

# Primary paraesophageal Ewing's sarcoma: an uncommon case report and literature review

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**Abstract:** Ewing's sarcoma is a rare and highly aggressive cancer most frequently arising in people under 20 years of age. We report an uncommon case of primary paraesophageal Ewing's sarcoma in a 25-year-old male harboring the infrequent EWSR1/ERG fusion transcript with multiple splice variants coexisting in the same tumor. The patient was totally refractory to chemotherapy and died 17 months after diagnosis. We underscore the need for better understanding of the molecular pathogenesis of the disease and improved systemic therapy options.

**Keywords:** Ewing's sarcoma, recurrence, immunohistochemistry, fusion genes

## Introduction

Ewing's sarcoma is the second most frequent primary malignant bone cancer, after osteosarcoma.

It was first described by James Ewing in 1921, as an undifferentiated tumor developing in the diaphysis of the ulna of a young female patient.<sup>1</sup>

Ewing's sarcoma is a rare disease, with approximately three cases per million per year. It is slightly more common in males than in females (55/45 ratio) and its incidence is nine times greater in Caucasians than in African-Americans. Over 50% of all patients are adolescents, although 20%–30% of the cases are diagnosed in the first decade of life.<sup>2,3</sup>

The tumor typically develops in the diaphyseal portion of flat bones of the axial skeleton and in long bones. At time of diagnosis, metastases are detectable in approximately 25% of the patients. The lungs, bone, or bone marrow are usually involved, while metastatic spread to the lymph nodes, liver, or central nervous system is infrequent.

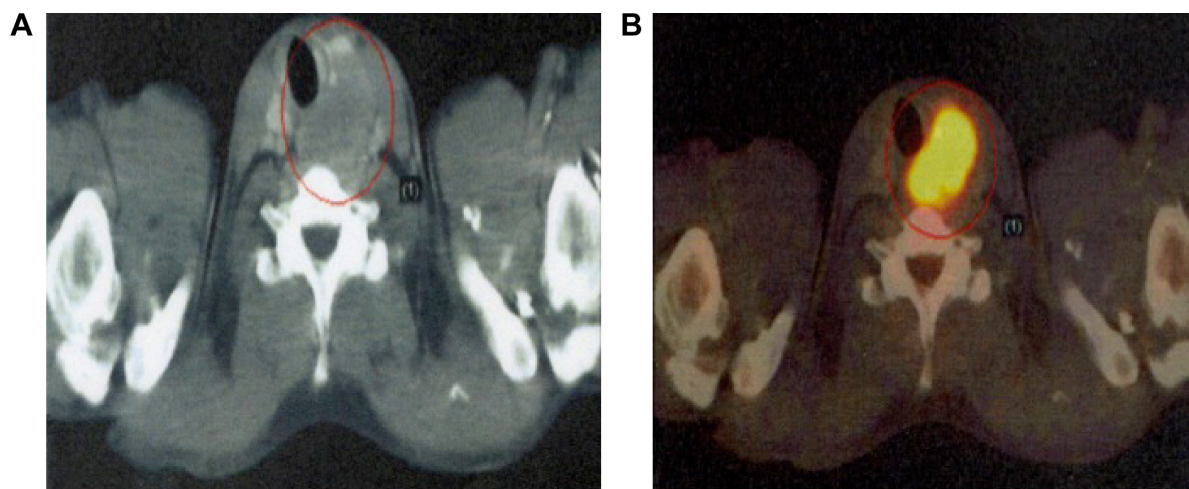
Extraskeletal Ewing's sarcoma is a very rare disease, accounting for 6%–47% of all cases of Ewing's sarcoma. It is mainly diagnosed in the trunk, extremities, retroperitoneum, and head and neck region. Patients with extraskeletal Ewing's sarcoma are more likely to be older, female, and not of Caucasian origin. An extraskeletal origin of the disease is correlated to poor prognosis.<sup>4–6</sup> We present an uncommon case of extraskeletal Ewing's sarcoma, and discuss its rare presentation and evolution. To our knowledge, this is the first reported case of paraesophageal primary Ewing's sarcoma and primitive neuroectodermal tumor.

