

Case Report

Running Title: Extraskelatal Ewing Sarcoma in the Pancreas

Received: October 16, 2022; Accepted: October 01, 2023

Primary Extraskelatal Ewing Sarcoma of the Pancreas - A Case Report

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Abstract

Extraskelatal Ewing sarcomas (EES) is a rare, aggressive malignancy that typically affects adolescents or young adults, primarily involving the deep soft tissues of the lower extremities and paravertebral regions. The occurrence of EES in the pancreas is even rarer. These tumors are characterized by small, round cell sarcomas displaying varying degrees of neuroectodermal differentiation, as revealed through light, electron microscopy, or immunohistochemistry. Diagnosing EES demands a high level of suspicion. Histopathologically, the presence of small round cell tumors in the pancreas, along with CD99 positivity in immunohistochemistry, assists in diagnosing EES. Molecular analysis demonstrating EWSR1 (22q12) rearrangement via interface fluorescence in situ hybridization is required to confirm the diagnosis. A comprehensive review of pancreatic EES cases revealed that the primary treatment modality typically involves surgical intervention, often complemented by chemotherapy and, in some cases, radiotherapy. In this report, we describe the case of a 28-year-old male presenting with abdominal pain and a loss of appetite, which, upon histopathological and molecular examination, was identified as EES of the pancreas. The patient underwent surgical resection of the pancreatic mass, followed by omentum, splenectomy, and chemotherapy. EES is a highly aggressive tumor with an insidious onset, and patients usually exhibit nonspecific clinical symptoms. Although exceedingly rare, it should be considered in the differential diagnosis of pancreatic masses.

Keywords: Extraskelatal, Sarcoma, Ewing, Pancreas, Case report

Introduction

Ewing sarcoma (ES) is an infrequent tumor, accounting for 6%–8% of primary malignant bone tumors.¹ The incidence of ES in the United States is 1 per million across all age groups.² Soft tissue extensions of the tumor without bone involvement are classified as primary extraskelatal Ewing sarcomas (EES). EES is a rare condition that predominantly affects adolescents or young adults, typically

involving deep soft tissues in the lower extremities and the paravertebral region.³ However, EES can manifest in various body sites, including the kidney, urinary bladder, uterus, gallbladder, lung, vagina, and vulva.⁴ The ES family of tumors (EFT) comprises classical bony ES, EES, Askin's tumor (ES of the thoracopulmonary region), and peripheral primitive neuroectodermal tumor (PNET).⁵ These tumors are characterized by small

round cells exhibiting varying degrees of neuroectodermal differentiation, as observed through light, electron microscopy, or immunohistochemistry. ES and EES share a common feature of recurrent balanced translocations involving the EWSR1 gene on chromosome 22 and a member of the ETS family of transcription factors. This genetic alteration leads to the formation of novel fusion oncogenes, which play a pivotal role in the pathogenesis of these tumors.¹ The occurrence of EES in the pancreas is exceedingly rare, with only 25 reported cases in the literature. Here, we present the case of a 28-year-old male who presented with abdominal pain and a month-long loss of appetite. Subsequent histopathological and molecular studies confirmed the diagnosis of EES in the pancreas. Surgical resection of the pancreatic mass, omentum, and splenectomy were performed, followed by chemotherapy.

Case Presentation

A 28-year-old male presented with abdominal pain that had persisted for a month and a loss of appetite and weight. There was no significant medical, family, or psychosocial history. Physical examination yielded average results; complete blood counts and biochemical examinations were normal. Magnetic resonance imaging (MRI) of the abdomen revealed a large, heterogeneous mass measuring 20 × 12 × 15 cm. This mass originated from the body and tail of the pancreas, extending anteriorly and infiltrating the anterior abdominal wall, including the diaphragm. It extended medially, abutted, and encased the celiac trunk, exerting a significant mass effect on the superior mesenteric and portal vein confluence. It also extended posteriorly, invading the left adrenal gland and its vessels while causing a severe mass effect on the left kidney through direct invasion. Additionally, it extended laterally, invading the left gastric artery and the lesser curvature of the stomach. The mass entirely encased the splenic and

superior mesenteric veins, but the spleen and colon were not directly affected (Figure 1). Surgical resection of the pancreatic mass and omentum and splenectomy were performed. Histopathological sections revealed a well-circumscribed, predominantly necrotic tumor invading the normal pancreas. It consisted of lobules separated by fibrous bands, comprising sheets of small round cells with focal acinar and pseudopapillary structures (Figure 2). The resection margin of the pancreas was free from tumor, but 8 out of 19 resected lymph nodes displayed metastatic tumor. Metastasis was also observed in the omentum, while the adrenal gland, peripancreatic tissue, and spleen showed no tumor infiltration.

