CME LIVE OPEN ACCESS

Journal of
Epidemiology and Public Health

Research Article

ISSN: 3065-9078

Pleural Ewing's Sarcoma in Young Women: A Report of Two Cases and Review of the Literature

Mehdi Alem*, Sara Nejjaria, Assiya Benamar, Mounir Belcadi Abbassi, Maryam Msakem, Diango Keita, Lamiae Amaadour, Karima Oualla, Zineb Benbrahim, Samia Arifi, Touria Bouhafa and Nawfel Mellas

Department of Medical and Radiation Oncology, University of Hospital Hassan, Morocco.

Corresponding Author: Mehdi Alem, Department of Medical and Radiation Oncology, University of Hospital Hassan, Morocco.

Received: 2026 Mar 06 **Accepted:** 2026 Mar 27 **Published:** 2026 Apr 09

Abstract

Background

Ewing's sarcoma (ES) arising from the pleura is an exceedingly rare entity, accounting for fewer than 2% of all ES cases. Its rarity and non-specific clinical presentation frequently result in diagnostic delays and therapeutic challenges.

Case Presentations

We report two young female patients with histologically confirmed pleural ES managed at our institution. The first, a 25-year-old woman, presented with a large locally advanced left pleural ES and received six cycles of VIDE (vincristine, ifosfamide, doxorubicin, etoposide) neoadjuvant chemotherapy, achieving an initial response followed by metastatic progression requiring second-line gemcitabine-docetaxel. The second, an 18-year-old woman, presented with a locally advanced right latero-thoracic soft-tissue ES with pleural involvement and was treated with three cycles of VDC-IE (vincristine, doxorubicin, cyclophosphamide alternating with ifosfamide and etoposide), achieving a 73% partial response; surgical resection was declined and she was referred for consolidative radiotherapy.

Conclusion

Pleural ES is an aggressive malignancy requiring multidisciplinary management. Immunohistochemical confirmation (CD99 positivity) and cytogenetic analysis are essential for diagnosis. Multimodal treatment including chemotherapy, surgery, and radiotherapy remains the cornerstone of management. Our cases highlight the rarity of this tumor, the importance of early diagnosis, and the significant therapeutic challenges posed by locally advanced disease.

Keywords: Sarcoma, Ewing, Pleural Neoplasms, Neuroectodermal Tumors, Primitive, Peripheral, Antineoplastic Combined Chemotherapy Protocols and Thoracic Neoplasms

1. Introduction

Ewing's sarcoma (ES) is the second most common primary malignant bone tumor in children and young adults, following osteosarcoma. It belongs to the Ewing's sarcoma family of tumors (ESFT), which encompasses a spectrum of small round-cell tumors including primitive neuroectodermal tumors (PNET) and Askin tumors of the chest wall, all unified by specific chromosomal translocations predominantly involving the EWS gene on chromosome 22 [1,2].

Although ES most commonly arises in the diaphysis of long bones, primary extraskeletal ES involving soft tissues or serosal surfaces has been increasingly recognized. Pleural ES is an exceptionally rare subtype, with fewer than 100 cases reported in the world literature to date The pleural location presents distinctive diagnostic and therapeutic challenges: the tumor must be distinguished from other aggressive pleural malignancies such as malignant mesothelioma, synovial sarcoma, and metastatic carcinoma, and the extensive local involvement frequently precludes complete surgical resection [3,4].

The prognosis of extraskeletal ES remains poor, particularly in cases with locally advanced disease or metastatic dissemination. Multimodal therapy incorporating intensive systemic chemotherapy and local control through surgery

and/or radiotherapy represents the standard of care; however, the optimal treatment strategy for pleural ES has not been established given the paucity of cases [5].

Herein, we report two young female patients with histologically confirmed pleural ES managed at our institution, with a review of the existing literature regarding this rare entity. All procedures were performed in compliance with the ethical standards of the Declaration of Helsinki, and written informed consent was obtained from both patients.

