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Case Report

A Rare Clinical Case of Extra-gastrointestinal Stromal Pancreatic Tumor

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Abstract

Extra-gastrointestinal stromal tumors arising from the pancreas are extremely rare. To date, just over 30 cases have been described in the world literature. A clinical observation of a 67-year-old patient with dull epigastric pain and a large cystic solid neoplasm instrumentally identified as an extra-gastrointestinal stromal tumor of the head of the pancreas is presented. The volume of surgical intervention consisted of pancreatogastroduodenectomy and right-sided hemicolectomy, since tumor invasion into the transverse mesocolon was detected intraoperatively. The final diagnosis of extra-gastrointestinal stromal sarcoma of the head of the pancreas with invasion into the mesocolon pT4N0M0, stage IIIb was made on the basis of histopathology and immunohistochemistry results.

Extra-gastrointestinal stromal pancreatic tumors require careful differential diagnosis with other large abdominal masses. Timely diagnosis and use of modern treatment algorithms make it possible to avoid further disease progression.

Keywords

CD117, extra-gastrointestinal stromal tumor, immunohistochemistry, pancreas, targeted therapy

INTRODUCTION

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal neoplasms of the gastrointestinal tract. They can occur in any segment, extending from the esophagus to the rectum, but in most cases, GIST are localized in the stomach and small intestine.[1-3] A group of stromal tumors similar to GIST in histological and immunohistochemical characteristics, but detected outside the gastrointestinal tract (mainly in the retroperitoneal space, omentum and mesentery), was called "extra-gastrointestinal stromal tumors" (EGIST).[3] There have been incidental cases of the of EGIST developing from the liver, kidneys, gallbladder, bladder, prostate, abdominal wall, pleura, mediastinum, etc.[2] EGISTs of the pancreas are extremely rare. To date, just over 30 cases have been described in the world literature.

CASE PRESENTATION

A 67-year-old female patient was routinely admitted to the Department of Hepatopancreatobiliary Surgery No. 50 of Botkin Hospital for additional examination and further

decision on treatment strategy. She had been having a dull pain in the epigastrium and a bad taste in her mouth for two months before hospitalization. A month before she had been admitted to the hospital, abdominal CT scan with IV contrast was performed, which revealed a mass in the epigastrium and mesogastrium on the right with a size of about 154×136×117 mm, intimately adjacent to the duodenum and transverse colon ***(Fig. 1)****.*

Upon admission, the patient did not have any symptoms, physical examination was unremarkable. Blood examination revealed mild anemia (hemoglobin, 99 g/l), biochemical indicators were without significant deviations, the main tumor markers levels were within the reference values ***(Table 1)****.*

During hepatobiliary ultrasound, a retroperitoneal mass in the right epi- and mesogastrium at the level of the head of the pancreas was found. It had an irregular shape with a cystic-solid structure and uneven clear margins, up to 150×135×125 mm in size. The central part of the mass was represented by heterogeneous liquid with an echogenic suspension. The walls of the cyst had increased echogenicity and were up to 10 mm in width. Septa were visualized in the cyst cavity. Doppler ultrasound revealed moderate vascularization along the margins. No signs of pancreatic or biliary hypertension were detected. Therefore, there was a volumetric partially cystic retroperitoneal mass on the right, most likely originating from the head of the pancreas. It was hard to differentiate between a cystic tumor and a post-necrotic cyst ***(Fig. 2)****.*

The patient underwent open surgery. Intraoperatively, a giant retroperitoneal mass was found in the region of the head of the pancreas and the uncinatum process. During the puncture of the mass, about 600 ml of hemorrhagic content

Table 1. Tumor markers levels in the blood serum

Tumor marker	Result	Unit of measurement	Reference values
AFP	3.58	ng/ml	0.2–10
CEA	384	ng/ml	0.2–5
CA 19-9	1.6	U/ml	0–35
CA 125	8,4	U/ml	0–35
CA 15-3	9.7	U/ml	0–31.3
CA 72-4	5.62	U/ml	0–6

