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【 CASE REPORT 】

Multiple Metastatic Extra-gastrointestinal Stromal Tumors with Plasmoid Differentiation: A Case Report and Review of Literature

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Abstract:

Extra-gastrointestinal stromal tumors (EGISTs) are rare mesenchymal tumors that arise from the abdominal, pelvic or retroperitoneal region, unrelated to the gastrointestinal tract. However, cases with a plasmoid morphology are extremely rare. we hererin report a 49-year-old man with abdominal pain who underwent magnetic resonance imaging that revealed an irregular tumor (103×71 mm) in size, in the space between stomach and pancreas, diagnosed as an EGISIT, we also reviewed the clinicopathological characteristics and immunohistochemical characteristics, molecular genetic features and differential diagnoses previously reported in the literature.

Key words: plasmoid differentiation, multiple metastatic, extra gastrointestinal stromal tumors, case report

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the digestive tract. Those that occur outside the gastrointestinal tract, e.g. in the omentum, mesentery, and retroperitoneum are called etra-GISTs (EGISTs) (1). The histological morphology of EGISTs is the same as that of GISTs, and the diagnosis depends on the immunohistochemistry and clinical history (2). However, cases with prominent plasmoid characteristics are rare, leading to an easy misdiagnosis as some other type of tumors.

We hererin report a case of multiple metastatic EGISTs with plasma cell differentiation characteristics and review its clinicopathological and immunohistochemical characteristics, molecular genetic features and differential diagnoses previously reported in the literature to improve our awareness of rare morphological characteristics of this tumor.

Case Report

A 49-year-old man was referred to our hospital due to an abdominal mass and pain. Two months earlier, the patient had felt a mass in the upper abdominal region with mild tenderness, abdominal distention, increased stool frequency (2-3 times/day) and a reduced food intake. Abdominal distention and pain appeared in the middle of May, so he visited our hospital for further treatment. His medical history was unremarkable.

A physical examination revealed a 70×80-mm mass in the upper abdomen and a 60×80-mm mass in the right lower abdomen, with unclear boundaries and positive tenderness, as well as the enlarged liver or spleen couldn't be touched. B-ultrasound detected a mass between the stomach and tail of the pancreatic body.

A laboratory examination showed that fibrin degradation product (FDP; 139.2 μg/mL), plasma D-dimer (D-D; >50 μg/mL), lactate dehydrogenase (LDH; 782 U/L), procalcitonin (PCT; 0.11 ng/mL) and carbohydrate antigen (CA125; 124 KU/L) values were significantly higher than the reference values. Magnetic resonance imaging (MRI) revealed an irregular mass of 103×71 mm in the space between the stomach and pancreas that was well demarcated with an uneven flat sweep signal and a long T1/T2 signal with uneven

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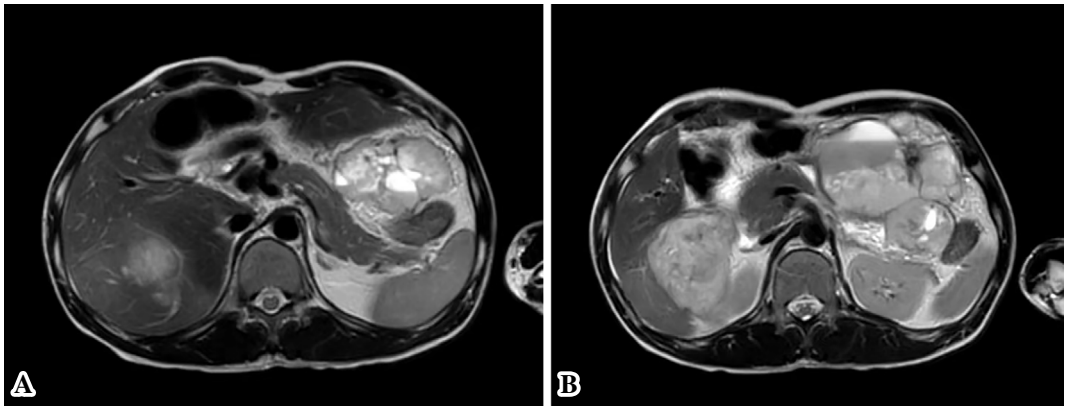

Figure 1. **MRI findings of EGIST. A: MRI showed a lobulated mass in the space between the stomach and pancreas that was well-demarcated. B: MRI showed an irregular mass in the right posterior lobe of the liver with an uneven high signal.**

