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Primary breast Ewing sarcoma in a young adult: diagnostic challenges and neoadjuvant chemotherapy success

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Key words: Extra-skeletal Ewing sarcoma (EES); *EWSR1/FLI1* fusion gene; breast neoplasm; neoadjuvant chemotherapy.

Abstract

Extra-skeletal Ewing Sarcoma (EES) is a malignant soft-tissue tumor morphologically indistinguishable from osseous Ewing Sarcoma (ES). The Ewing family includes ES, EES, Askin tumor, and peripheral primitive neuroectodermal tumor. About 85% harbor the t(11;22) (q24;q12) fusion by fluorescence in situ hybridization producing a chimeric protein central to pathogenesis. EES is rare, highly aggressive, and prone to recurrence, typically affecting adolescents and young adults and arising in the trunk or lower limbs; primary breast origin is exceptionally uncommon and carries a poor prognosis relative to other breast malignancies and versus other extra-skeletal ES sites. We report the case of a 37-year-old woman with a rapidly enlarging breast mass. Imaging

suggested a cyst-like lesion; a core biopsy was non-diagnostic. Wide excision established ES. She received neoadjuvant chemotherapy with complete response, followed by mastectomy. This case and literature review underscore the rarity of primary breast ES and the value of neoadjuvant chemotherapy in management.

Introduction

The Ewing family includes Ewing Sarcoma (ES), extra-skeletal Ewing sarcoma (EES), Askin tumor, and peripheral Primitive Neuroectodermal Tumor (PNET).
ES is a rare malignant neoplasm first described by James Ewing in 1921.[1-3] It most frequently arises in children and adolescents, particularly in the age group between 10 and 20 years, with a predilection for the trunk and lower limbs.[4,5] In 1975, Argevall and Ensinger described the first case of extra-skeletal Ewing sarcoma. These are highly aggressive and recurrent malignant neoplasms, once believed to originate from embryonic neural crest cells. While the exact origin remains unknown, the current hypothesis favors a mesenchymal stem cell origin.[6] ESS most commonly arises in the soft tissues of the thoracic wall, paravertebral region, retroperitoneal space, and gluteal region.[7] Clinically, they present as painless, rapidly growing masses. Initially, the histopathological diagnosis was made under the microscope based solely on the presence of small round blue cells within the neoplasm after hematoxylin-eosin staining.

Currently, the diagnosis of ES is based on a biopsy and subsequent immunohistochemical analysis, which in 85% of cases, detects a (11;22) (q24; q12) translocation through Fluorescence In Situ Hybridization (FISH). The genetic mutation underlying Ewing sarcoma involves the *EWSR1* gene located on chromosome 22 and the *FL*I gene on chromosome 11; the (11;22) translocation results in the fusion of part of the *EWSR1* gene with part of the *FLI* gene, forming the *EWSR1/FLI1* fusion gene. This somatic mutation is not hereditary and is present only in tumor cells. The chimeric protein produced by the *EWSR1/FLI1* fusion gene, known as Ewing Sarcoma Breakpoint Region 1-Friend leukemia integration 1 appears to aberrantly activate and deactivate the transcription of a variety of genes; this dysregulation of transcription processes is consequently responsible for abnormal cell proliferation, maturation, and survival, leading to the development of the neoplasm.[8,9]

In adults these tumors are exceedingly uncommon, and breast localization is exceptionally rare. In 20-25% of cases, the diagnosis is made at the metastatic phase, with the most commonly affected

organs being the lungs (10%), bone/bone marrow (10%), and other sites (5%). The prognosis for the EES of the breast is worse compared to both other malignant breast tumors and other extra-osseous Ewing sarcomas. The 5-year survival rate is less than 10% in cases treated with surgery or radiotherapy. In localized disease, a combined approach including chemotherapy yields a 5-year survival rate of approximately 60-75%, and in metastatic cases, about 20-40%.[10] In addition to standard chemotherapy regimens, new targeted therapies specifically directed against molecules implicated in the genesis and tumor progression of ES have been tested; among them we have: insulin-like Growth Factor Receptor 1 (IGF-1R), mammalian Target Of Rapamycin (mTOR), tyrosine kinases such as Platelet-Derived Growth Factor Receptor (PDGFR), Receptor Tyrosine Kinase (KIT CD 117), Epidermal Growth Factor Receptor (EGFR), Vascular Growth Factor Receptors (VEGFR), etc. These experimental therapies aim to increase survival, having achieved clinical benefits in some patients.

