2 neutropenia (without febrile neutropenia) and grade 2 asthenia.

After three cycles, restaging CT imaging demonstrated a marked reduction in the size of the primary pleural mass, which measured 100 × 90 × 102 mm, compared with the baseline pre-treatment CT scan (149 × 144 × 147 mm) (Figure 2). Regression of the left cardiophrenic lymph node was also noted (3.5 mm vs 7 mm). However, progression of bone metastases was observed, with new osteolytic lesions in the right sacral ala involving the S1 foramen and in the left iliac wing, as well as an increase in the number and size of axial skeletal lesions.

A bone scan performed early during treatment suggested progression of osseous disease, consistent with the findings observed on subsequent CT imaging.

Despite radiological progression of bone metastases, the patient showed clinical improvement, including better performance status, reduction in mass-related symptoms, and relief of pleuritic pain. In light of this mixed response, the decision was made to continue the same chemotherapy regimen. The patient ultimately received a total of five cycles. During the fifth cycle (day 15, October 30, 2023), he developed acute clinical deterioration characterized by increased mass volume, oxygen desaturation (SpO₂ 89% on room air), suprasternal retractions, tachycardia, and tachypnea.

A chest X-ray revealed a large homogeneous opacity occupying approximately three-quarters of the left hemithorax, with suspected mediastinal shift to the right, suggestive of massive pleural effusion and/or tumor progression.

The patient was transferred to the emergency department for further evaluation. Ultrasound-guided thoracentesis was attempted but yielded milky fluid despite confirmed pleural effusion on imaging, raising suspicion of chylothorax or highly cellular malignant effusion.

The patient was subsequently lost to follow-up. His family later reported that he had died before the scheduled CT scan could be performed.

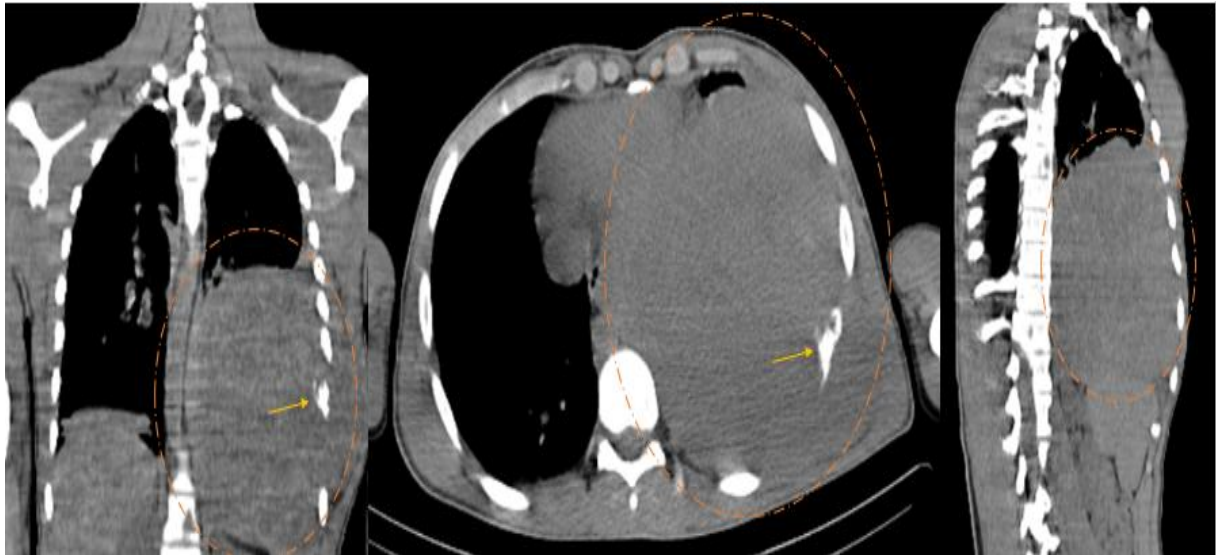


Figure 1: Baseline non-contrast CT of the chest (native scan) in the coronal, axial, and sagittal planes, showing a soft tissue mass originating from the left chest wall. The mass invades the adjacent 8th rib, which demonstrates osteolytic destruction.