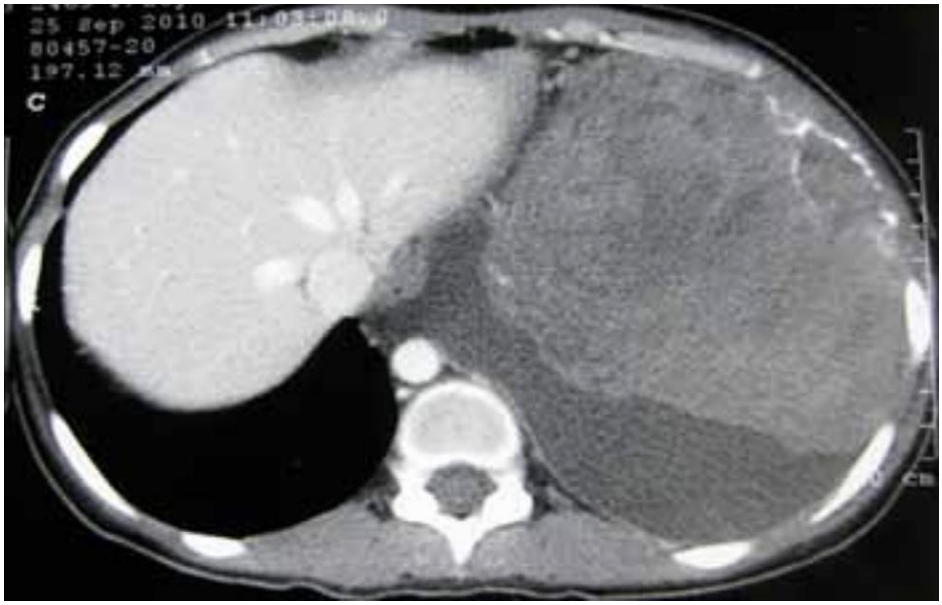

Figure 1 : Computed Tomography of the Thorax Revealing a Large Heterogeneous Soft-Tissue Mass With Gross Left Pleural Effusion, Collapse Of The Left Lung, Cortical Destruction And Expansion of the Adjacent 7th Rib

2. Case Report

2.1. Clinical Presentation

A 25-year-old woman with no significant past medical or surgical history presented with a two-month history of progressive dry cough, exertional dyspnea, and left-sided chest pain associated with weight loss. Chest radiography performed by the referring physician revealed a large left pleural effusion. She was hospitalized locally where three non-diagnostic pleural taps were performed before being referred to our center for further evaluation.

2.2. Diagnostic Work-up

On physical examination, the patient had an Eastern Cooperative Oncology Group (ECOG) performance status of 1. Computed tomography (CT) of the chest, abdomen, and pelvis demonstrated a massive left pleural process with an associated loculated pleural effusion (Fig. 1). A CT-guided pleural biopsy confirmed the diagnosis of PNET/Ewing's sarcoma of pleural location. Histological sections showed cells with scanty cytoplasm, hyperchromatic nuclei and rosette formation (Fig. 2). Immunohistochemistry (IHC) demonstrated strong and diffuse membranous CD99 positivity (Fig. 3). Fluorescence in situ hybridization (FISH) analysis for EWSR1 gene rearrangement [t(11;22)] was requested to confirm the diagnosis. A bone marrow trephine biopsy showed no medullary infiltration, and bone scintigraphy revealed no skeletal secondary lesions.

2.3. Treatment and Clinical Course

After multidisciplinary team (MDT) discussion, the patient commenced neoadjuvant chemotherapy with the VIDE protocol (vincristine 1.5 mg/m^2, ifosfamide 3 g/m^2/day for 3 days, doxorubicin 20 mg/m^2/day for 3 days, etoposide 150 mg/m^2/day for 3 days), administered every 21 days. Following three cycles, re-evaluation demonstrated a significant clinical and radiological response, and the decision was made to complete a total of six cycles before reassessing surgical feasibility.