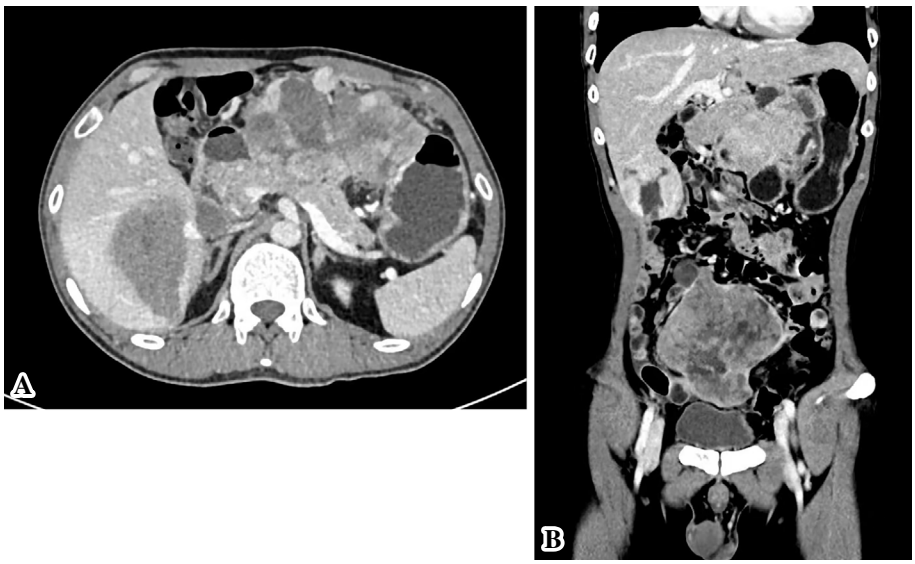

Figure 2. **CT findings of EGIST. A: Enhanced CT showed an abdominal mass with uneven enhancement and no enhanced necrotic area. B: Coronal multiplanar reconstruction showed a lobulated mass in the lower abdominal mesenteric areas.**

arterial lesion enhancement (Fig. 1A). There were multiple nodules of different sizes in the right abdominal wall, greater omentum, lower abdomen and pelvic cavity that also seemed to be unevenly enhanced. Under the liver parenchyma and capsule, there were multiple masses, the biggest of which was located in the right posterior lobe (73×55 mm), and some lesions protruded outside the liver (Fig. 1B); all of these lesions were considered likely to be malignant and metastatic.

Enhanced computed tomography (CT) revealed that the abdominal mass was unevenly enhanced, with no enhanced necrotic area, while the lesions in the lower segment of the right posterior lobe of the liver showed mild to moderate uneven enhancement (Fig. 2A). Coronal multiplanar reconstruction showed a lobulated mass in the lower abdominal mesenteric area, with moderately uneven enhancement, pushing against the surrounding small intestine and compressing the bladder (Fig. 2B). As a result of the unclear nature of the tumor, a B-ultrasound-guided biopsy was performed for the left upper abdominal mass (Fig. 3A) and liver mass (Fig. 3B), both of which showed the same morphology on Hematoxylin and Eosin (H&E) staining microscopically. The tumor was found to be composed of oval cells with abundant cytoplasm that were distributed in sheets and nests. Most of the nuclei were deviated, showing plasmoid and fine nuclear chromatin.

Immunohistochemical testing showed diffuse immunoreactivity for CD117 (Fig. 4A); CD34 (Fig. 4B), succinate dehydrogenase B (SDHB), vimentin and DOG1 (Fig. 4C) were partially positive; smooth muscle actin (SMA) was focally positive; and the Ki-67 labeling index was 5% (Fig. 4D). Cells were completely negative for cytokeratin (CK), low cytokeratin (L-CK), synaptophysin (Syn), chromogranin A (CgA), HMB45, S-100, CD38, CD138, kappa light chain (κ), lambda light chain (λ), Fli-1, TEF3 and CD99. Given the location of the tumor, the patient was diagnosed with