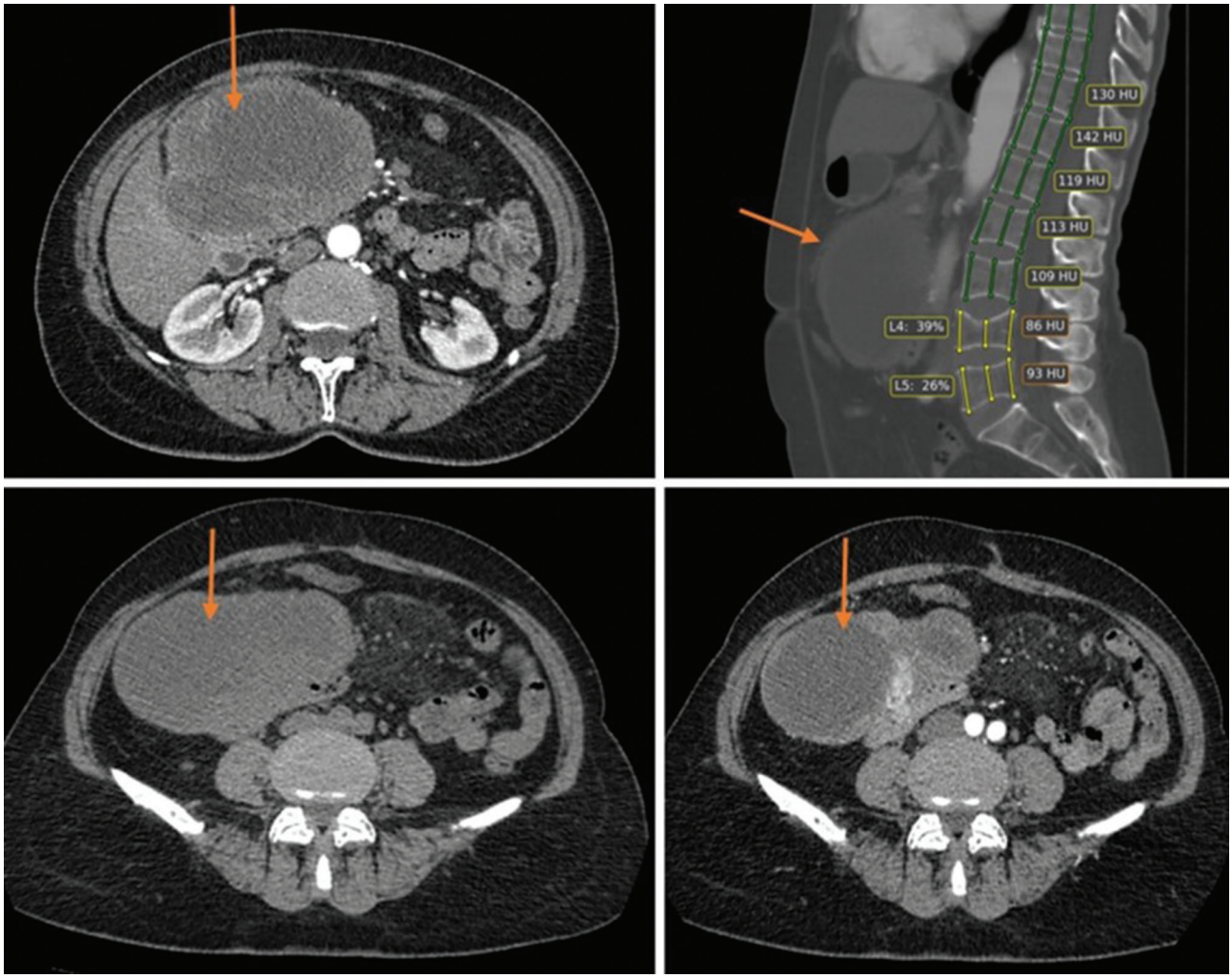

Figure 1. CT image of the mass formation of the abdominal cavity.