## Case report

A 25-year-old man with a history of herpes esophagitis 6 years prior to admission presented with progressive dysphagia and a palpable and painless right cervical mass for the past approximately 5 months.

Computed tomography (CT) and F-18 fluorodeoxyglucose-positron emission tomography revealed an eccentric hypermetabolic mass (4.1×6.8 cm; SUV >12) in

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**Figure 1** Images of the tumor.

**Note:** CT (A) and positron emission tomography (B) showing a paraesophageal soft tissue mass (4.1×6.8 cm; max: 12.9 SUV).

**Abbreviations:** CT, computed tomography; SUV, standard uptake value.

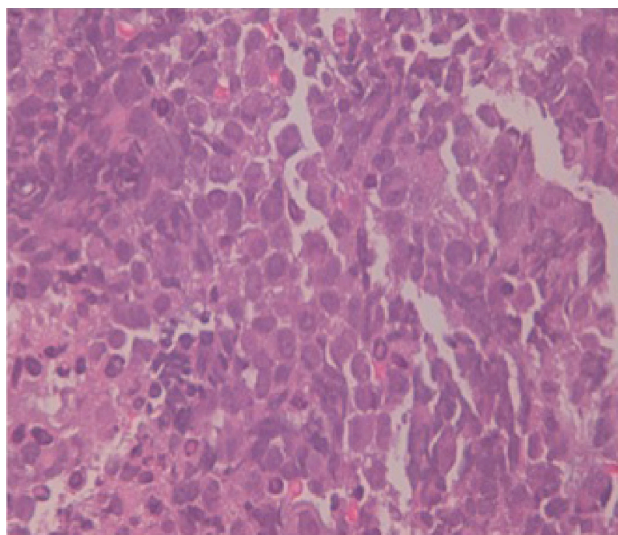
the right esophageal wall, causing an important mass effect with tracheal and esophageal deviation. Neither lymph nodes nor other organs were involved (Figure 1).

The pathology report on the neck biopsy informed of an immature neoplasm with round and basophil cell proliferation forming a diffuse infiltrate compatible with round cell malignancy (Figure 2). The immunohistochemical study revealed intense expression of CD99/MIC2 +, c-kit +, FLI-1 +, and Ki67 + in 60% of the neoplastic cells (Figure 3). The rest of the tumor markers were negative. Reverse-transcription polymerase chain reaction (RT-PCR) identified a chimeric EWSR1/ERG fusion transcript distinctive of the t(21;22)

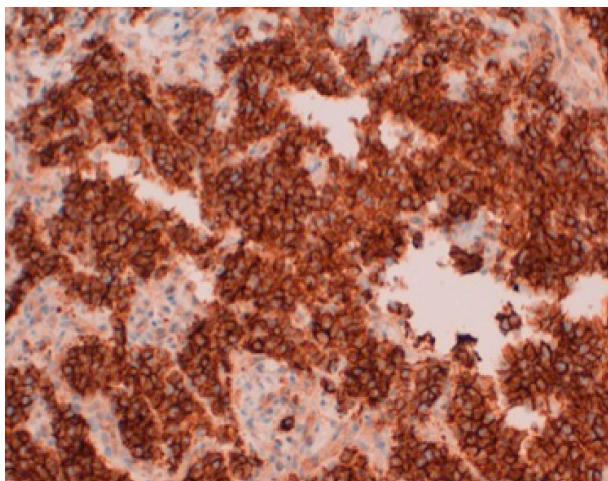
(q22;q21) translocation. To our surprise, RT-PCR revealed two splice variants coexisting within the same tumor (EWSR1(ex7)-ERG(ex6) and EWSR1(ex7)-ERG(ex7)) (Figure 4). The diagnosis of extraskeletal Ewing's sarcoma with high proliferation was confirmed.

Chemotherapy based on the therapeutic schedule vincristine, doxorubicin, and cyclophosphamide alternated with ifosfamide and etoposide every 3 weeks was administered for a total of 17 cycles. Locoregional treatment consisted of radiation therapy with a total dose of 54 Gy performed from the fourth month, while receiving concomitant chemotherapy.