Immunohistochemical analysis indicated that the tumor cells were diffusely positive for CD99 and vimentin, with focal positivity for neuron-specific enolase (NSE) (Figure 3). They tested negative for leukocyte common antigen (LCA), synaptophysin, chromogranin, S100, pan-cytokeratin, desmin, smooth muscle actin (SMA), Human melanoma black (HMB-45), and thyroid transcription factor (TTF1). Morphologically and immunohistochemically, as well as through EWSR1 (22q12) rearrangement confirmed by interface fluorescence in situ hybridization (FISH), the findings were consistent with ES of the pancreas (EES pancreas).

This study received approval from the Academic Affairs and Training Center (ACH) Ethics and Internal Review Board (IRB) Committee.

Discussion

The history of ES dates back to 1918 when Arthur Purdy Stout reported a case of a 42-year-old man with an ulnar nerve tumor composed of undifferentiated round cells that formed rosettes. In 1921, James Ewing described a round cell tumor in the radius of a 14-year-old girl, proposing an endothelial

derivation and calling it "diffuse endothelioma of bone".⁶ EES is a rare entity that can affect virtually any site in the body. It was initially described in 1969 as a soft tissue tumor that closely resembled the ES of the bone when examined under light microscopy. However, it was not until 1975 that Angervall and Enzinger reported the first case of ES arising in soft tissue, now referred to as EES. In 2002, the World Health Organization (WHO) unified undifferentiated small round blue cell neoplasms of soft tissue and bone, previously classified as ES and PNET (primitive neuroectodermal tumor), into one category due to extensive histomorphologic, immunohistochemical, and cytogenetic similarities.⁷ In 2014, PNET was no longer considered a synonym for ES; these tumors are now collectively called the Ewing family of tumors (EFT). In the 2020 WHO classification, a new chapter was introduced, covering undifferentiated small round cell sarcomas of bone and soft tissue, including ES, and categorizing them into three main groups: round cell sarcomas with EWSR1–non-ETS fusions, CIC-rearranged sarcomas, and sarcomas with BCOR genetic alterations.⁸

A study of 600 primary pancreatic neoplasms revealed only two cases of pancreatic PNETs.⁹ In a literature review, cases of EES in the pancreas ranged in age from 2 to 60 years, with an average age of 23 years and no significant gender predominance. The most commonly reported symptoms included abdominal pain (68%), jaundice (20%), nausea (16%), and anemia (16%). The most common site of occurrence was the head of the pancreas, with tumor sizes ranging from 3.5 cm to 11 cm.⁴ In our case, a 28-year-old male presented with abdominal pain and loss of appetite, and the tumor was located in the body and tail of the pancreas.

Radiologically, abdominal computed tomography (CT) and MRI are the two most common modalities for visualizing

pancreatic tumors, with MRI being the more sensitive imaging study. Tan et al. reported that the radiographic characteristics of the lesion include isodensity or hypodensity on unenhanced CT, isointensity on T1-weighted imaging, and variable isointensity or hyperintensity on T2-weighted imaging as revealed by MRI. Pancreatic tumors typically have ill-defined borders and irregular shapes with heterogeneous enhancement. Some tumors may show enhancement in focal areas on CT during the arterial phase despite no close relationship with the arteries. Advanced-stage tumors may invade surrounding organs and exhibit metastasis.¹⁰ Histopathologically, most cases exhibit uniform small round cells with round nuclei containing fine chromatin, scanty clear or eosinophilic, PAS-positive cytoplasm, and indistinct cytoplasmic membranes (classic ES). Classic ES does not display neural differentiation and typically demonstrates diffuse membranous CD99 positivity.¹ Approximately 85% of ES cases involve a somatic reciprocal chromosomal translocation, t(11;22)(q24;q12), resulting in the fusion of EWSR1 and FLI1 to generate the EWSR1-FLI1 oncoprotein. EWSR1-FLI1 acts as an aberrant transcription factor that dysregulates genes critical for the oncogenic phenotype of ES. The differential diagnosis for ES/PNET includes various other small round cell tumors, particularly lymphoblastic lymphoma, desmoplastic small cell tumor, embryonal/alveolar rhabdomyosarcoma, undifferentiated carcinoma, small cell carcinoma-neuroendocrine type, olfactory neuroblastoma, melanoma, synovial sarcoma, lymphoma, pancreatic neuroendocrine tumor, pancreatoblastoma, extra-renal Wilms tumor, extra-adrenal neuroblastoma, hepatoblastoma, rhabdomyosarcoma, desmoplastic small round cell tumor, and visceral small cell neuroendocrine carcinoma.