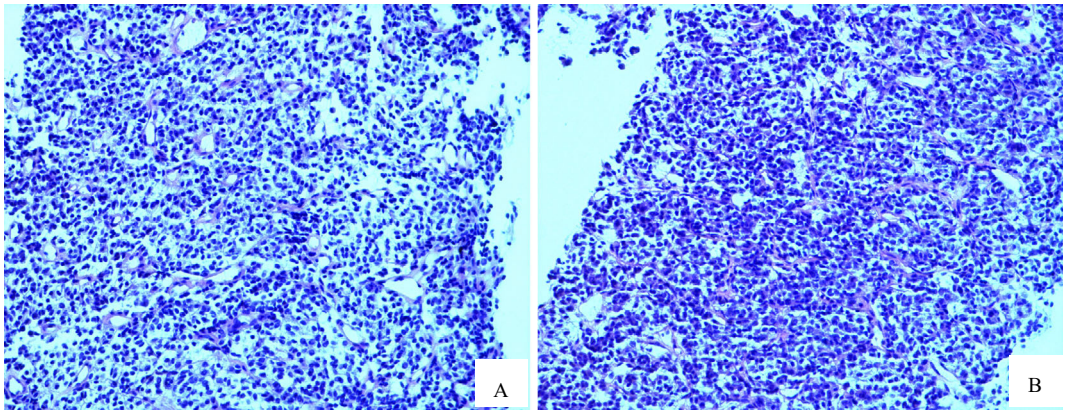

Figure 3. **Histopathological features of EGIST by a puncture biopsy guided by B-ultrasound (Hematoxylin and Eosin staining, ×200). A: The cells were oval-shaped with plasmoid characteristics in the abdominal tumor. B: Similar to the abdominal tumor, the metastatic cells of the liver showed plasmoid morphology.**

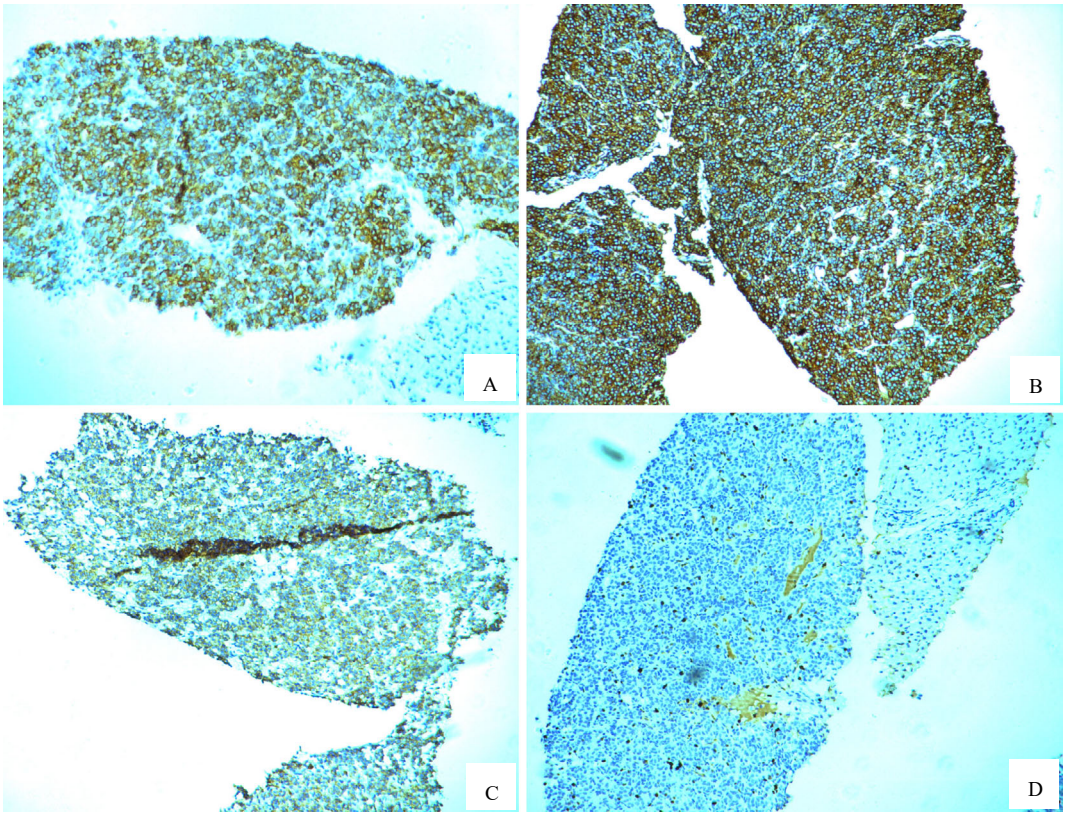

Figure 4. **Immunohistochemical staining of EGIST (Envision, ×100). A: The tumor cells were positive (+) for CD117. B: The tumor cells were strongly positive (++) for CD34. C: The tumor cells were positive (+) for DOG1. D: The Ki-67 index was about 5%.**

EGIST with liver metastasis.

