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Case Report

# Ewing's Sarcoma of the Small Intestine with Liver Metastasis Mimicking Gastrointestinal Stromal Tumor

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## Abstract

Ewing's sarcoma (ES) is the second most common primary bone malignancy of childhood, whereas extraosseous ES (EES) is more common in older patients. EES of the small intestine is an extremely rare disease. We present a case of ES of the small intestine with liver metastasis mimicking a gastrointestinal stromal tumor. The diagnosis of ES requires a combination of histological, immunohistochemical, and molecular techniques. Further studies to investigate whether multimodality treatments can improve the survival of metastatic EES are needed.

**Keywords:** Ewing's sarcoma, extraosseous Ewing's sarcoma, extraskeletal Ewing's sarcoma, gastrointestinal stromal tumor

## Introduction

The Ewing's sarcoma (ES) family of tumors is small round cell neoplasms of neuroectodermal origin and is usually highly aggressive. The ES family includes extraosseous ES (EES), peripheral primitive neuroectodermal tumor (PNET), Askin's tumor (tumor from the chest wall), and atypical ES.[1] Due to the similarity of the genomic alteration (EWSR1 gene fusion with a nonrandom partner) between ES and PNET, the 2013 update of the World Health Organization pathology classification system regrouped them into a single entity – the ES family of tumors.[2] ES is the second most common primary bone malignancy of childhood, whereas EES is more common in older patients. First recognized by Tefft *et al*.[3] in 1969. EES may originate from the retroperitoneum, omentum, mesocolon, liver, pancreas, lung, and any part of the body. However, EES of the small intestine is extremely rare, and only 33 cases have been reported in the literature. Due to its rarity, ESS of the gastrointestinal tract may not be recognized at first impressions and can easily be mistaken for other more common gastrointestinal tract malignancies such as gastrointestinal stromal tumors (GISTs).[4-6] Here, we report a case of ES of the small intestine with liver metastasis, mimicking GIST.

## Case Report

A 50-year-old woman with a 2-month history of epigastric pain was referred to our hospital in 2021. The pain was dull

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and with radiation to her back. There was no fever, loss of appetite, or body weight loss. She had hypertension and type 2 diabetes mellitus which were under medical control. Her medical history also included duodenal Brunner's gland hyperplasia, which had been found during a health examination 7 years previously.

A computed tomography (CT) scan of the abdomen and pelvis [Figure 1a and b] obtained after the administration of intravenous contrast material showed an enhanced soft-tissue mass measuring 51 mm in the jejunum, enlarged regional lymph nodes, and a hypodense liver tumor measuring 22 mm at S6. A jejunal GIST with liver metastasis was considered. The serum carcinoembryonic antigen (CEA) level was 22.88 ng/mL (standard <5 ng/mL), whereas other tumor markers (cancer antigen [CA19-9], alpha-fetoprotein (AFP) and CA125) were normal. A magnetic resonance imaging scan of the abdomen and pelvis disclosed multiple confluent enlarged mesenteric lymph nodes in the left abdomen, with encasement of the mesenteric vessels [Figure 1c] and a hepatic tumor in S6 with mild hyperintensity on T2-weighted image [Figure 1d]. A pathology study of a CT-guided biopsy of the liver tumor showed nests of epithelioid tumor cells and small blue round cells [Figure 2a]. An immunohistochemical (IHC) stain was focally positive for CD117 [Figure 2b] and cytokeratin (CK) [Figure 2c]. The tumor was negative for CD3, CD20, and insulinoma-associated protein 1, discovered on GIST-1 (DOG1) and synaptophysin [Figure 2d]. There was no expression of the Epstein–Barr encoding region. The initial diagnosis was a metastatic epithelioid GIST. The patient decided to receive palliative surgery to remove the primary intestinal GIST. On laparotomy, a huge tumor involving the small bowel at about 40 cm from the Treitz ligament with invasion to the mesenteric root and numerous mesenteric and omental seeding tumors were found. Small bowel segmental resection and omentectomy for tumor excision were performed. The pathology report revealed an infiltrative tumor composed of epithelioid cells with hyperchromasia and coarse chromatin arranged in a sheet-like pattern with focal discohesion and small blue round cells [Figure 2e]. Tumor cells were detected in two regional lymph nodes. IHC of the tumor was focally positive for CD117 (KIT protein) and CK. The tumor was consistently negative for DOG-1, synaptophysin, erythroblast transformation-specific (ETS)-related gene (ERG), ETS variant transcription factor 4 (ETV4), desmin, S100, SOX10, CD3, CD20, CD79a, CD43, CD30, myeloperoxidase, human melanoma black-45, CD34, anaplastic lymphoma kinase 1, CD138, nuclear protein in testis, mouse double minute 2 homolog, and spalt-like transcription factor 4. Gene mutation tests by Sanger sequencing were negative for KIT and platelet-derived growth factor receptor A. The tentative diagnosis was revised to poorly differentiated epithelioid malignancy.

