

Primary Ewing Sarcoma of the Stomach

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To the Editor

Ewing sarcoma (ES), a malignant tumor of small round blue cells, arises usually in skeletal tissues and lacks neuroectodermal differentiation [1]. It was reported firstly by James Ewing in 1921. Although previously regarded as a separate entity from primitive neuroectodermal tumor (PNET), which exhibits neuroectodermal features, nowadays, they are treated as the same tumor due to the similarity in chromosomal translocation and immunohistochemical characteristics [1]. These tumors belong to the ES family of tumors which include skeletal ES/PNET, extraskeletal ES/PNET and Askin tumor (thoracopulmonary PNET). These tumors originate from distinctive mesenchymal progenitor cells due to their similar histologic and immunohistochemical characteristics. ES is a highly metastatic type of sarcoma and represents almost 10-15% of bone sarcomas, and is regarded as the second most common primary malignant bone tumor [2]. Although 5-year survival and overall survival have been improved significantly recently, the recurrence rate of such tumors remains high.

Classification

ES/PNET tumors can be categorized as skeletal affecting bones and deep soft tissues [3] and extraskeletal affecting other organs. Skeletal ES/PNET represents the most common type at about 80-85% of cases. Extraskeletal organs affected, including the pancreas, small bowel, kidneys, stomach, esophagus, ovaries and vagina, represent almost 15-20% of ES/PNET tumors [4]. Other cohort series including 120 - 2,202 patients reported an incidence rate of 21-31% [5, 6]. Both types usually affect children and young adults, with the extraskeletal type affecting slightly older children than skeletal

ES by 5 - 10 years, with an average age of 20 years, thus, granting the extraskeletal subtype particular importance in the adult population. Although skeletal ES/PNET has slight male predilection (M/F ratio = 1.5:1), extraskeletal subtypes have an equal sex predilection (Table 1, [4]). Even though patients suffering extraskeletal ES/PNET are treated by the same protocol of skeletal ES/PNET, there is no consensus on whether the two diseases carry a similar prognosis.

Diagnosis

Accurate diagnosis of ES/PNET can be made by immunohistochemical staining for different markers which show variable results. Immunohistochemical staining for a monoclonal antibody to cluster of differentiation (CD)99 (HBA/71, 12E7, and 013) is positive in almost all cases of ES/PNET, while immunohistochemical staining for intermediate filament vimentin is usually positive [7, 8]. Immunohistological reagents show variable immunohistochemical staining include synaptophysin, chromogranin A, S100 and neuron-specific enolase [9].

Fluorescent *in situ* hybridization (FISH) or reverse transcription polymerase chain reaction can also be used for the diagnosis of said tumors, by testing the presence of genetic mutations (11;22) (q24;q12) translocation (*EWS/FLI1* fusion) [9]. The previously mentioned genetic mutations are essential criterion for the diagnosis of ES/PNET, although sometimes these tests are negative. FISH tests are used particularly for ES/PNET tumors at unusual sites (extraskeletal ES/PNET).

Extraskeletal ES/PNET

Extraskeletal ES/PNETs are rare, aggressive and highly malignant soft tissue tumors indistinguishable morphologically from the skeletal types. Extraskeletal ES/PNET was firstly reported by Angervall and Enzinger in 1975 [10], and are characterized by high incidence of recurrence and distant metastasis. The most common sites to be involved by extraskeletal ES/PNET are lower extremities, retroperitoneal space, chest wall and gluteal region. Other less commonly involved organs include the kidneys, prostate, gastrointestinal (GI) tract, brain, adrenal glands, breast, ovaries and endometrium.

Primary gastric ES/PNET is an extremely rare entity, with a paucity of cases reported in the English literature.

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Table 1. The Differences Between ES/PNET Subtypes

	Skeletal ES/PNET	Extraskelatal ES/PNET
Incidence	80-85%	15-20%
Organs involved	Bone and deep soft tissues	Pancreas, kidneys, stomach, small bowel, esophagus, ovaries and vagina
M/F ratio	1.5:1	1:1
Average age at presentation	15 years old	20 years old

ES: Ewing sarcoma; PNET: primitive neuroectodermal tumor; M: male; F: female.