Complete response after eight cycles was achieved, and the patient remained asymptomatic for 1 month after the last chemotherapy cycle. Subsequently, progressive dysphonia



**Figure 2** Glass slide stained with hematoxylin-eosin (magnification ×40), showing small, round blue and basophil cells with scant cytoplasm and large nuclei infiltrating through the paraesophageal soft tissue.



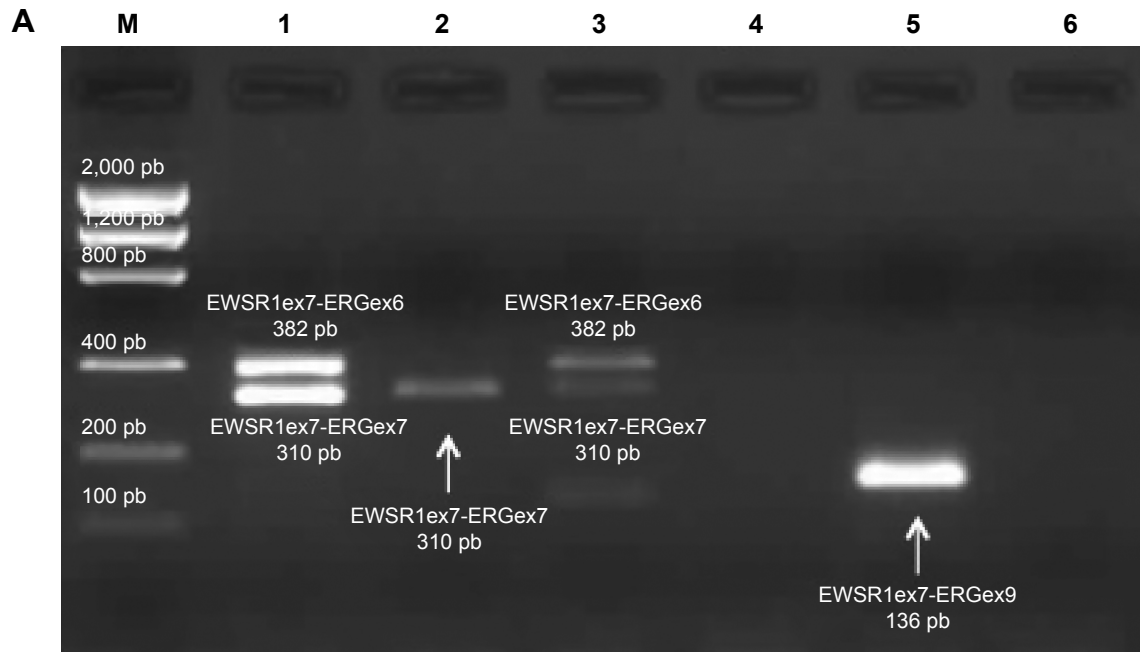
**Figure 3** Immunohistochemistry of tumor cells.

**Note:** Immunoreactivity for CD99 is strongly positive on the membrane of tumor cells.

was detected, and laryngoscopy revealed right vocal cord paralysis, while the CT scan showed a well-delimited paraesophageal mass (4.5 cm) suggesting local recurrence. The latter was confirmed by the histological study (Figure 4).

After relapse, the patient was treated with a combination of irinotecan and temozolomide. Following the first cycle, he

experienced rapid clinical progression. High-dose ifosfamide was therefore administered, with no clinical benefit after one cycle. Considering the aggressiveness of the disease, a gemcitabine-docetaxel regimen was started. The tumor remained totally refractory to chemotherapy after three cycles, with both locoregional and lung progression.



**B** Primers used for RT-PCR to detect the EWSR1-ERG fusion transcripts

Primer	Gene	Position	Sequence
EWSR1-7A	EWSR1	Exon 7	5'-TCCTACAGCCAAGCTCCAAGTCAATA-3'
ERG-9B	ERG	Exon 9*	5'-CCCAGGTGATGCAGCTGGAGTTG-3'
FLI1-6B	FLI1	Exon 6	5'-ATTGCCCAAGCTCCTCTTCTGAC-3

Translocations and resulting EWSR1/ERG transcripts amplicons tested for the RT-PCR assay