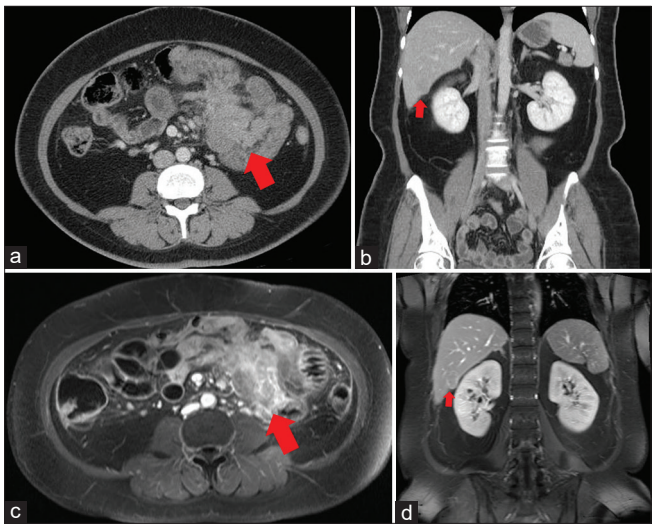


**Figure 1:** Contrast-enhanced CT and MRI of the abdomen and pelvis showed (a and c) an enhanced soft-tissue mass in the jejunum with enlarged regional lymph nodes; (b and d) a liver tumor at S6 (arrow). CT: Computed tomography, MRI: Magnetic resonance imaging

To confirm the diagnosis, next-generation sequencing (NGS) (FOUNDATIONONE Heme®) study of the surgical specimen was performed. Surprisingly, EWSR1-FLI1 fusion (type 2;

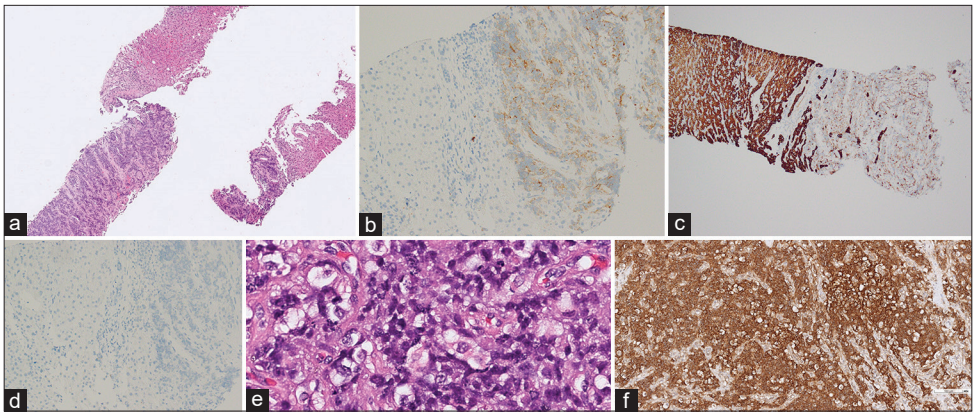


**Figure 2:** The pathology study of the CT-guided biopsy of the liver tumor showed (a) nests of epithelioid tumor cells and small blue round cells. They were immunoreactive for (b) CD117 and (c) CK, whereas (d) negative for synaptophysin. The pathology report of the surgical specimen revealed (e) an infiltrative tumor composed of epithelioid cells with hyperchromasia and coarse chromatin and small blue round cells, and the follow-up immunohistochemical stain was positive for CD99 expression (f). CT: Computed tomography, CK: Cytokeratin