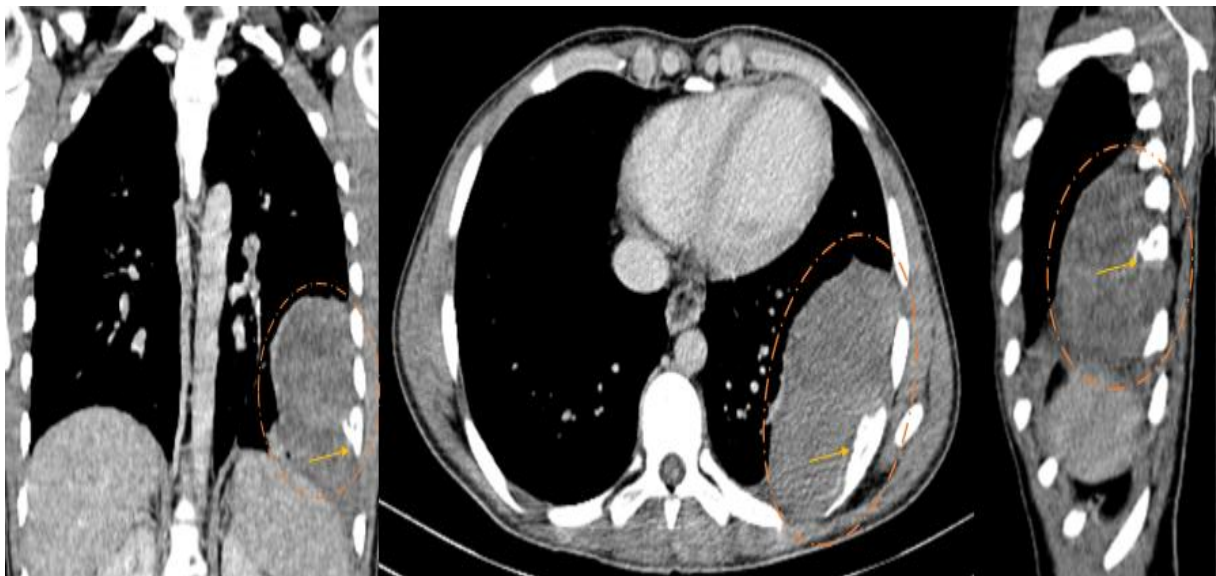


Figure 2: Interval contrast-enhanced CT of the chest (coronal, axial, and sagittal) showing a significant regression of the tumor mass, consistent with therapeutic response of the Ewing's sarcoma. Persistent osteolytic destruction of the ipsilateral 8th rib remains visible.

116 Discussion

117 We report a case of primary pleural Ewing sarcoma in a 20-year-old male with initial
118 metastatic disease who demonstrated a paradoxical response to dose-dense VDC/IE
119 chemotherapy—good local control of the primary pleural mass but progressive bone
120 metastases—ultimately succumbing to pleural complications. This case adds to the limited
121 literature on primary pleural EES, and we compare our findings with previously reported
122 cases. Zou et al. reported a case of a 14-year-old male with primary pleural EES who
123 presented with fever and dyspnea, with radiology revealing a soft tissue mass associated with
124 massive pleural effusion [7]. Despite receiving chemotherapy and radiotherapy, their patient
125 died one year after diagnosis, mirroring the fatal outcome observed in our case. This parallel
126 outcome underscores the aggressive nature of primary pleural EES, particularly when
127 associated with massive pleural effusion at presentation. Several similarities exist between
128 the two cases: both were young males (14 and 20 years old), both had pleural-based masses
129 with significant pleural involvement, both required immunohistochemistry to exclude
130 lymphoma and other small round cell tumors for diagnosis, and both patients died despite
131 receiving chemotherapy. Zou et al. emphasized that primary EES of the pleura is challenging
132 to diagnose due to its non-specific clinical and radiological features, often mimicking
133 mesothelioma, lymphoma, or other small round cell tumors [7]. In their case, diagnosis was
134 ultimately confirmed by thoracoscopy and biopsy with fluorescence in-situ hybridization
135 (FISH) detection of *EWSR1* gene rearrangement. In our patient, FISH for *EWSR1* was pending
136 at the time of treatment initiation due to logistical constraints—a common challenge in
137 resource-limited settings that is also acknowledged in the pediatric primary pulmonary Ewing
138 sarcoma case reported by Li et al., where molecular verification was not performed due to
139 socio-economic constraints and clinical urgency [12]. A case series by Weissferdt and Moran
140 reported six cases of primary pleural Ewing sarcoma, with chest pain and dyspnea being the
141 most common presenting symptoms [8]. Their series confirmed that primary pleural EWS
142 shares the same immunohistochemical profile (CD99 positivity) and molecular features as
143 skeletal EWS, and the prognosis in their series was uniformly poor, with most patients dying
144 within two years of diagnosis. Karatziou et al. described a case of extraskeletal Ewing sarcoma
145 originating from the visceral pleura in a young patient who presented with pleural effusion
146 and respiratory distress, further supporting the notion that pleural origin is associated with
147 aggressive behavior and poor outcomes [9]. In contrast to our case with extensive bone
148 metastases, Bhaskaran et al. reported a 34-year-old woman with primary pleural EES who had
149 synchronous limited metastases to mediastinal and supraclavicular nodes and a single
150 vertebra [10]. Their patient was managed with a combination of multiagent chemotherapy,
151 surgery, and radiotherapy, suggesting that patients with limited metastatic burden may
152 achieve better outcomes with aggressive multimodal therapy. Strikingly different outcomes
153 have been reported for localized disease. Munaf et al. recently reported a 23-year-old female
154 athlete with primary pleural EES who was successfully treated with surgical excision alone and
155 remains under close follow-up with no evidence of recurrence [11]. Similarly, a 10-year-old
156 girl with primary pulmonary Ewing sarcoma reported by Li et al. achieved successful surgical
157 resection following neoadjuvant chemotherapy-enabled tumor conversion, with no
158 recurrence after six adjuvant chemotherapy cycles [12]. These contrasting outcomes highlight
159 the critical importance of disease stage at diagnosis; patients with localized, resectable
160 disease have an excellent prognosis, while those with metastatic disease at presentation face
161 a uniformly poor outcome. Wolf et al. reported a 17-year-old boy with massive pleural