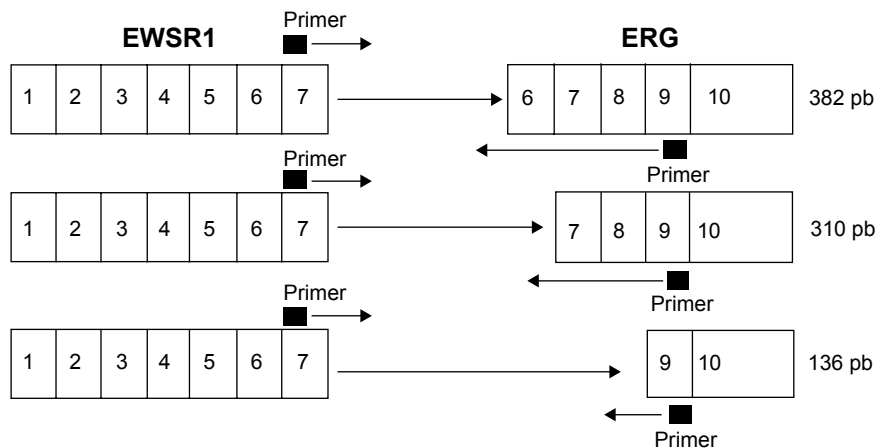


Figure 4 (Continued)



those of other small round cell tumors of childhood. For this reason, an expanded panel of immunohistochemical studies, fluorescent in situ hybridization and RT-PCR are strictly necessary to exclude other entities such as neuroblastoma, lymphoblastic lymphoma, poorly differentiated synovial sarcoma, etc.<sup>10</sup>

Typically, Ewing's sarcoma cells express glycoprotein CD99/MIC2 and may be immunoreactive for VIM, NSE, S-100 protein, Leu-7, and/or PgP 9.5.<sup>11,12</sup>

The cytogenetic aberrations leading to activation of chimeric transcription factors are the most relevant features of these tumors. Among recurrent cytogenetic alterations, the t(11;22)(q24;q12) translocation has been detected in approximately 90% of all cases, leading to fusion between the EWSR1 on chromosome 22 and the FLI1 on chromosome 11, but t(21;22)(q22;q12)(EWSR1/ERG) and others may also occur.<sup>13,14</sup>

The EWSR1 gene is one of the genes most sensitive to translocation in soft tissue tumors and encodes the EWS protein, which is a member of a growing family of highly conserved RNA-binding proteins mediating interaction with RNA or single-stranded DNA. The codified protein takes part in transcriptional regulation for specific genes and in mRNA splicing. Specifically, EWSR1 is involved in transcription initiation. Concerning EWSR1 breakpoints, the main areas susceptible to breakage are EWSR1 exons 7, 8, 9, or 10.<sup>15,16</sup> The proteins encoded by FLI1 and ERG genes are members of the ETS family of transcription factors, which represent the main gene family translocated with EWSR1, and are implicated in the control of cellular proliferation, development, and tumorigenesis.<sup>17</sup> The chimeric protein resulting from fusion interferes with different molecular pathways crucial for cell growth, differentiation and proliferation, and which are frequently involved in the pathogenesis of soft tissue tumors.<sup>18</sup>

The transcription factor Erg is necessary in definitive hematopoiesis, adult hematopoietic stem cell function, and for the upkeep of peripheral blood platelet numbers.<sup>19</sup> Chromosomal rearrangements involving ERG are found in myeloid leukemia, acute lymphoblastic leukemia, Ewing's sarcoma, and most prostate cancers. However, the normal physiological function of Erg is unknown. Approximately, 10% of all Ewing's sarcomas carry the t(21;22)(q22;q12) (EWSR1-ERG) translocation. ERG shares 68% overall amino acid identity with FLI1 and 98% identity within their ETS DNA-binding domains. Considering the structural similarities of EWSR1/FLI1 and EWSR1/ERG fusions, it is likely that the two proteins deregulate similar target genes in

Ewing's sarcoma. A retrospective study comparing EWSR1/FLI1 to EWSR1/ERG fusions in Ewing's sarcoma cases demonstrated no significant differences in pathological and clinical features, in addition to overall survival. The most common breakpoint described for EWSR1 and ERG is EWSR1 exon 7, which translocates to ERG exon 6, 7, or 9.<sup>20</sup>