exon 7/5) [Figure 3] was identified. A follow-up IHC stain for ES with CD99 was positive [Figure 2f]. Both the genomic study and IHC results supported the diagnosis of EES of the small intestine.

Chemotherapy with vincristine, doxorubicin, and cyclophosphamide (VDC) was administered as the first-line treatment. After three cycles, a CT scan of the abdomen and pelvis showed a partial response with a reduction in the size of the liver tumor. Unfortunately, after another two cycles of VDC, disease progression with enlargement of the hepatic and peritoneal tumors was confirmed. Microwave ablation therapy to the hepatic tumors (at S4 and S5) was done. The systemic treatment was then shifted to lenvatinib plus ifosfamide and etoposide (IE). After three cycles of lenvatinib plus IE, a CT scan revealed disease progression with new multiple hepatic metastatic tumors and an increased amount of ascites. Due to poor performance status, hospice care was provided, and she passed away 3 months later (overall survival [OS]: 14 months).

## Discussion

ES/PNET is usually very challenging for pathologists. The diagnosis of ES is usually made postoperatively and requires histological, IHC, and molecular studies. The tumors consist of primitive-appearing round cells with high nucleus-to-cytoplasm ratios. IHC for CD99 (a cell surface glycoprotein encoded by the MIC2 gene) is often positive in ES, but it may also be expressed in other cancer types such as synovial sarcoma, rhabdomyosarcoma, desmoplastic small round cell tumor, and solitary fibrous tumors. ES shows diffuse membranous positivity for CD99, whereas synovial sarcoma shows strong cytoplasmic positivity[4,7] Another IHC reagent that may aid in the diagnosis is vimentin, which is usually positive. Other variable markers include S100, chromogranin A, synaptophysin, and neuron-specific enolase.[8] CD117 is usually expressed in GIST, while it has also been reported to be positive in 38% of EES[9,10] Other IHC tests which are useful in the diagnosis of malignant GIST are DOG-1 and CD34, which were all negative in our case.

Genetically, ES is characterized by balanced translocations involving the EWSR1 gene on chromosome 22 and members of the erythroblast transformation-specific family of transcription factor genes. The most frequent translocation, EWSR1-FLI1, occurs in 85% of cases of ES. The second most common translocation is EWSR1-ERG (5%–15%), and such tumor cells are immunohistochemically positive for ERG.[11-13]

Clinical molecular testing for translocations of ES is most commonly performed using fluorescence *in situ* hybridization (FISH) or reverse transcription-polymerase chain reaction (RT-PCR). However, due to technical limitations, tests for all of the less common TET-ETS fusion pairings (e.g., EWSR1-ETV1, EWSR1-ETV4, and EWSR1-FEV) and non-TET-ETS fusion drivers (e.g., CIC-DUX4 or CIC-FOXO4 and BCOR-CCNB3) are usually not feasible. Therefore, NGS may be an important diagnostic tool for patients with a high clinical suspicion of EES and negative results by FISH or RT-PCR.[14]

EES and GIST share some clinical characteristics but are different in IHC staining, genetic alterations, recommended treatments, and prognosis [Table 1]. If EES manifests in an atypical pattern or if the pathologist is unaware of the possibility of EES, it is possible to miss important IHC findings for the differential diagnosis. In our case, EES-specific genetic mutations were found by NGS and a clear pathological diagnosis was made.