effusion and dyspnea as the first sign of Ewing sarcoma [13], and Ozge et al. described an 18-year-old girl with similar presentation [14]. These cases, along with ours and that of Zou et al., collectively suggest that young age, pleural origin, and massive pleural effusion may be associated with particularly aggressive behavior and poor prognosis. The pattern of metastatic spread in our patient is notable. Unlike the case reported by Bhaskaran et al. where metastases were limited, our patient presented with extensive bone metastases at diagnosis (ribs, multiple vertebral levels, sacrum, ilium), placing him in a very high-risk category. The median overall survival for metastatic EWS remains poor, with 5-year survival rates of approximately 20-30% [6]. The paradoxical response observed in our patient—good local control of the primary pleural mass with concurrent progression of bone metastases—has been described in Ewing sarcoma but is uncommon. This mixed response pattern may be explained by several hypotheses: tumor heterogeneity with clonal selection of chemoresistant bone metastatic clones, differences in the tumor microenvironment between the primary pleural site and bone (osteoblastic niche protecting metastatic cells), or inadequate drug penetration into bone metastases despite effective systemic concentrations. The final complication in our patient—massive pleural effusion with mediastinal shift—likely resulted from either rapid tumor progression or malignant pleural effusion. Zou et al. also noted massive pleural effusion in their patient, which was managed with transthoracic catheter drainage followed by thoracoscopy and biopsy [7]. In our case, ultrasound-guided thoracentesis was attempted but returned white fluid, which could represent chylothorax (due to thoracic duct compression by tumor) or a highly cellular malignant effusion. Unfortunately, the patient died before definitive imaging or drainage could be completed, underscoring the rapid and fatal evolution of this disease. The optimal management of primary pleural EES remains undefined due to its rarity. Most authors recommend extrapolating from skeletal Ewing sarcoma treatment guidelines, which include neoadjuvant chemotherapy (VDC/IE or VAC/IE), local control (surgery and/or radiotherapy), and adjuvant chemotherapy [6]. For metastatic disease, the prognosis remains poor despite intensive therapy. Recent advances, including tyrosine kinase inhibitors (such as pazopanib, regorafenib, and cabozantinib), IGF-1R inhibitors (ganitumab, cixutumumab), PARP inhibitors (olaparib, niraparib), and immunotherapy (CAR-T cells targeting GD2 or B7-H3, checkpoint inhibitors), offer hope for patients with chemoresistant metastatic Ewing sarcoma, but access to these agents remains limited in resource-constrained settings [15,16].

In conclusion, this case adds to the limited literature on primary pleural Ewing sarcoma and highlights several key lessons for clinicians. First, primary pleural EES should be considered in the differential diagnosis of pleural-based masses in young adults, particularly when associated with massive pleural effusion. Second, early molecular confirmation (FISH for *EWSR1* rearrangement) is essential for definitive diagnosis and should be prioritized. Third, the prognosis for patients with metastatic disease at diagnosis remains poor despite intensive chemotherapy. Fourth, the paradoxical response pattern—good local control but progressive metastatic disease—represents a therapeutic challenge that may require novel treatment strategies. Finally, multidisciplinary management involving medical oncology, thoracic surgery, and radiation oncology is essential for optimizing outcomes in these rare and aggressive tumors.