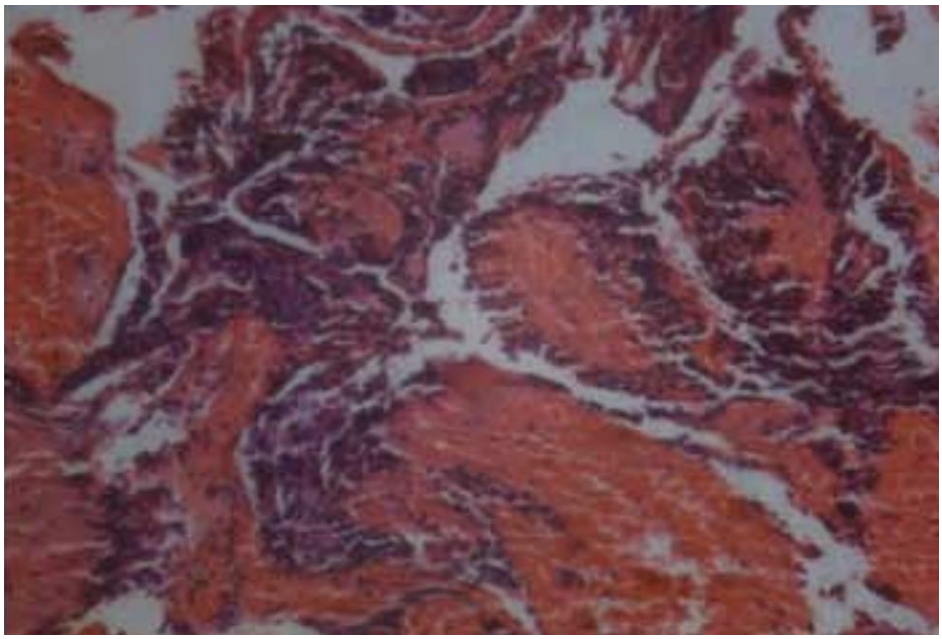

Figure 2 : Microphotograph of the Biopsy Specimen Showing Tumour Cells With Scanty Cytoplasm and Rosette Formation Haematoxylin And Eosin, ×125 Digital Magnification

After completing six cycles of VIDE, restaging CT showed apparent stability of the left pleural tumor process but with the new appearance of left pulmonary secondary nodules—consistent with frank metastatic progression. Second-line chemotherapy with gemcitabine (900 mg/m^2 on days 1 and 8) and docetaxel (75 mg/m^2 on day 8) every 21 days was initiated. The patient experienced significant haematological toxicity including grade 3 thrombocytopenia necessitating dose reductions, anaemia requiring red blood cell transfusion, and a febrile pancytopenia episode complicated by Escherichia coli bacteraemia, which was managed with broad-spectrum intravenous antibiotics with full recovery. Given the metastatic progression and cumulative toxicity, palliative care was ultimately recommended. The patient's condition deteriorated progressively and she died from disease progression.

3. Case Report

3.1. Clinical Presentation

An 18-year-old woman with no relevant personal or family medical history presented with a 12-month history of a rapidly enlarging right sub-mammary paracostal soft-tissue swelling. Initial plain radiography described a right basal pleural homogeneous opacity (Fig. 4) and recommended CT or MRI for further characterization.

Figure 3 : Immunohistochemical Analysis Demonstrating Strong Membranous Positive Staining For CD99

3.2. Diagnostic Work-up

CT of the chest, abdomen, and pelvis revealed a large right-sided pleural mass (Fig. 5). A soft-tissue biopsy performed at the referring institution showed an undifferentiated malignant small round-cell tumor consistent with Ewing's sarcoma (Fig. 6). IHC confirmed strong CD99 membrane

positivity (Fig. 7). A bone scan suggested secondary osseous involvement of the right eighth rib by contiguity, with no evidence of further distant bone metastases. Thoracocentesis drained a straw-colored exudative pleural fluid. Echocardiography confirmed preserved biventricular function with a left ventricular ejection fraction of 65%.

3.3. Treatment and Clinical Course

Following MDT discussion, chemotherapy was initiated with the alternating VDC-IE protocol: vincristine (2 mg flat), doxorubicin (75 mg/m^2), and cyclophosphamide (1,200 mg/m^2) alternating every three weeks with ifosfamide (1,800 mg/m^2/day for 5 days) and etoposide (100 mg/m^2/day for 5 days), with granulocyte colony-stimulating factor (G-CSF) support. Three cycles were completed with good clinical tolerance (ECOG PS 1), and doxorubicin was replaced by dactinomycin after the cumulative dose of 375 mg/m^2 was reached.