Primary Gastric ES/PNET

Reviewing the current English literature reveals only eight cases of primary ES/PNET of the stomach [3, 4, 9, 11-15]. Of the eight patients, five were females while three were males (F/M ratio = 1.6:1), and the average age at presentation was 47 years old (range: 24 - 68). These findings contradict other extraskelatal subtypes of ES/PNET which usually affect younger patients with equal sex predilection. The most common clinical presentation was abdominal pain, noticed in six patients (75%), followed by vomiting and upper GI hemorrhage in three and two patients, respectively (Table 2 [3, 4, 9, 11-15]). Basma et al reported a case with an asymptomatic presentation, in which the tumor was incidentally found during upper endoscopy [10], while Kim et al reported a case of palpable abdominal mass on presentation [11]. Pre-operative diagnosis was not confirmed in most patients, as it was available in only three patients. The most common endoscopic finding for primary ES/PNET of the stomach was ulcerated protruding mass, detected in six patients (75%), with the antrum as the most common part to be affected (62%). Endoscopic findings were not available in one case in which the patient underwent surgical wedge resection of the tumor along with part of the lesser curvature with the pre-operative primary differential diagnosis being GI stromal tumor (GIST) [15]. Even though pre-operative diagnosis is not always available in all cases, the aforementioned case emphasizes the importance of pre-operative endoscopy during the workup. Primary gastric ES/PNETs of the lesser curvature and gastric body were diagnosed in one patient each. On abdominopelvic computed tomography (CT) scan, primary ES/PNET of the stomach usually presents as a large (9 - 11 cm) exophytic mass (most commonly) or as a circumferential hypodensic mass. All patients were treated by surgical resection, with the addition of neoadjuvant/ adjuvant chemotherapy in selected patients. Molecular study using FISH or reverse transcription polymerase chain reaction for *EWSR1* gene rearrangement was done in six patients, and was found to be positive in five [3, 9, 12-14], and negative in one case [11]. Immunohistochemical staining for monoclonal antibody to CD 99 (HBA/71, 12E7 and 013) was positive in all reported cases, while it was found to be positive for vimentin and FL1 in four and three cases, respectively. These molecular studies indicate the importance of *EWSR1* gene fusion translocation and monoclonal antibody for CD99 for precise diagnosis.

The extreme rarity of such entity, along with the absence of treatment guidelines, emphasizes the immense importance of a multidisciplinary team approach for optimal management.

This multidisciplinary team should include GI surgeons, GI oncologists, gastroenterologists, pathologists and GI radiologists for optimal management.

Conclusions

Although primary ES/PNET of the stomach is an exceedingly rare entity, it should be part of the differential diagnosis of primary gastric tumors, especially in adult females with characteristic endoscopic ulcerated mass located at the gastric antrum. Multidisciplinary approach is advised for optimal care of such patients. Authors are encouraged to report such rare cases to gain knowledge about the different characteristics of these tumors.

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Conflict of Interest

The authors have no conflicts of interest to declare.

Informed Consent

Not applicable.

Author Contributions

Kenan Halloun and Subhi Mansour designed the research; Amir Farah, Meriam Obeid, Mira Damouny, Rozan Marjiyeh and Jawad Ghalia collected and analyzed data. Safi Khuri wrote and approved the final paper.

Data Availability

The authors declare that data supporting the findings of this

Table 2. Reported Cases of Primary Ewing Sarcoma of the Stomach

Case report	Age	Sex	Clinical presentation	Pre-operative diagnosis	Endoscopic findings	CT scan findings	Treatment	<i>EWS/FLII</i> fusion genetic mutation (11;22) translocation
Khuri et al, 2016 [9]	31	F	Abdominal pain and coffee ground vomiting (UGIB)	Confirmed	Large ulcerated mass at the lesser curvature	9-cm circumferential hypodense mass at the lesser curvature	Surgical resection	Positive
Soulard et al, 2005 [3]	66	F	Abdominal pain and vomiting	Not confirmed	Ulcerated mass at the antrum	Not available	Surgical resection	Positive
Hopp et al, 2019 [4]	24	M	Abdominal pain and vomiting	Confirmed	Ulcerated mass at the antrum	10-cm exophytic mass at posterior gastric wall	Neoadjuvant chemotherapy and surgical resection	Not reported
Kim et al, 2012 [11]	35	F	Asymptomatic	Not confirmed	Protruding mass at the antrum	Not available	Surgical resection	Negative
Rafailidis et al, 2009 [12]	68	M	Abdominal pain and palpable abdominal mass	Not confirmed	Ulcerated mass at the antrum	Exophytic large mass outgrowing from stomach body	Surgical resection and adjuvant chemotherapy	Positive
Song et al, 2016 [13]	55	M	UGIB (melena)	Not confirmed	Ulcerated mass at the stomach body	Not available	Surgical resection	Positive
Maxwell et al, 2016 [14]	63	F	Abdominal pain and symptomatic anemia	Confirmed	Large ulcerated mass at gastric antrum	Homogeneous circumferential mass involving the antrum	Surgical resection and adjuvant chemotherapy	Positive
Kumar et al, 2016 [15]	32	F	Abdominal pain	Not confirmed	Not available	11-cm exophytic mass at the lesser curvature	Surgical resection and adjuvant chemotherapy	Not reported

F: female; M: male; UGIB: upper gastrointestinal bleeding; CT: computed tomography.

study are available within the article.

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