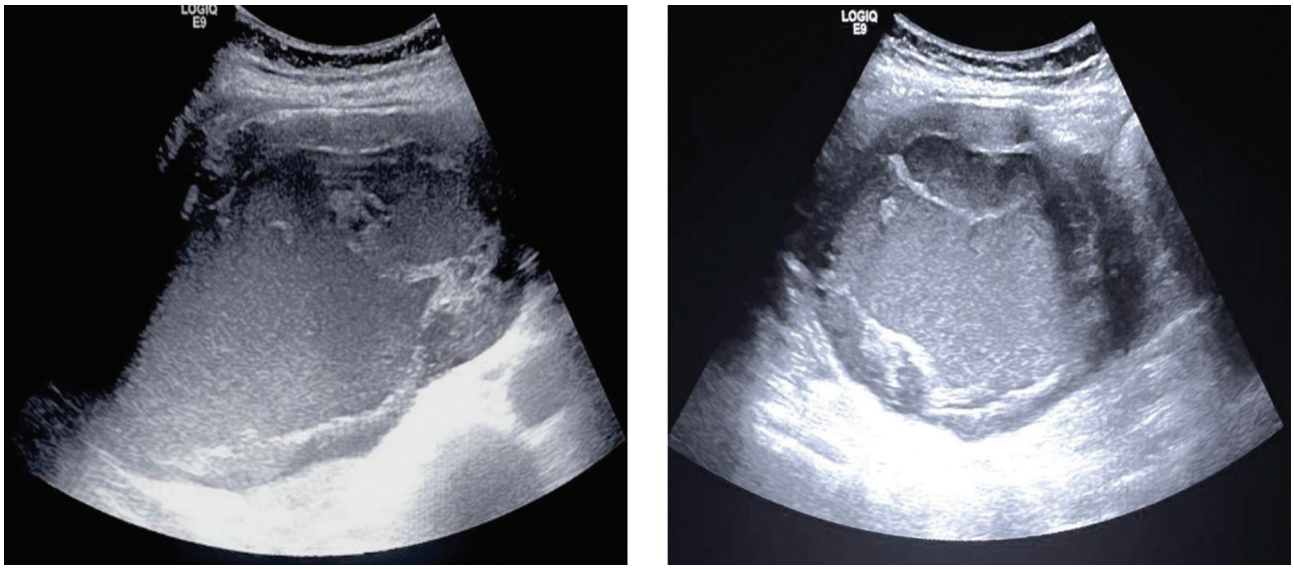

Figure 2. Ultrasound image of a retroperitoneal complex cyst.

was obtained. The adjacent visceral and parietal peritoneum walls were without signs of carcinomatosis. The tumor invaded the transverse mesocolon and compressed the duodenum. There were no signs of vascular invasion. Taking into account the localization of the mass and invasion into the transverse mesocolon, pancreatogastroduodenectomy was performed in combination with right-sided hemicolectomy, side-to-side ileotransversoanastomosis, pancreaticojejunoanastomosis, hepaticojejunoanastomosis, end-to-side entero-enteroanastomosis, and gastroenteroanastomosis ***(Fig. 3)****.*

During pathomorphological examination, the tumor node macroscopically was with cystic transformation. Its walls were grey, lobular, with foci of hemorrhages, up to 1.5-2.0 cm in width. Blood clots were seen in the cyst lumen. Microscopically, the tumor was represented by intertwining spindle and epithelial cells with edema, foci of hemorrhage and necrosis. Resection margins were without tumor growth (R_0). Immunohistochemical analysis (IHC) showed presence of CD34 and CD117 and absence of S100 and DOG1 markers. Ki67 proliferative activity index was 15%. Based on the intraoperative data, tumor morphology and immunophenotype, the final diagnosis was extra-gastrointestinal stromal sarcoma of the head of the pancreas with invasion into the mesocolon, epithelioid-spindle cell variant, $pT_4N_0M_0$ stage IIIb ***(Fig. 4)****.*

In the early postoperative period, no signs of fluid accumulation or inflammatory infiltrates in the abdominal cavity were detected; however, delayed food passage through the stomach was noted. Esophagogastroduodenoscopy identified