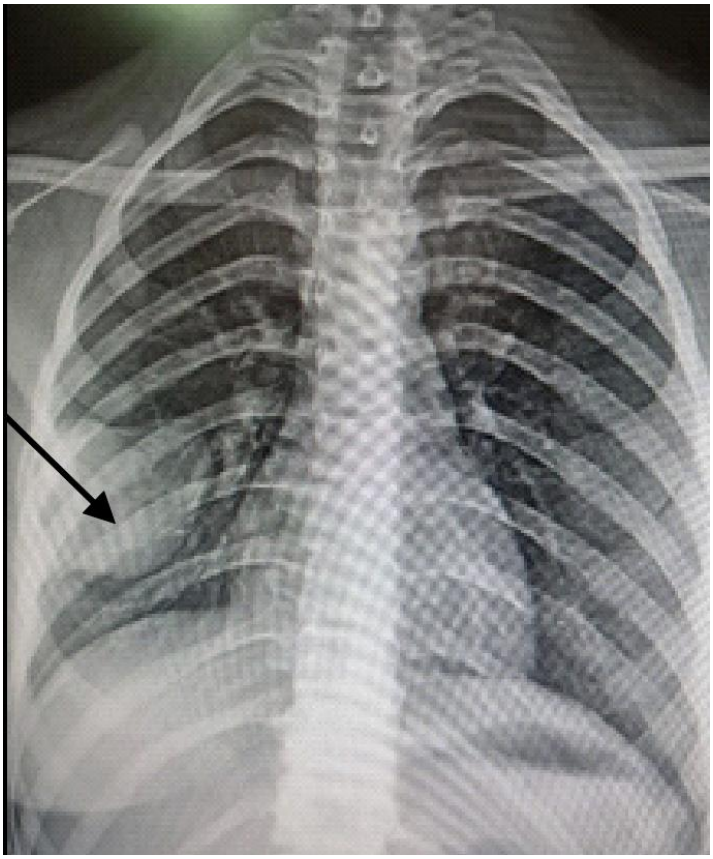

Figure 4 : Chest Radiograph Showing A Right-Sided Basal Pleural Opacity Black Arrow

Restaging CT demonstrated a marked partial response with significant regression of the primary mass (30 × 38 × 49 mm versus 115 × 111 × 89 mm at baseline a reduction of approximately 73% in longest diameter), together with partial regression of the right pleural effusion. Surgical resection was declined given the very high surgical morbidity and limited oncological benefit, and the patient was referred for consolidative radiotherapy. The patient is currently under regular follow-up.

4. Discussion

Ewing's sarcoma of the pleura is a rare and aggressive malignancy that poses substantial diagnostic and therapeutic challenges. Our two cases align with the established literature regarding the typical patient profile: young women in their second or third decade of life presenting with large, locally advanced thoracic masses. The rarity of this condition estimated at fewer than 2% of all ES cases means that most published data derive from case reports and small series, and no prospective randomized trial has specifically addressed the management of pleural ES [3-6].

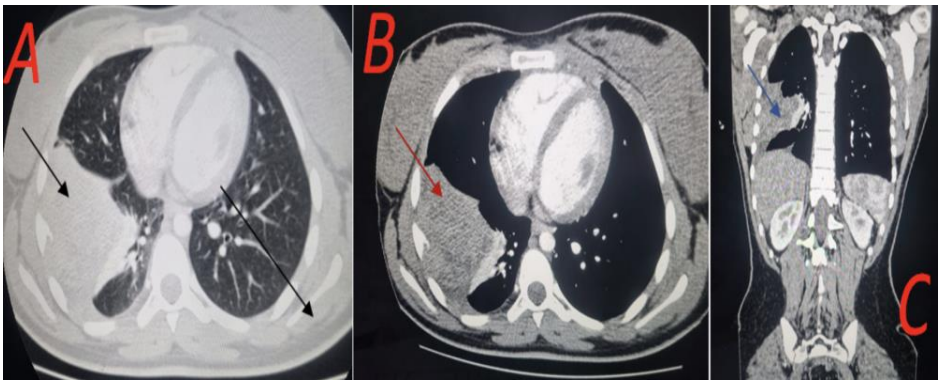

Figure 5 (A) : Parenchymal CT Section Showing A Right-Sided Pleural Mass Black Arrow 5 (B) : Mediastinal CT Section Revealing The Pleural Mass In The Right Chest (Red Arrow) Without Associated Mediastinal Adenopathy. (C) Coronal chest CT Scan Revealing The Right-Sided Pleural Mass (Blue Arrow) With Heterogeneous Enhancement After Contrast Injection

The clinical presentation of pleural ES is non-specific, with dyspnea, chest pain, and weight loss being the most frequently reported symptoms. Pleural effusion, often of large volume, is a characteristic radiological finding. CT demonstrates a large, heterogeneous, extra-pleural mass with variable osseous involvement; periosteal sunburst reaction may be identified when rib involvement is present, as in our second patient [7,8].