Unfortunately, the patient refused to undergo genetic testing because of a poor economic status. His condition worsened, and in the end of June, the patient started self-administering imatinib at 400 mg/day, dying after 1 month (July 2021) of follow-up.

Discussion

GISTs tend to arise with a lower frequency than epithelial tumors in the digestive tract (3), and EGISTs are even less common, accounting for <5% of cases. They are insidious, and the clinical manifestations vary from benign to malignant (4). In 1998, Kindblom suggested that cells originated from Cajal interstitial cells (ICC) or immature cells differen-

Table 1. The Similarities and Differences of Clinicopathological Characteristics between GSIT and EGIST.

		GIST	EGIST
Similarites		1. Gender ratio and the patient's age range. 2. Nonspecific symptoms. 3. Liver metastasis is the most common metastasis pattern. 4. Morphological findings and histopathological type. 5. IHC staining for CD117, CD34 and DOG-1 6. KIT exon 11 and 9 mutation 7. Responsive to TKIs	
Differences	Common sites of tumor	Stomach, small intestinal	Mesentery, retroperitoneum
	Tumor size	Small (4-7 cm)	Large (7.5-15 cm)
	Imaging findings	Exophytic growth with well-defined borders	Large mass with necrosis and haemorrhage
	Tumor necrosis	Absence	Presence
	Mitotic counts	Low (4-8/50 HPF)	High (10-15/50 HPF)
	Risk grade	Low	High
	Treatment method	Radical resection	Adjuvant treatment with imatinib
	Prognosis	Lower morbidity rate, neither recurrence nor distant metastasis after sugery	Greater risk to recurrence or distant metastasis
	Median survival time	3-5 years	26.4-53.3 months
	Postoperative recurrence rate	2.63-7.1%	2-23%

tiated from ICC (5). While several hypothesis concerning the origin of EGISTs have been proposed, such as originating from extraintestinal undifferentiated mesenchymal cells (6) or stem cells (7), the precise origin remains unclear due to the lesion's rarity, so the further accumulation of EGIST cases and related studies is needed.

Some studies have reported similar epidemiological findings between EGISTs and GISTs (8-10). However, EGISTs show several differing characteristics from GISTs, as summarized in Table 1. Based on the tumor site, this case was diagnosed as an EGIST originating from the abdominal cavity. The liver is the most common site of metastasis, followed by the peritoneum in about 50%; lung, bone, and lymph node metastases are rare. Gaitanidis et al. reported that about 10% of GIST patients had liver metastasis at the diagnosis (11), which was considered simultaneous liver metastasis, as this case was. Due to the absence of typical gastrointestinal manifestations and the large abdominal space, EGIST is difficult to diagnose in the early stage, tending to result in a delayed diagnosis with many patients having large tumor volumes at the initial diagnosis. In the present case, the tumor diameter was >10 cm, placing the patient in the high-risk group with malignant biological behavior.

While there are no specific symptoms for EGIST, some radiographical findings can aid in distinguishing EGIST from GIST preoperatively (12) (Table 1). Importantly, the current diagnosis of EGIST is mainly based on the confirmation of the tumor site by CT and MRI. Furthermore, it is wort noting that a solid and cystic mixed or even cystic mass is generally observed in EGIST cases with tumor sizes larger than GISTs and showing peripheral enhancement with central necrosis, as was observed in our case.

Similar to GIST, the definitive diagnosis of EGIST is based on the pathological characteristics of the tissue sample and incorporates both the morphological and immunohistochemical characteristics. The histological morphology of spindle cell, epithelioid cell and mixed cell type is mainly observed, with the epithelioid type more strongly present in EGIST than in GIST; very few cases show a signet ring cell type (13). Thus far, no cases with plasmoid cell differentiation have been reported, and a careful review of the literature found that some cases presenting with inconspicuous plamoid cells were actually classified as the epithelioid type, in marked contrast to our case. Classical histopathology is easy to identify, but the confusing morphology in the present case where most tumor cells were plasmoid cells made it much more difficult to associate with GIST or EGIST. In addition to appropriate morphological findings, immunohistochemistry is extremely useful for the diagnosis of EGIST, based on positive staining findings for CD117 (94-96%), DOG1 (94-98%) and CD34 (60-82%) (2). However, SDHB should be assessed to confirm the diagnosis of non-SDHB-deficient GIST. Other markers, such as SMA, desmin, valponin (14) and S-100 (15) are expressed to varying degrees, while CK is occasionally positive, necessitating differentiation from other tumors, such as plasma cell neoplasms, hematolymphoid system tumors, Ewing's sarcoma, malignant melanoma, tumor with perivascular epithelioid differentiation and seminoma (Table 2). In the present case, CD117, DOG1 and CD34 were all positive, indicating the classical expression pattern on immunohistochemistry. Therefore, based on immunohistochemistry findings, non-SDHB-deficient EGIST was able to be diagnosed. Immunohistochemical biomarkers are therefore valuable for validating the diagnosis in the absence of typical features of morphology. For some cases with a special histological morphology and both DOG1 and CD117 negativity or single positivity, genetic testing is required to confirm the diagnosis.