Ultrastructurally, EES, like ES of bone, lacks a collagenous intercellular matrix, and its cells contain pools of glycogen but do not contain cytoskeleton or intracellular collagen.⁵

Based on a review of cases, the primary treatment for pancreatic EES involves surgery in combination with chemotherapy, with or without adjunctive radiotherapy.⁴ Nearly all patients are diagnosed with occult disseminated disease, making chemotherapy a standard part of the treatment plan. In the intergroup ES study III, Grier HE and colleagues established a five-drug regimen as the gold standard chemotherapy protocol for this family of tumors. This regimen includes vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide.¹¹ It has significantly improved outcomes for patients with non-metastatic ES, primitive neuroectodermal tumor of bone, or primitive sarcoma of bone. Factors that adversely influence the disease outcome include the presence of metastatic disease at initial diagnosis, large tumor size, extensive necrosis, central axis tumors, and poor response to initial chemotherapy.⁶

Conclusion

In summary, EES represents an exceptionally aggressive tumor with a subtle onset, often devoid of specific clinical symptoms in patients. A high degree of suspicion is paramount when diagnosing EES in the context of a pancreatic mass displaying round cell morphology. Confirmation of this diagnosis is achieved through a molecular analysis of EWSR1 (22q12) rearrangement. Most patients already present with disseminated disease at diagnosis, making chemotherapy the primary treatment modality. It is imperative to emphasize the significance of considering EES as a potential differential diagnosis for pancreatic masses, as this can significantly enhance the prognosis and overall survival of affected individuals.

Informed Consent

Written informed consent was duly obtained from the patient.

Conflicts of Interest

None declared.

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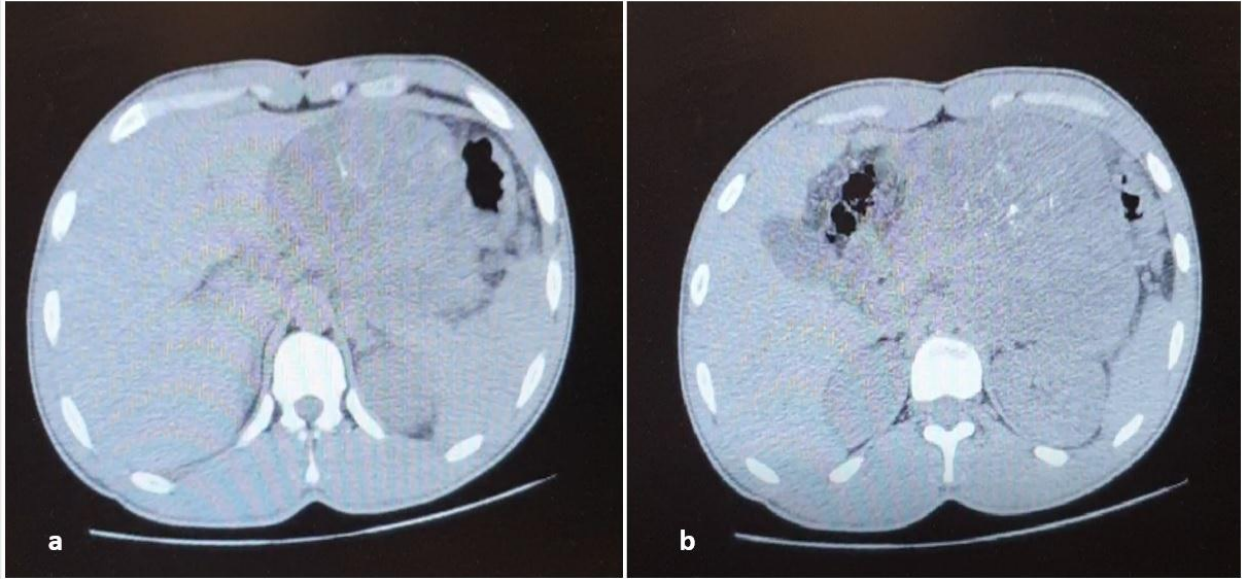


