Primary gastric Ewing sarcoma/primitive neuroectodermal tumor

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Abstract
A rare and highly malignant small round cell tumor, Ewing sarcoma/primitive neuroectodermal tumor (ES/PNET) usually occurs in the pelvis, long-axis bones, and femur. In contrast, extraossseous ES is more often found in the paraspinal region, limbs, and retroperitoneum, but is extremely rare in the stomach. We report a case of a 55-year-old woman who presented with fatigue, fever, and black stool. Preoperative computed tomography (CT) imaging showed a large ulcerative lesion of approximately 5.5 × 5.0 cm in the stomach and irregular thickening of the ulcer wall. Upper endoscopy revealed a large, irregular ulcer in the posterior wall of the stomach. Histopathological examination suggested that the mass with the largest diameter (7.5 cm) was ES. Immunohistochemistry indicated positivity for CD99. Enhanced CT of the whole body was performed but no definite masses were found in other organs, and the patient was diagnosed with primary gastric ES. The patient underwent radical distal gastrectomy with Roux-en-Y gastrojejunostomy, but refused chemoradiotherapy.

Keywords
Ewing sarcoma, primary, gastric, stomach, primitive neuroectodermal tumor, cluster of differentiation 99

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Introduction

Ewing sarcoma (ES) and primitive neuroectodermal tumors (PNETs) are highly malignant, small round cell tumors. Despite having different degrees of neuroectodermal differentiation, they both contain EWSR1-ETS fusion proteins and belong to the Ewing sarcoma family. The most common chromosomal rearrangement is a translocation between chromosomes 11 and 22, t(22;11)(q24;q12), which can lead to new EWSR1-ETS fusion proteins as transcription factors that regulate target genes and lead to cell transformation, resulting in tumors with the morphology and gene expression characteristics of ES. ES usually occurs in the pelvis, long-axis bones, and femur. Extraosseous ES (EES) is more often found in the paraspinal region, limbs, and retroperitoneum but is extremely rare in the stomach. Herein, we report a case of primary gastric ES to aid in disease recognition for clinicians and radiologists.

Case report

A 55-year-old woman presented with a 10-day history of fatigue and fever, and having defecated mushy black stool twice 4 days prior. During the course of the disease, the patient suffered from poor mental health and sleep, and she had lost some weight. She had a 3-year history of hypertension and a 2-year history of type 2 diabetes and was taking oral medications (nifedipine, acarbose, metformin, and glimepiride) to treat these conditions. She had no family history of genetic disorders. Physical examination showed an anemic appearance, with no obvious enlarged lymph nodes and normal signs in the heart, lungs, and abdomen. Routine blood work indicated a red blood cell count of $2.26 \times 10^{12}$/L (reference range: 3.5–5.5 $\times 10^{12}$/L) and hemoglobin (Hb) of 57 g/L (reference range: 110–150 g/L). Kidney, liver function, and gastrointestinal tumor markers were within normal limits.

Imaging examination using a 64-row and 128-slice spiral computed tomography (CT) system (LightSpeed, General Electric Co., Boston, MA, USA) showed that the gastric wall in the gastric body was irregularly thickened, nodular mass shadows were positioned locally, and enlarged lymph nodes were absent around the stomach (Figure 1a). The coronal profile showed a large ulcerative lesion of approximately $5.5 \times 5.0$ cm, with irregular thickening of the ulcer wall (Figure 1b). The volume rendering technique (VRT) of 3-dimensional (3D) post-processing volume reconstruction showed that the gastroduodenal artery was thicker than normal and passed through the gastric wall at the greater curvature of the gastric body (Figure 1c). The maximum density projection of 3D post-processing technology showed that the distal small branches of the gastroduodenal artery entered the thickened gastric wall vertically, and the local vessels were thickened and moved relatively gently (Figure 1d). Enhanced CT of the whole body was performed but we did not find any definite masses in other organs.