Conclusion

Primary pleural Ewing sarcoma is a rare and highly aggressive malignancy with a poor prognosis, particularly in the presence of metastatic disease at diagnosis. This case highlights the diagnostic and therapeutic challenges associated with this entity, including discordant treatment responses and rapid clinical deterioration. Early molecular confirmation, careful assessment of metastatic burden, and access to novel therapeutic strategies are essential to improve outcomes in these patients.

References

- [1] Grünewald TGP, Cidre-Aranaz F, Surdez D, et al. Ewing sarcoma. *Nat Rev Dis Primers*. 2018;4(1):5. doi:10.1038/s41572-018-0003-x. PMID: 29977059
- [2] Applebaum MA, Worch J, Matthay KK, et al. Clinical features and outcomes in patients with extraskeletal Ewing sarcoma. *Cancer*. 2011;117(13):3027-3032. doi:10.1002/cncr.25840. PMID: 21264836
- [3] Weissferdt A, Moran CA. Primary Ewing sarcoma of the pleura: a clinicopathologic study of six cases. *Am J Clin Pathol*. 2015;144(6):918-925. doi:10.1309/AJCP4F5GQGWWZGPYI. PMID: 26586799
- [4] Huang T, Xu Z, Liu Y, et al. Primary pleural Ewing's sarcoma: a case report and literature review. *J Cardiothorac Surg*. 2020;15(1):328. doi:10.1186/s13019-020-01371-8. PMID: 33198786
- [5] Sbaraglia M, Righi A, Gambarotti M, Dei Tos AP. Ewing sarcoma and Ewing-like tumors. *Virchows Arch*. 2020;476(1):109-119. doi:10.1007/s00428-019-02720-8. PMID: 31802229
- [6] Womer RB, West DC, Krailo MD, et al. Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group. *J Clin Oncol*. 2012;30(33):4148-4154. doi:10.1200/JCO.2011.41.5703. PMID: 23091096
- [7] Zou X, Chang W, Gao H. A primary Ewing's sarcoma of pleura: Case report and literature review. *Respir Med Case Rep*. 2021;34:101516. doi:10.1016/j.rmcr.2021.101516
- [8] Weissferdt A, Moran CA. Primary Ewing sarcoma of the pleura: a clinicopathologic study of six cases. *Am J Clin Pathol*. 2015;144(6):918-925. doi:10.1309/AJCP4F5GQGWWZGPYI
- [9] Karatzidou C, et al. A case of extraskeletal Ewing sarcoma originating from the visceral pleura. *Hippokratia*. 2011;15(4):363-365
- [10] Bhaskaran A, Sethi P, Toi PC, Penumadu P. Dilemma in diagnosis and management of rare primary pleural Ewing's sarcoma with synchronous limited metastatic disease. *BMJ Case Rep*. 2021;14(6):e243495. doi:10.1136/bcr-2021-243495
- [11] Munaf F, Shaikh A, Malik RA. When the unexpected strikes the pleura: A case of Ewing Sarcoma: Pleural Ewing Sarcoma. *Pak J Radiol*. 2025;35(4)

- 239 [12] Li B, et al. Neoadjuvant chemotherapy-enabled tumor conversion and surgical resection in
240 pediatric primary pulmonary Ewing sarcoma: a case report. *Front Oncol.* 2026;16:1723340.
241 doi:10.3389/fonc.2026.1723340
- 242 [13] Wolf M, et al. Massive pleural effusion with dyspnea in a 17-year-old boy as the first sign of
243 Ewing sarcoma. *J Pediatr Hematol Oncol.* 2002;24(5):420-422
- 244 [14] Ozge G, et al. Massive pleural effusion in an 18-year-old girl with Ewing sarcoma. *Can Respir J.*
245 2004;11(5):363-364
- 246 [15] Grignani G, Palmerini E, Dileo P, et al. A phase II trial of sorafenib in relapsed and unresectable
247 high-grade osteosarcoma after failure of standard multimodal therapy: an Italian Sarcoma Group
248 study. *Ann Oncol.* 2012;23(2):508-516. doi:10.1093/annonc/mdr151
- 249 [16] Stewart E, Goshorn R, Bradley C, et al. Targeting the DNA repair pathway in Ewing sarcoma.
250 *Cell Rep.* 2014;9(3):829-840. doi:10.1016/j.celrep.2014.09.028