According to the SEER database, the prognosis of localized ESS is better than skeletal ES, with a 5-year OS of 69.7% versus 62.6%. However, the OS is similar for metastatic ESS and ES. The most important prognostic factor for EES is the presence or absence of distant metastasis. The 5-year survival rate for localized disease is 70%, but only about 30% for patients with distant metastasis.[18,19]

Due to the poor results of surgery alone for localized EES/PNET, the current recommendation is multimodal treatment including surgery, chemotherapy, and radiotherapy. For metastatic EES, the backbone of treatment is chemotherapy,

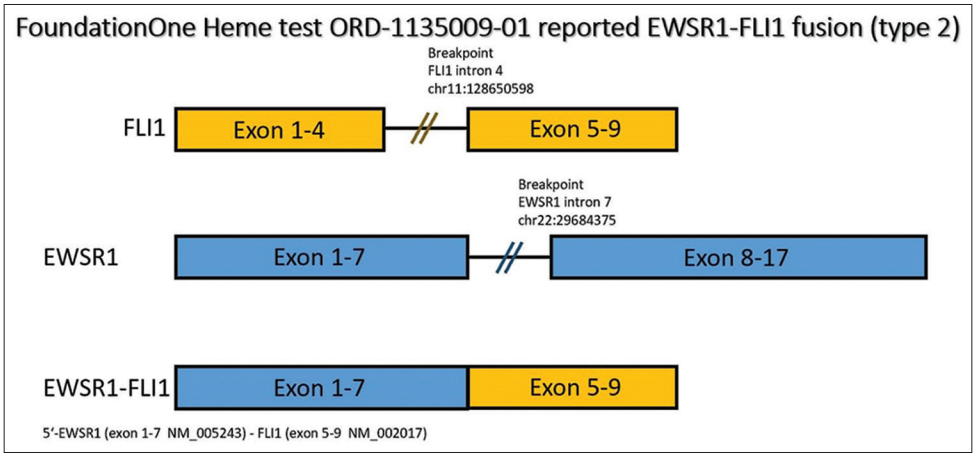


**Figure 3:** NGS disclosed EWSR1-FLI1 fusion (type 2; exon 7/5). NGS: Next-generation sequencing

**Table 1: Differences between EES and GIST**

| | EES | GIST |
|---|---|---|
| Histopathology | Epithelioid tumor cells and small blue round cells | Spindle cell type (70%), epithelioid type (20%), or mixed type (10%) |
| IHC staining | CD99, CD117 (38%), and ERG (5%–15%) | CD117 (95%), DOG-1, CD34, and smooth muscle actin[15] |
| Genetic alterations | Translocation of EWSR1-FLI1 (85%), EWSR1-ERG (5%–15%), less common TET-ETS or non-TET-ETS fusion drivers | Mutations in KIT, PDGFRA, and the family of SDH genes[16] |
| Treatments for advanced disease | VDC, IE | Tyrosine kinase inhibitors (imatinib, sunitinib, regorafenib, ripretinib, and avapritinib) |
| Prognosis | Localized: 5-year OS 70%, 10-year OS 65%<br>Metastatic: 5-year OS 30% | Advanced/metastatic: Median OS 57 months[17] |

EES: Extraosseous Ewing's sarcoma, GIST: Gastrointestinal stromal tumor, VDC: Vincristine, adriamycin, and cyclophosphamide, IE: Ifosfamide and etoposide, IHC: Immunohistochemical, ETS: Erythroblast transformation-specific, ERG: ETS-related gene, OS: Overall survival, PDGFRA: Platelet-derived growth factor receptor A, DOG-1: Discovered on GIST-1, TET: Translocated in liposarcoma/Ewing sarcoma breakpoint region 1/TATA box binding protein-associated factor

usually with VDC and IE. In some institutions, alternating cycles of VDC and IE may be used.[20-22] Whether adding local treatment is beneficial for patients with metastatic EES is still unknown.

In conclusion, EES of the small bowel is exceedingly rare, and the diagnosis usually requires histological, IHC, and molecular studies. NGS may play an important role in providing additional clues, especially when the presentation is atypical.

## Ethical approval

This study was approved by the IRB of the National Taiwan University Hospital (IRB approval number: 202205001W). The need for patient consent was waived by the IRB.

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## Conflicts of interest

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