Upper endoscopy revealed a large irregular ulcer located at the posterior wall of the stomach, with a dirty, smelly ulcer surface and exposed blood vessels in the center (Figure 2). However, gastric biopsy suggested chronic inflammation of the mucosal tissue. Therefore, a laparoscopic exploration was performed on 14 May 2020. During the operation, an ulcerative mass of approximately $9 \times 8$ cm was found near the gastric antrum at the greater curvature of the stomach. The mass penetrated through the serous membrane and showed nodular infiltration of the surrounding area. No effusion was observed in the abdominal or pelvic cavity, and no obvious metastasis was found in the liver, gallbladder, spleen, pancreas, omentum, or
mesentery. The patient underwent radical distal gastrectomy with Roux-en-Y gastro-jejunostomy, which was performed using the laparoscopic technique. The operation lasted 4 hours; the patient had blood loss of 200 mL and received 2 units of red blood cells. The postoperative hospital stay was 10 days, without obvious complications.

Histopathological examination revealed that the mass with the largest diameter (7.5 cm) was an ES (Figure 3a), which invaded the entire layer of the gastric wall, with positive lymph nodes at the lesser curvature of the stomach (2/14) and all negative at the greater curvature of the stomach (0/10); the tumor did not invade the proximal and distal anastomosis or omentum. Immunohistochemistry was positive for cluster of differentiation (CD)99 (Figure 3b), CD57, CD56, and vimentin; focally positive for neuron-specific enolase (NSE); and negative for cytokeratin 7 (CK7), epithelial membrane antigen (EMA), CD117, CD34, DOG-1 (discovered on GIST-1), synaptophysin (Syn), chromogranin-A (CgA), leukocyte common antigen (LCA), S-100, human melanoma black (HMB45), MelanA, and desmin. The tumor cells were 40% positive for Ki-67. The patient was thus diagnosed with primary gastric ES. After surgical treatment, the patient refused postoperative

Figure 1. Preoperative computed tomography (CT) images: (a) enhanced CT axial showing the irregularly thickened wall in the gastric body and nodular mass shadows and the absence of definite enlarged lymph nodes; (b) coronal profile showing a large ulcerative lesion of approximately 5.5 × 5.0 cm with irregular thickening of the ulcer wall; (c) volume rendering technique of 3-dimensional post-processing volume reconstruction showing the dilated gastroduodenal artery passing through the thickened gastric wall at the greater curvature of the gastric body; (d) maximum density projection showing distal branches that were slightly dilated and relatively normal and curvature entering the thickened gastric wall vertically.
chemoradiotherapy and was discharged. Until now, no recurrence has been observed during follow-up.

**Discussion**

The ES/PNET group consists of classic ES of bone, EES, and peripheral PNETs of bone and soft tissue (including the so-called Askin tumor of the chest wall). The histogenesis of these tumors remains unclear, but the tumor cells are most likely derived from primitive mesenchymal cells with the potential for limited neural differentiation, hence their location in bone, peripheral nerve, and soft tissue.

ES is an aggressive tumor and tends to occur in adolescents and young adults. It is common in the pelvis, long-axis bones, and femur but can occur outside the bone. Ewing et al. first reported the disease in 1921. Its main specific imaging
| Reference                  | Sex, age (years) | Clinical presentation                        | Location               | Tumor size (cm) | Distant metastasis | Neoadjuvant chemotherapy | Surgery            | Postoperative chemotherapy | Follow-up (months) | Outcome |
|---------------------------|------------------|---------------------------------------------|------------------------|-----------------|--------------------|--------------------------|-------------------|---------------------------|-------------------|---------|
| Czekalla et al. (2004)    | M, 14            | Inappetence, fatigue, epigastric pain        | Anterior wall body     | 5               | Liver              | Yes                      | SG                | No                        | 24                | Alive   |
| Colovic et al. (2009)     | F, 44            | Epigastric pain                             | Posterior wall body    | 10              | No                 | No                       | Excision          | No                        | 20                | Alive   |
| Kim et al. (2012)         | F, 35            | No special symptoms                         | Antrum                 | 5.5             | No                 | No                       | WR                | No                        | 11                | Alive   |
| Song et al. (2016)        | M, 55            | Upper abdominal pain, vomiting              | High body              | 6.5             | Lymph nodes        | No                       | TG                | Yes                       | 13                | Alive   |
| Kumar et al. (2016)       | F, 32            | Epigastric pain                             | Lesser curvature       | 11              | No                 | No                       | Excision          | Yes                       | 12                | Alive   |
| Khuri et al. (2016)       | F, 31            | Upper gastrointestinal hemorrhage           | Lesser curvature       | 11              | Pancreas, Splenic hilum | No                       | TDPSLA            | No                        | 36                | Alive   |
| Soulard et al. (2005)     | F, 66            | Epigastric pain                             | Antrum                 | 8               | No                 | No                       | Gastrectomy        | Yes                       | 10                | Dead    |
| Rafailidis et al. (2009)  | M, 68            | Abdominal pain, dyspepsia, weakness         | Body                   | 12              | Liver              | No                       | SG                | Yes                       | 13                | Dead    |
| Inoue et al. (2011)       | F, 41            | Abdominal pain                              | Anterior wall body     | 9               | Enterocoelia       | No                       | DG                | Yes                       | 110               | Dead    |
| Maxwell et al. (2016)     | F, 66            | Anemia, abdominal pain                      | Antrum                 | 11              | No                 | No                       | DG                | Yes                       | NA                | NA      |
| Hopp and Nguyen (2019)    | M, 24            | Abdominal pain, nausea, vomiting           | Posterior wall         | 10              | NA                 | Yes                      | DG                | NA                        | NA                | NA      |