Here, we report a remarkably rare case of Ewing sarcoma with primary breast localization in a 37-year-old woman presenting with a progressive, palpable left breast mass. We conducted a literature review, focusing on cases with primary breast localization and the type of treatment administered, with particular attention to the pathological response following chemotherapy.

Case Report

We observed a 37-year-old woman who reported the recent discovery of a rapidly growing mass in her left breast. The patient has a significant family history of breast cancer (mother, maternal grandmother, and maternal great-grandmother). Physical examination revealed a visually protruding fibro-elastic, painless mass about 30 mm in diameter in the upper-inner quadrant of the left breast; the remaining quadrants, the right breast, and both axillary regions were clinically normal.

The patient had previously undergone a mammogram (Figure 1), which showed a bilobed opacity with a diameter of 24 mm in the left breast, and an ultrasound (Figure 2) that revealed a large, mixed hypoechoic-anecogenic area with a maximum diameter of approximately 21 mm, for which anti-inflammatory therapy and re-evaluation with ultrasound examination were prescribed.

As the mass had a predominant liquid component, a fine-needle aspiration with cytological examination was performed, yielding no neoplastic cells. Two months later, the patient returned to our department, complaining of progressive growth of the breast mass and the entire left breast, which appeared doubled in size compared to the contralateral breast at physical examination. Ultrasound examination revealed a mixed echostructure mass, resembling a “complex cyst,” from

which approximately 45 mL of bloody fluid was aspirated and stored in a tube with 96% alcohol; given the dual structure of the lesion, an ultrasound-guided core biopsy was also performed on the solid component, which unfortunately was non-diagnostic. Due to the rapid increase in the size of the breast mass, which had reached approximately 14 cm, the patient underwent wide local excision of the lesion.

Histological examination revealed a malignant mesenchymal neoplasm with epithelioid, polygonal, and occasionally spindle cells with prominent nucleoli, indistinct and partly vacuolated cytoplasm; necrosis was present in 25%, and the mitotic index was 68 mitoses/10 high-power fields (Figure 3a, b). Immunophenotypic analysis revealed positivity for CD99, ETS-RelatedGene-Integrase Interactor 1, focal positivity for FLI 1, SATB 2, smooth muscle actin, and S100, and negativity for cytokeratins AE 1/3, cytokeratin 5/6, desmin, CD 34, and CD 31. Conventional cytogenetic studies using FISH documented the absence of rearrangement of the 22q12 (EWSR1), 16p11 (FUS), Xp11.4 (BCOR), 19q13.2 (CIC), and 18q11 (SS18) loci. The immunophenotypic and molecular findings were initially interpreted as compatible with an undifferentiated round cell sarcoma (Ewing-like). Due to the significant family history of breast cancer, the patient was referred for genetic counseling and subsequent testing, which was positive for a *BRCA1* gene mutation. Due to excessive swelling at the surgical site associated with local hardening, a total body Computed Tomography (CT) scan with contrast was performed two weeks later, revealing several nodular formations in the left breast, the largest with a maximum diameter of 40 mm and associated deformation of the overlying skin profile; no abnormalities were noted in other body sites.

Following an oncological consultation at another facility, the patient was started on a Vincristine, Adriamycin, Ifosfamide (VAI) chemotherapy regimen administered for three cycles at reduced doses with progressive objective response: the first cycle was administered at a reduced dose and the second at a further reduced dose, resulting in G4 myelotoxicity, asthenia, and fever; Ifosfamide was discontinued at the third cycle due to the onset of mental confusion and cystitis.

At the end of the third chemotherapy cycle, a total body CT scan with contrast was performed, with a negative result except for the residual known breast pathology, which had nonetheless reduced. One month later, the patient underwent surgery at another hospital for a left mastectomy *en bloc* with resection of the major and minor pectoral muscles and reconstruction with a prosthesis. No surgical and/or clinical complications were reported.