Interestingly, in our patient two different fusion transcripts within the same tumor, EWSR1(ex7)-ERG(ex6) and EWSR1(ex7)-ERG(ex7), were detected. However, this circumstance is a well-known phenomenon in human tumors, such as desmoplastic small round cell tumors, synovial sarcomas, clear cell sarcomas, and ETV6-ABL1 or PML-RARA-positive leukemia. Likewise, the coexistence of multiple fusion transcripts in the same patient seems to be distinctive but atypical for Ewing's sarcoma. Of the 17 cases with different fusion transcripts within the same tumor reported in the literature, just one case exhibited splice variants derived from an ERG gene fragment, (erg-3), and the rest showed alternative splicing of exons from EWSR1 or FLI1 gene.<sup>21</sup> Thus, we present the first case reported in the literature in which two fusion transcripts in the same patient arise from splicing out of exons from the ERG gene. Two feasible explanations have been suggested to account for this phenomenon. One may be the occurrence of two distinct chromosomal rearrangements in the same patient, leading to either polyclonality of the same tumor or the unlikely development of two different Ewing's sarcomas. The second and most probable explanation would be mRNA splicing based on most of the reported cases to date.

The etiology of Ewing's sarcoma is unknown. Our patient had a history of herpes esophagitis 6 years before diagnosis of the tumor. However, the association between viral infections and Ewing's sarcoma remains unclear. There is no evidence that herpes simplex virus is related to the origin of Ewing's sarcoma. In the past, it was believed that cytomegalovirus and Epstein Barr virus could play a role in the pathogenesis of Ewing's sarcoma though no sound supporting evidence has been obtained to date.<sup>22,23</sup>

Ewing's sarcoma and primitive neuroectodermal tumor requires multimodal therapeutic strategies. The standard treatment for localized Ewing's sarcoma is similar to that used in metastatic disease, and is based on the combination of doxorubicin, cyclophosphamide, ifosfamide, vincristine, dactinomycin and etoposide, along with local therapy for 10–12 months.<sup>24</sup> The choice of local therapy includes surgery, radiotherapy, or both. The INT-0091 trial was the first randomized trial to demonstrate that there is no difference among the different local control modalities in terms of local

recurrence and event-free survival.<sup>25</sup> With surgery or radiotherapy alone, 5-year survival was <10% but on including chemotherapy, the survival rate increased by 60%–70% in localized and 20%–40% in metastatic disease. Although relevant progress has been made in the treatment of Ewing's sarcoma in recent years, patients with localized tumor disease at the time of diagnosis show a 4-year relapse rate of 20%.

Ewing's sarcoma patients presenting with recurrence or progressive disease less than 2 years from initial diagnosis present a 5-year survival of only 30%. At the same time, patients with metastatic disease at diagnosis, females, those with elevated LDH at diagnosis, and patients whose sites of first recurrence include both local and distant metastatic disease have a significantly poorer post-recurrence survival rate.<sup>26</sup>

There is no a standard treatment for refractory Ewing's sarcoma. Treatment options including irinotecan, temozolomide, ifosfamide, gemcitabine, docetaxel, etoposide, platinum or vincristine have demonstrated response rate between 29% and 66%.<sup>27–31</sup> However, many patients do not respond to these agents, and further chemotherapeutic options are limited in this setting. In the clinical setting, target cancer therapies under investigation in Ewing's sarcoma include inhibitors of the IGF-1 receptor plus an inhibitor of mTOR, which has resulted in tumor regression in approximately 25%–30% of patients with refractory metastatic disease. In turn, bevacizumab, a VEGF inhibitor, administered as monotherapy, resulted in stable disease at the most during at least 4 months in three out of five patients enrolled in the COG Phase I trial. In preclinical models of Ewing's sarcoma, a dual PI3K/AKT inhibitor and a combination of PARP inhibitors and temozolomide enhanced sensitivity to actinomycin D and synergistic effects in Ewing's sarcoma, respectively.<sup>32–35</sup> Unfortunately, the prognosis of patients with refractory or recurrent Ewing's sarcoma remains dismal. This underlines the need for further research in this field.

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## Disclosure

The authors state that they have no potential conflicts of interest.

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