Figure1. (a, b) MRI of the pancreas reveals a sizable, heterogeneous mass originating from the body and tail of the pancreas, measuring $20 \times 12 \times 15$ cm. This mass extends anteriorly, infiltrating the anterior abdominal wall, including the diaphragm. It also extends medially, closely abutting and encasing the celiac trunk, exerting a significant mass effect on the left kidney. Notably, the spleen and colon remain uninvaded.

MRI: Magnetic Resonance Imaging

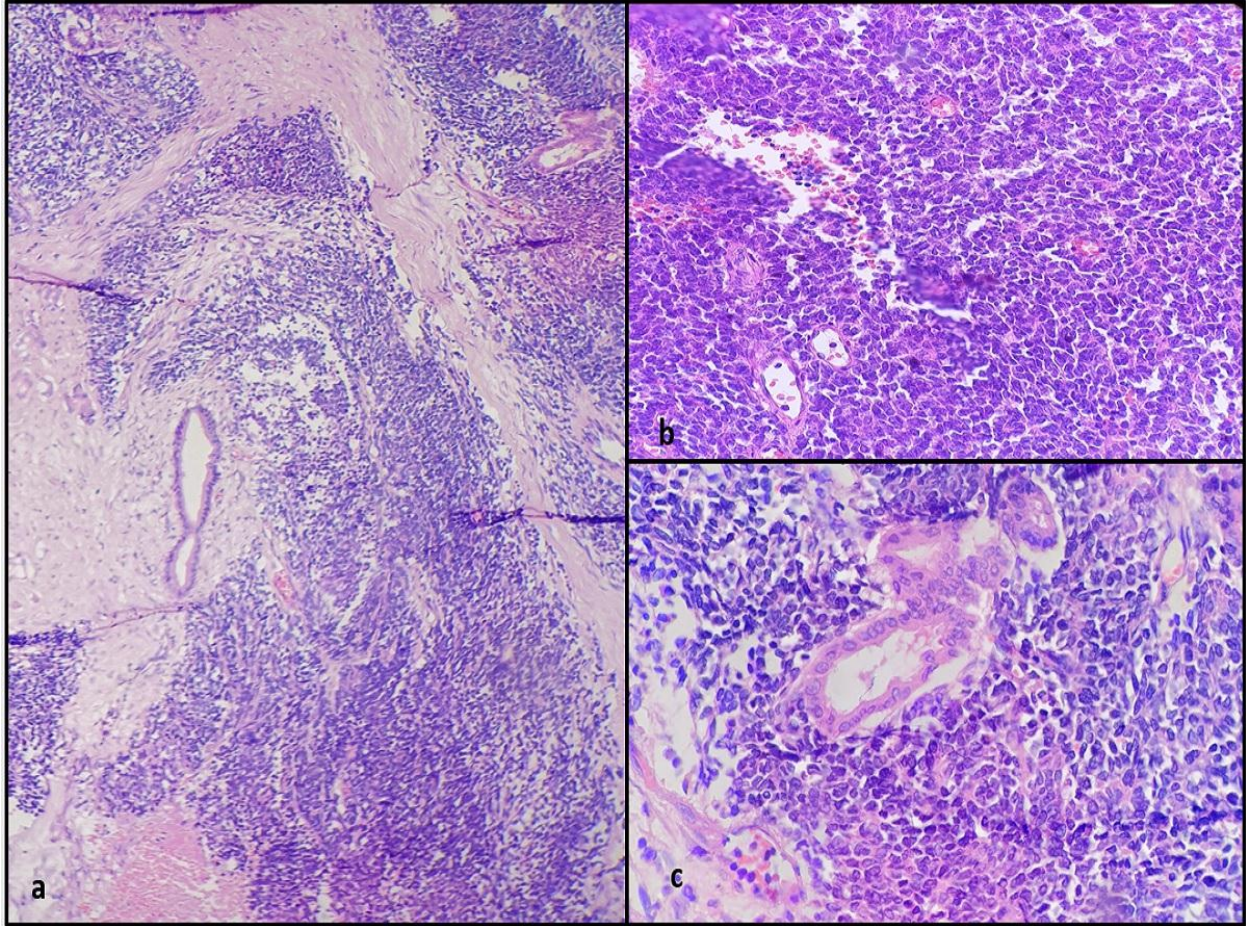