Given the absence of tumor pathology in the submitted material, the administration of three chemotherapy cycles at the maximum tolerated dose, and the subsequent complete pathological response achieved, adjuvant radiotherapy was recommended at a dose of 60 Gy over 30 sessions,

which was interrupted at the twenty-seventh session due to pain in the prosthetic area. Three months later, the patient underwent a total body CT scan with contrast, negative for disease recurrence.

Due to the *BRCA1* gene mutation, the patient underwent prophylactic oophorectomy eight months later and a skin-nipple-sparing right mastectomy with placement of a definitive implant one year and four months after the former. The patient was prescribed a follow-up schedule of breast ultrasound and total body CT scan with contrast every six months.

Nearly three years after the diagnosis of Ewing sarcoma with breast localization, the patient is in good general health, and follow-up imaging shows no signs of local or distant disease recurrence.

Discussion

The Ewing family includes ES, EES, Askin tumor, and peripheral PNET.

ES/PNET belongs to a group of rare malignant neoplasms composed of small round blue cells, most frequently occurring in adolescents and young adults. Primary PNETs tend to favor the soft tissues of the trunk, including the thoracic wall (Askin tumor), extremities, and paravertebral region. ES and PNET are undifferentiated neoplasms, and in approximately 90% of cases, their hallmark is a t (11;22) (q24;q12) translocation identified through genetic analysis. In cases where other small round cell neoplasms have been excluded via immunohistochemical analysis, the expression of the cell surface antigen CD99, as in our case, is crucial in supporting the diagnosis of ES/PNET. Most patients with ES/PNET are between the ages of 10 and 20; some studies in the literature conducted on adult patients at the Royal Marsden, Memorial Sloan-Kettering, and Dana-Farber Cancer Centers have reported an average age of 24-27 years.[11,12]

In our case, the patient's age at diagnosis was 37 years, an unusual finding. Primary breast localization of ES at a young age is exceedingly rare and poses a diagnostic challenge. Differential diagnosis must consider fibroadenoma, phyllodes tumor, and carcinoma. Mammography and ultrasound do not provide specific diagnostic information: the former reveals a large, lobulated, high-density opacity; on ultrasound, the appearance ranges from a hypoechoic oval mass to a heterogeneous echogenicity mass due to the presence of necrotic areas.[13] Sometimes, such lesions have been mistakenly considered cystic and thus benign in nature,[14,15] delaying treatment. In our patient, initial ultrasound examination showed a cystic formation with hypoechoic content, mistakenly considered benign.

Wide local excision was performed, and the definitive diagnosis was provided by histopathological examination and immunohistochemical analysis. The unusual site of occurrence and the patient's age contributed to the diagnostic and, consequently, treatment delay. ES/PNET are aggressive malignant neoplasms with a high incidence of local recurrence and distant metastasis. Recommended treatment involves local disease control through an R0 surgical resection followed by adjuvant systemic treatment. Systemic chemotherapy in the treatment of localized forms has improved the 5-year survival rate from 10% to 65%;[16] the first-line chemotherapy regimen includes vincristine, adriamycin, cyclophosphamide and actinomycin D; however, an optimal combination of these drugs has not yet been established. Therapeutic management of Ewing sarcoma, including extra-skeletal and breast-localized forms, relies on an intensive multimodal strategy combining dose-dense multiagent chemotherapy with local control by surgery and/or radiotherapy. Current pediatric and young adult protocols commonly use interval-compressed Vincristine–Doxorubicin–Cyclophosphamide Alternating With Ifosfamide–Etoposide (VDC/IE) as the standard backbone for localized disease, achieving 5-year event-free survival rates around 65–75%, whereas outcomes in metastatic or relapsed presentations remain markedly poorer.[5-16] Other regimens, such as VAI or vinCRISTine iFOSFamide DOXOrubicin (VID) are also adopted, particularly in adults and in extra-skeletal primaries, with the choice of schedule influenced by age, comorbidities, and the feasibility of conservative local treatment.[5,16] In the refractory and relapsed setting, conventional salvage chemotherapy provides limited long-term disease control, and patients are increasingly considered for clinical trials exploring targeted strategies against IGF-1R/mTOR and other signaling pathways, DNA-damage-response and epigenetic regulators including Lysine-Specific Demethylase 1 inhibitors, and agents that directly or indirectly interfere with the Ewing Sarcoma Breakpoint Region 1- Friend leukemia integration 1 fusion oncoprotein.[5,9,10]
In our patient, the neoadjuvant VAI chemotherapy regimen administered for three cycles at reduced doses resulted in a progressive objective response of the disease, and the definitive post-surgical histological examination was negative for neoplasia. Primary breast localization of ES/PNET is extremely rare. A review of the literature revealed sixteen reported cases of breast-localized Ewing sarcoma (Table 1), treated with both conservative surgery and mastectomy. Of the 16 cases reported, three underwent mastectomy, with two receiving subsequent systemic chemotherapy. Seven cases underwent wide local excision/breast-conserving surgery, followed by systemic chemotherapy in four cases and Neoadjuvant Chemotherapy (NAC) in only one case. Notably, none of these patients showed experienced disease recurrence during follow-up.