The definitive diagnosis of pleural ES rests on histopathological and immunohistochemical analysis. Morphologically, ES is characterized by sheets of small, monotonous round cells with scant cytoplasm, fine chromatin, and inconspicuous nucleoli, often with foci of necrosis . CD99 strong membranous positivity is the most sensitive immunohistochemical marker, present in more than 95% of ES cases; it was demonstrated in both our patients [10]. Molecular confirmation of EWSR1-ETS gene rearrangement most frequently t(11;22)(q24;q12) producing the EWS-FLI1 fusion transcript is the gold standard for diagnosis [11]. Given the morphological overlap with other small round-cell tumors of the chest, a comprehensive immunohistochemical panel is mandatory [9-12].

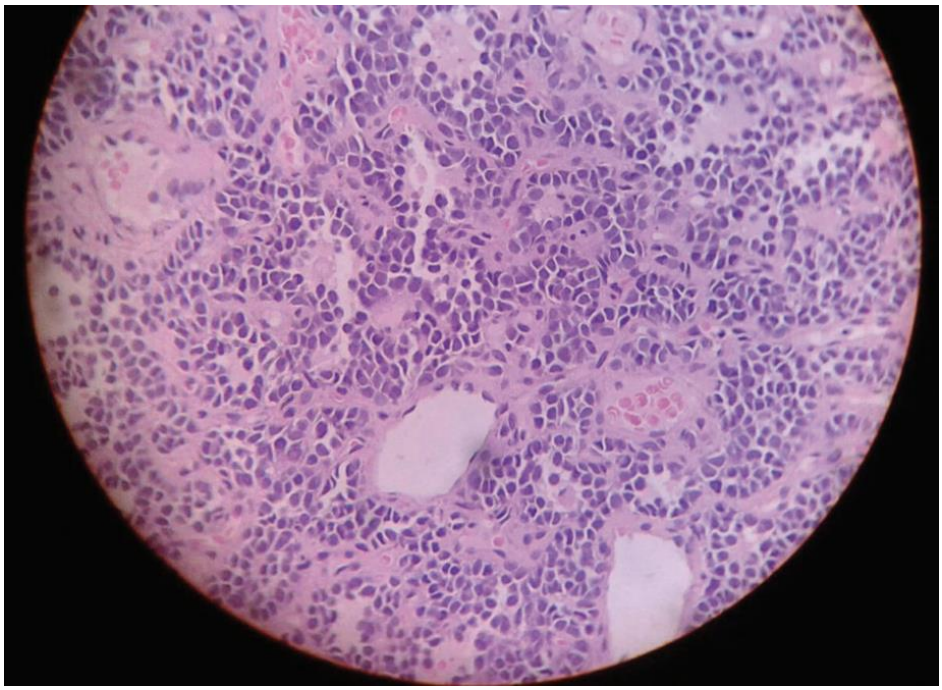

Figure 6 : Trucut biopsy From The Mass Showing Uniform Round Cells With Hyperchromatic Nuclei, Inconspicuous Nucleoli And Scanty Cytoplasm With Areas Of Necrosis, Characteristic Of A Malignant Small Round-Cell Tumour Compatible With Ewing's Sarcoma/PNET

The standard chemotherapy regimens for ES VIDE/VAIA in the European tradition and VDC-IE in the North American approach were both employed in our patients, reflecting current international guidelines. An objective clinical and radiological response was documented in both cases, consistent with published series reporting response rates of

60–80% to first-line chemotherapy in ES. Our first patient ultimately developed frank metastatic progression after six VIDE cycles, requiring second-line gemcitabine-docetaxel; this combination has demonstrated modest activity in relapsed/refractory ES, with overall response rates of approximately 17–37% in small series [13-15].

Local control in ES is achieved through surgery, radiotherapy, or a combination of both. Complete surgical resection with adequate margins is associated with improved event-free and overall survival. However, the pleural location frequently renders complete excision technically impossible or associated with unacceptable morbidity. Definitive radiotherapy to doses of 45–56 Gy represents the standard alternative for unresectable ES, with local control rates of approximately 60–70% . The delay in initiating radiotherapy in our second patient due to administrative and social barriers underscores the important role of social determinants of health in oncological outcomes in resource-limited settings [16-18].

Haematological toxicity including febrile neutropenia, anaemia, and thrombocytopenia represents the most clinically significant treatment complication, as documented in our first patient, who required transfusional support, dose reductions, and antibiotic therapy for bacteraemic neutropenic fever. These findings emphasize the importance of close haematological monitoring, prophylactic G-CSF, and prompt management of infectious complications during intensive chemotherapy [19].