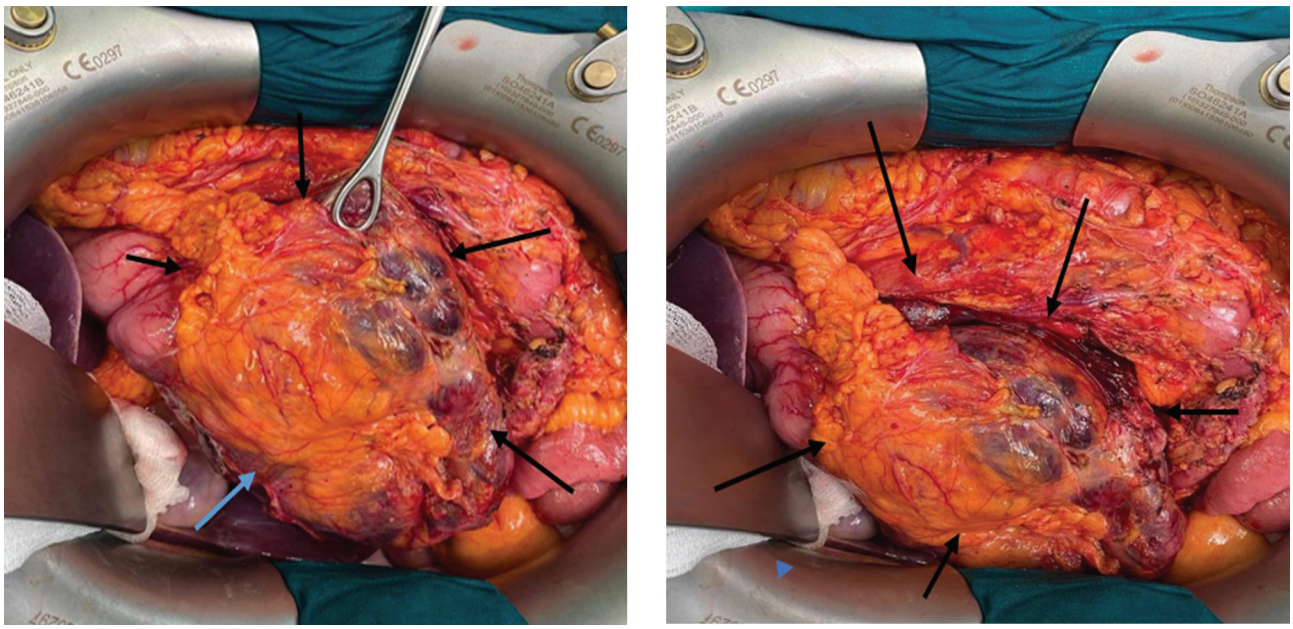

Figure 3. Intraoperative image of the tumor (arrows mark the tumor).