The remaining six cases were treated with chemotherapy alone or combined treatment (chemotherapy and radiotherapy). Srivastava *et al*.[26] described a case of a patient who underwent

NAC with more than a 50% reduction in tumor size, followed by local excision. Suebwong *et al*.[19] and da Silva *et al*.[14] described local and systemic recurrence in patients treated with Chemoradiotherapy (CTRT), asserting that surgical treatment represents the gold standard for local disease control.

There is still no established standard treatment for breast Ewing sarcoma. The role of radiotherapy remains unclear, although it can be combined with chemotherapy to achieve local control. When negative margins can be achieved, breast-conserving surgery is equivalent to mastectomy. In our case, for diagnostic purposes, after non-diagnostic (fine needle aspiration) and ultrasound-guided core biopsy, the patient initially underwent wide excisional biopsy of the lesion. Subsequently, due to the appearance of hardening and excessive swelling at the surgical site, a total body CT scan with contrast was performed, revealing some nodular formations in the left breast. After three cycles of reduced-dose VAI chemotherapy, the patient underwent mastectomy with resection of the major and minor pectoral muscles and prosthetic reconstruction; the definitive histological examination was negative for neoplasia, and the patient underwent adjuvant radiotherapy. In retrospect, the diagnostic process in our patient might have been shortened. Although the lesion was initially interpreted as benign because of its predominantly cystic appearance, the combination of rapid breast enlargement and atypical ultrasound features should prompt early tissue diagnosis (repeat core or vacuum-assisted biopsy of the solid component) and referral to a dedicated breast or sarcoma centre in similar cases. Nevertheless, given the extreme rarity and non-specific radiologic presentation of primary breast Ewing sarcoma, a certain delay in establishing the definitive diagnosis is probably difficult to avoid in real-world practice.

At follow-up, the patient still shows no signs of disease. This case demonstrated that in large neoplasms arising in medium-small volume breasts, an R0 resection may necessitate mastectomy rather than breast-conserving surgery. Furthermore, a neoadjuvant chemotherapy regimen can represent a valid therapeutic option in cases of locally advanced neoplasms, leading to a significant reduction or, as in our patient, complete pathological response.

Conclusions

Breast-localized Ewing sarcoma is exceedingly rare, presenting both a diagnostic and therapeutic challenge. The treatment of these neoplasms involves local surgical control followed by systemic therapy. Breast-conserving surgery is equivalent to mastectomy for local disease control in small tumors in medium-large volume breasts; in small breasts, to achieve an R0 resection, demolitive

surgery (mastectomy) is required. Neoadjuvant chemotherapy may offer a valuable therapeutic strategy for locally advanced breast Ewing sarcoma, potentially improving outcomes. The multimodal approach combining chemotherapy, surgery and, in some cases, radiotherapy, is a key to optimising clinical outcomes and improving prognosis. In summary, the management of Ewing sarcoma with breast localization requires careful multidisciplinary evaluation and the adoption of personalized therapeutic strategies, considering the specific characteristics of the neoplasm and the clinical condition of the patient.