Figure 2. (a, b, and c) Pancreatic sections illustrate the tumor's infiltration into the normal pancreas tissue. It consists of lobules composed of sheets of small, round cells exhibiting a focal acinar and pseudorosette arrangement, separated by fibrous bands. (Hematoxylin and Eosin: a: 10 \times , b: 20 \times , c: 40 \times).

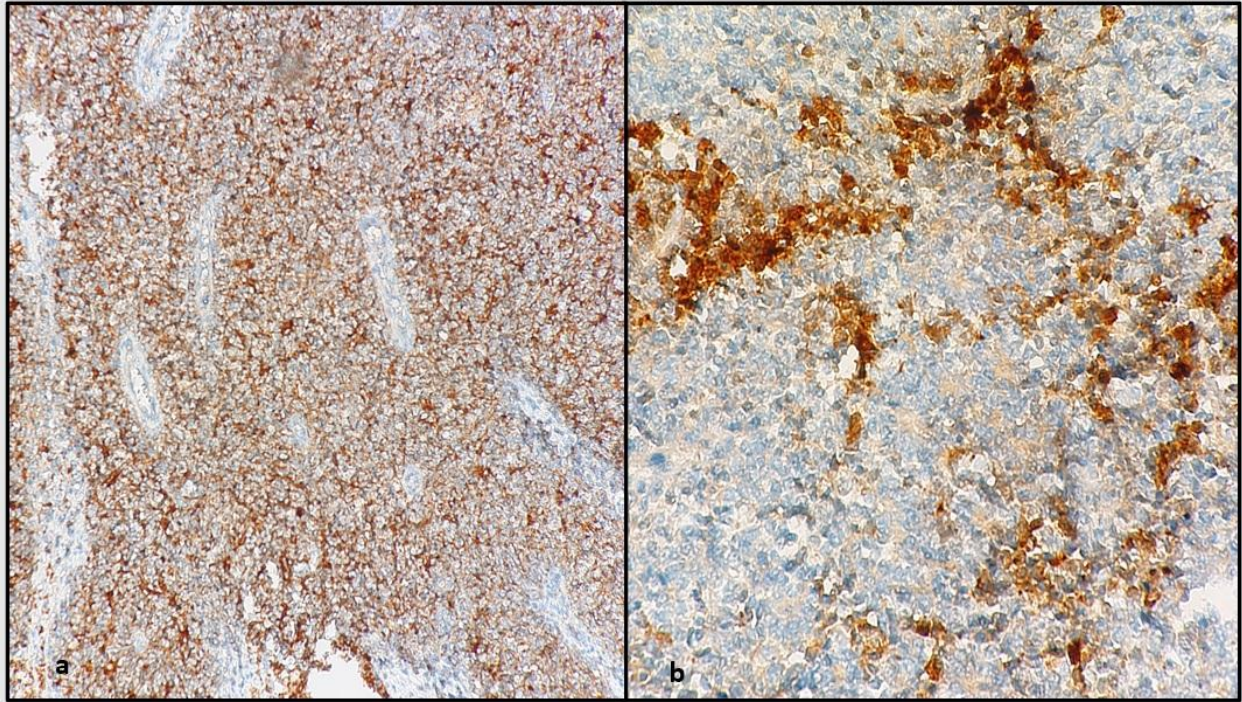


Figure 3. Immunohistochemical examination reveals that a. CD99 displays membranous positivity in the tumor cells (CD99: 20×). b. NSE exhibits focal positivity in the tumor cells (NSE: 20×).

NSE: Neuron specific enolase