Table 2. The Differential Diagnosis between EGIST and Other Tumors.

	Histopathological feature	Immunohistochemical staining							
		CD117	DOG1	CD34	LCA	CD138	CD99	HMB45	OCT3/4
EGIST	Spindle cell, epithelioid cell or mixed cell	+	+	-	-	-	-	-	-
Plasma cell neoplasms	Plasmoid cell	-	-	-	-	+	-	-	-
Hematolymphoid system tumors	Naked nucleus or rare cytoplasm	-	-	-	+	-	-	-	-
Ewing's sarcoma	Small round cells with lobulated distribution	-	-	-	-	-	+	-	-
Malignant melanoma	Obvious nucleoli and pigmentation	-/+	-	-	-	-	-	+	-
Tumor with perivascular epithelioid differentiation	Cells are arranged around the blood vessels in a sheet	-	-	-	-	-	-	+	-
Seminoma	Round cells with diffused lymphocyte	+	-	-	-	-	-	-	+

The identification of mutation sites and types is important for the accurate treatment and prognosis determination in patients. As the pathogenesis of GIST is already understood, it is recommended to sequence KIT (Exon 9, 11, 13, 17) and PDGFRA (Exon 12, 14, 18) mutations or perform second-generation sequencing detection of SDHA, SDHB, SDHC, SDHD, NF1, BRAF, K/N-RAS, PIK3CA and ETV 6-NTRK3 gene mutations and NTRK3 and FGFR1 rearrangement (16-18). The standard treatment for EGIST without metastasis is complete surgical resection with healthy margins (19) or enucleation surgery as an alternative, approaches that have resulted in neither recurrence nor distant metastasis (20). Tyrosine kinase inhibitors, represented by imatinib, have been widely used in first-line clinical therapy for metastatic cases and high-risk patients following complete surgical removal of the EGIST, and new-type targeted drugs, such as third-line regorafenib, fourth-line ripretinib, the KIT/PDGFRA-resistant gene mutation inhibitor avaprinib and NTRK inhibitors, have also achieved good clinical effects in the treatment of metastatic GIST (21). Mutation analyses for KIT and PDGFRA are strongly recommended, as they proved useful for verifying the diagnosis of EGISTs which are negative for CD117 and the curative effect of adjuvant therapy. In this report, the genetic status of the patient was unknown, and the patient died one month after blind administration of imatinib, suggesting that imatinib did not prolong his survival. Further studies are therefore needed to clarify the role of imatinib in EGIST.

The primary tumor site, R0 resection, tumor size, number of mitosis, Ki-67 level, risk grade, histological type and imatinib mesylate targeted therapy were found to be significant predictors of the survival in patients with EGIST (22-27). Most EGIST patients are in the high-risk group, and studies have shown that EGIST patients have a worse prognosis, shorter progression-free survival and higher recurrence rate than GIST patients (19, 28). However, definite prognostic factors are not included in the current guidelines, and whether the prognosis was good or bad even had controversial results. Although our patient had a low Ki-67 index, the prognosis was very poor. Therefore, more data are needed to accurately and comprehensively evaluate the prognosis of EGIST patients.

In conclusion, it is easy to diagnose EGIST with a typical histological morphology; however, when making the differential diagnosis, physicians should be alert for clinical cases with a special histological structure in order to avoid a misdiagnosis or missed diagnosis. In addition, although there are many clinicopathological and genetic similarities between EGIST and GIST, other differences in clinical manifestations, imaging findings, risk classification, treatment method, the prognosis and other aspects still exist between these entities. The further characterization of EGIST will require multi-center, large-scale and prospective studies.

The authors state that they have no Conflict of Interest (COI).

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