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S.no	**Case reports [references]**	**Age**	**Size (cm)**	**Treatment**
1	[11]	47	2.1×1.8	Mastectomy
2	[15]	35	1.8	Lumpectomy + CT (unspecified therapy)
3	[14]	35	12×7.5	CT (Cisplatin; Etoposide; Doxorubicin) + RT
4	[17]	36	2.5×2	Lumpectomy
5	[18]	26	3×2	WLE + CT (Vincristine; Doxorubicin; Cyclophosphamide)
6	[8]	49		CT (Doxorubicin and Cisplatin)

7	[19]	46	4	CT (Cyclophosphamide; Doxorubicin; Vincristine) + RT
8	[20]	30	7-RIGHT,5-LEFT	CT (Cyclophosphamide; Doxorubicin; Vincristine alterned with Etoposide)
9	[21]	50	10×14	Mastectomy + CT (Ifosfamide and Etoposide alterned with Vincristine, Doxorubicin and Cyclophosphamide)
10	[22]	61	6×6	CT (Protocol EFT1 2001) + RT
11	[23]	43	3cm	Breast Conservation Surgery + CT (Cyclophosphamide; Adriamicin; Vincristine)
12	[24]	35	2×2cm	MRM + CT (Vincristine; Adriamicin; Cyclophosphamide) + RT
13	[25]	14	9.5×7×5	WLE
14	[26]	25	11.6cm×9.2cm×6cm	NACT (Vincristine; Cyclophosphamide; Doxorubicina) + WLE
15	[27]	33		CT (Vincristine; Adriamicina; Cyclophosphamide)
16	[28]	55	1.8cm×1.5cm	Breast Conservation Surgery + CT (unspecified therapy)

Table 1. Summary of reported adult cases of primary breast Ewing sarcoma. Only variables that were consistently reported across the original sources (age, tumour size, and treatment) were tabulated. Outcome and duration of remission were not uniformly available in the published reports and are therefore not included. CT, Chemotherapy; RT, Radiation treatment; WLE, Wide local excision; MRM, Modified Radical Mastectomy; NACT, Neoadjuvant Chemotherapy

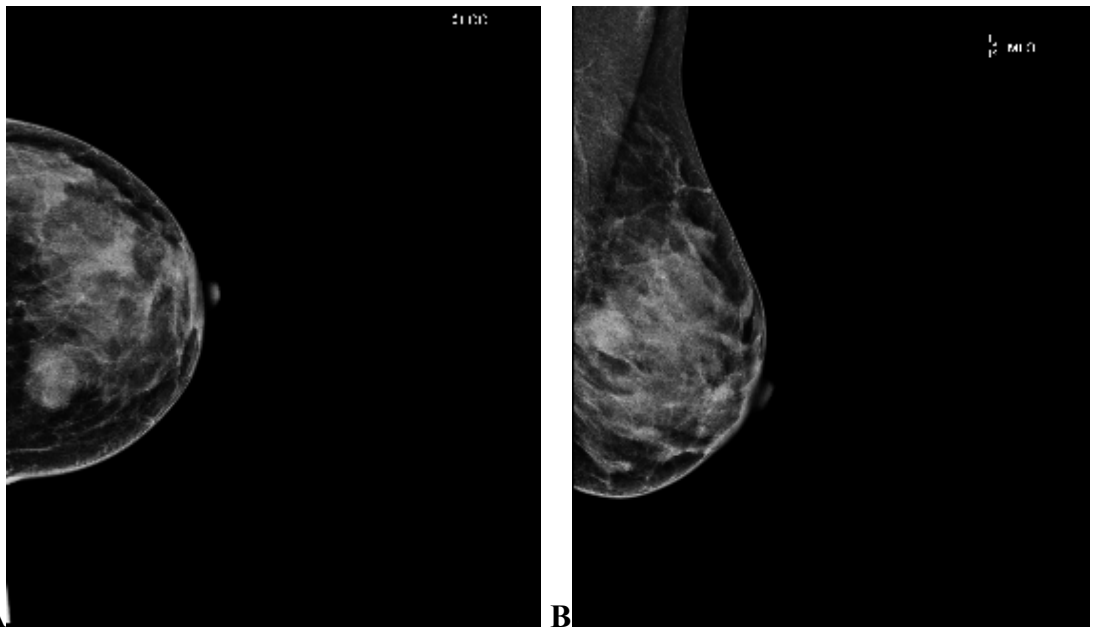


Figure 1. Mammography of the left breast. The cranio-caudal (A) and oblique medio-lateral (B) projections show a bilobed opacity to the upper-inner quadrant.