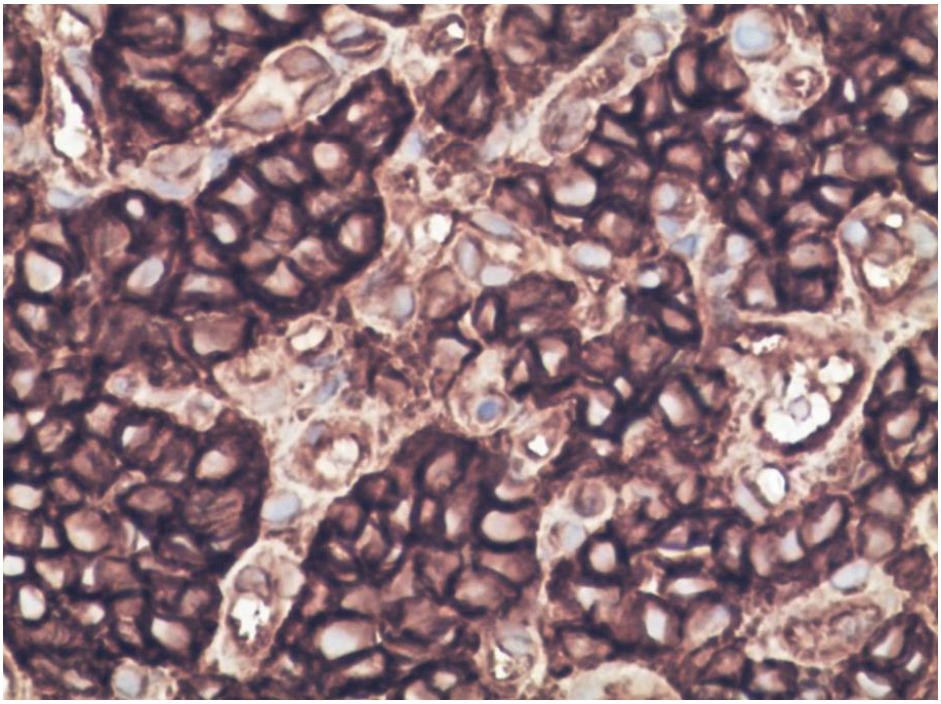

Figure 7 : Immunohistochemistry Showing Strong Membranous Positivity For CD99

The prognosis of localized ES treated with multimodal therapy is relatively favorable, with 5-year overall survival rates of 60–70%; however, metastatic or unresectable disease carries a substantially worse prognosis, with 5-year survival rates below 30% [20]. The specific prognostic impact of pleural location is difficult to assess given the small number of reported cases.

5. Conclusions

Pleural Ewing's sarcoma is an exceptionally rare and aggressive malignancy that should be considered in the differential diagnosis of young patients presenting with large thoracic masses and pleural effusion. Diagnosis requires a combination of histopathological, immunohistochemical (CD99), and molecular analyses. Multidisciplinary management incorporating intensive chemotherapy and local control through surgery when feasible, or radiotherapy for unresectable disease remains the cornerstone of treatment. Our two cases illustrate both the diagnostic challenges and the therapeutic complexity of this entity, and highlight the need for international collaborative studies to optimize treatment strategies in this rare tumor.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Generative AI and AI-assisted Technologies in the Manuscript Preparation Process

During the preparation of this work the authors used Claude (Anthropic) in order to assist with language editing and formatting. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

CRediT Author Contribution Statement

Mehdi Alem: Conceptualization, Data curation, Writing – original draft, Writing – review and editing. Sara Nejjari: Data curation, Writing review and editing. Assiya Benamar: Resources, Writing – review and editing. Mounir Belcadi Abbassi, Maryam Msakem, Diango Keita, Lamiae Amaadour, Karima Oualla, Zineb Benbrahim: Writing review and editing. Samia Arifi, Nawfel Mellas: Supervision, Writing – review and editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical Approval and Consent

All procedures were performed in compliance with relevant laws and institutional guidelines and in accordance with the ethical standards of the Declaration of Helsinki. Written informed consent was obtained from both patients (or their legal guardians) for the publication of their anonymized clinical data and images.

Data Availability

No data were used for the research described in this article.

Acknowledgements

The authors thank the medical and nursing staff of the Medical Oncology and Radiotherapy Departments at Hassan II University Hospital, Fez, for their dedicated care of these patients.

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