SG, subtotal gastrectomy; CG, curative gastrectomy; WR, wedge resection; TG, total gastrectomy; TDPSLA, total gastrectomy + distal pancreatectomy + splenectomy + left adrenalectomy; DG, distal gastrectomy; NA, not available.
manifestations are bone destruction in the metaphysis of long bone. EES accounts for 15% to 20% of tumors in the Ewing’s family (ES/PNET plus EES). Primary gastric ES is exceptionally rare, with only a few cases reported in the literature. The growth rate of EES is relatively slow, and some lesions may grow into masses larger than 20 cm in diameter, but the clinical symptoms of a patient with EES are not obvious. In our case, the lesion was large and the patient had no specific clinical manifestations. Thus, EES is not conducive to early detection and diagnosis; its diagnosis mainly depends on the pathological characteristics of small round cells and positive staining for CD99 on immunohistochemistry. We summarize 12 reported cases of primary gastric ES in Table 1, describing clinical presentation, treatment, and outcome. We found that primary gastric ES is more common in female patients, the clinical presentation is not specific, most tumors are larger than 5 cm, and comprehensive treatment (combining surgery, radiotherapy, and chemotherapy) is often chosen.

The treatment of EES has no unified standard, and combination chemoradiotherapy and surgical excision are the main treatments. In our case, the lesion was relatively limited, did not spread to the abdominal and pelvic cavities, and was thus completely excised. The patient declined to undergo chemotherapy and radiotherapy after radical surgery.

Few reports have described the imaging features of primary gastric ES. In our case, enhanced CT showed obviously irregular thickening of the gastric wall in the gastric body, multiple nodular mass in the greater curvature and the gastric wall of the gastric body, and mild progressive strengthening after enhanced CT. The CT imaging features were similar to those described in the literature by Khuri et al. VRT showed that the gastroduodenal artery supplied the lesion. The vessels in the area of the lesion were dilated and tortuous, but no definite vascular erosion was observed. The imaging differential diagnoses included Borrmann IV gastric adenocarcinoma and gastric lymphoma. However, Borrmann IV gastric adenocarcinoma retains part of the mucosa and is stratified with the submucosa due to the infiltrating growth of tumor cells in the fibrous matrix along the submucosal layer; the strengthening pattern of the adenocarcinoma is stratified. Gastric lymphoma is a primary tumor of lymphatic follicular cells in the lamina propria and submucosa, and its cells are densely arranged. The gastric wall shows diffuse thickening with relatively uniform density and no gastric stenosis.

In conclusion, we present this rare primary gastric ES that, because of its rarity and lack of specific characteristics in symptoms, signs, and imaging, is difficult to diagnose early. Early recognition and diagnosis of this rare tumor by clinicians and radiologists is important and could be improved.

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Ethics statement
Local ethics committee approval was not necessary because this was a case report. Written consent for publication was obtained from the patient.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

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Author contributions
YY and JXM carried out data collection; ALZ and XMQ drafted the manuscript; and DYH reviewed the manuscript.

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