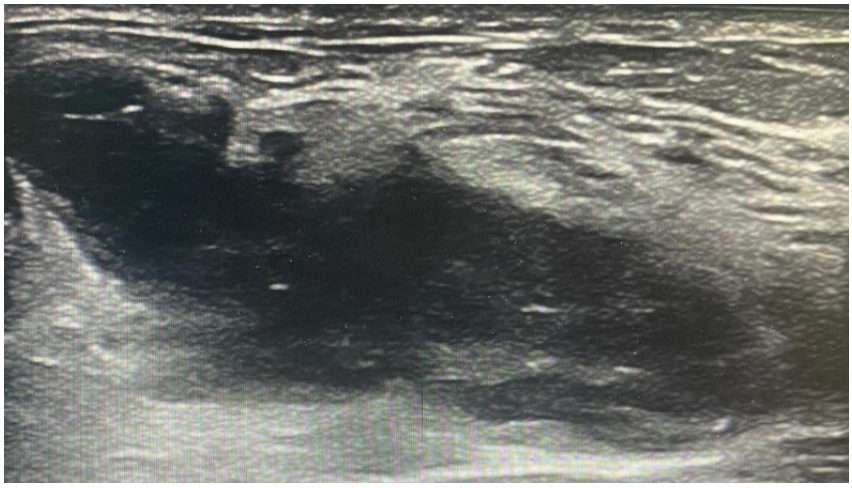


Figure 2. Ultrasound shows extensive hypo-anechoic formation.

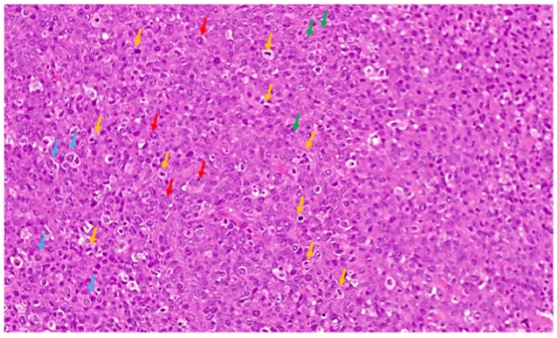
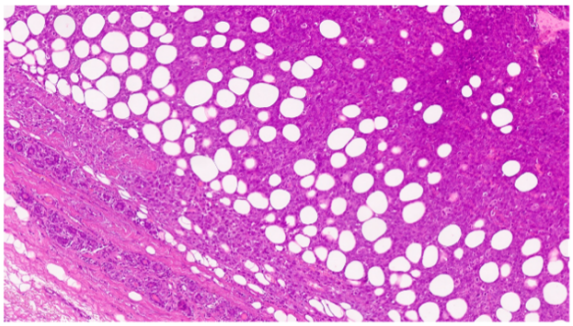
A  B 

Figure 3. Histological preparation of the lesion characterized by epithelioid, polygonal (magnification 200×) (A) and sometimes fused cells with prominent nucleolus (magnification 50×) (B). In figure A is possible to see epithelioid polygonal cells (blue arrows), occasionally spindle cells (green arrows) with prominent nucleoli (red arrows). Yellow arrows indicate mitosis. In panel B is possible to underline the invasive character of the neoplasia that invaded surrounding tissues.

Contributions: MS contributed to the concept and designed the research study. MFF, GNZ, AF, SB, GA and PV contributed to the manuscript revising. AP supervised the work. All authors equally contributed to editorial changes in the manuscript and draft preparation.

Conflict of interest: the authors have no conflicts of interest to declare.

Ethics approval and consent to participate: the patient signed the written informed consent to participate to the study, allowing the publication of anonymized data and images.

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