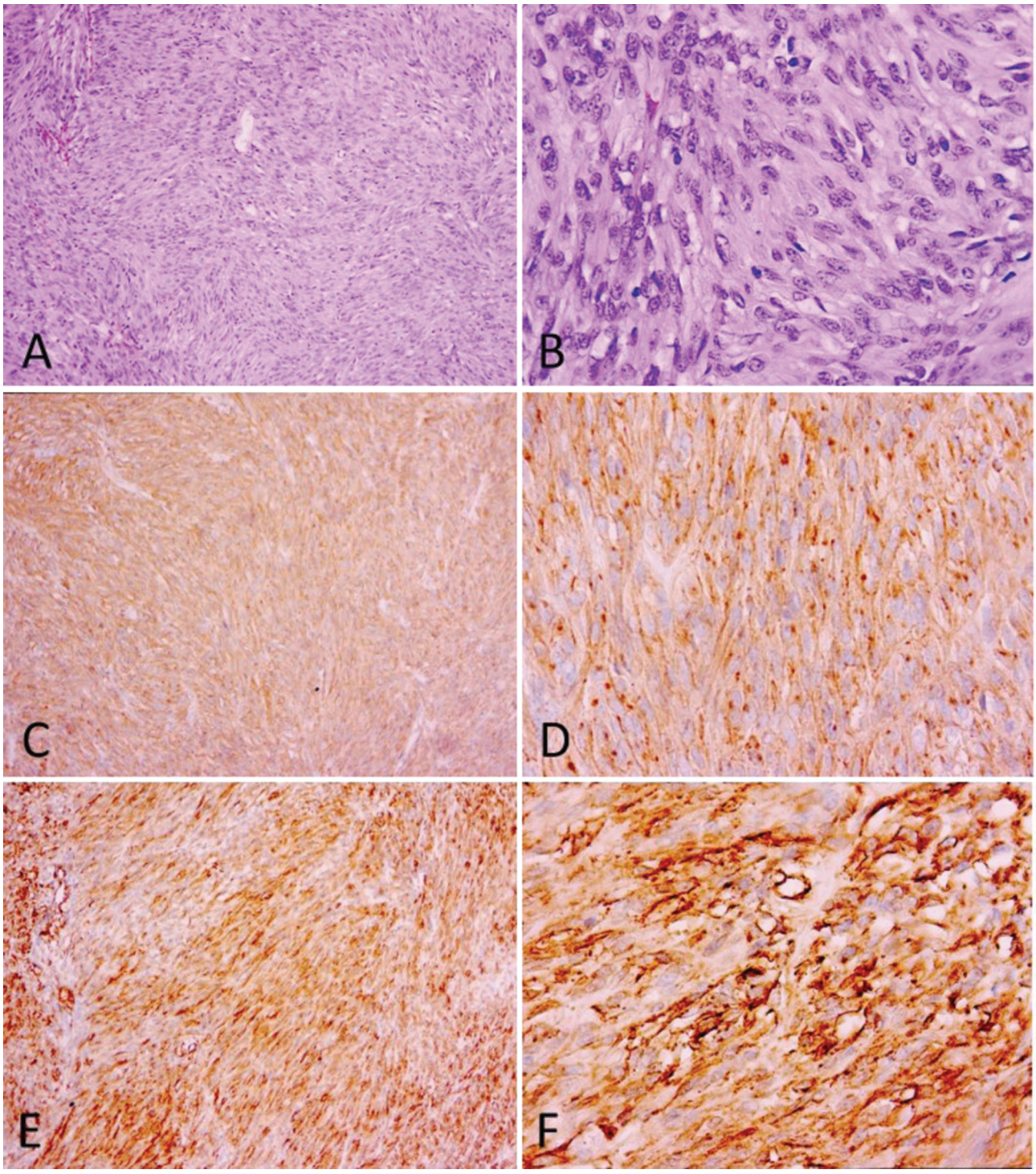

Figure 4. Tumor specimen histopathological image. **A**. H&E stain (×100); **B**. H&E stain (×400); **C**. CD117+ (×100); **D**. CD117+ (×400); **E**. CD34+ (×100); **F**. CD34+ (×400).

a deformity of gastroenteroanastomosis without signs of stenosis. After a failed attempt to endoscopically dilate the anastomosis area, a gastric stasis persisted and laparoscopic adhesiolysis was performed. The postoperative period was without any other complications. The patient was discharged 11 days after operation. At the 1-year follow-up examination, there was no evidence of relapse.

DISCUSSION

The term "gastrointestinal stromal tumors" was introduced in 1983 by MT Mazur and HB Clark, who for the first time identified a special subgroup of non-epithelial tumors of the gastrointestinal tract, differing in their immunohistochemical and ultrastructural characteristics from tumors

with true neurogenic and smooth muscle differentiation.[3,4] GIST are the most common mesenchymal tumors of the gastrointestinal tract, although they comprise only 1-3% of all primary neoplasms of this localization. These tumors most often occur in the stomach (60%–70%), but they also can be found in the small intestine (20%–25%), the large intestine (5%), and in the esophagus (<5%). EGISTs were first described in 2000. They are much less common than their gastrointestinal counterparts and account for less than 5% of all stromal tumors.[5]

GIST is believed to originate from Cajal interstitial cells, located between the circular and longitudinal muscle fibers of the walls of the gastrointestinal tract and regulating their spontaneous peristaltic activity.[4-5] The origin of EGIST currently remains controversial. Some authors believe that EGIST can be the result of extensive extramural growth of GIST, leading to their loss of contact with the wall of the gastrointestinal tract. Others suggest that EGISTs arise from Cajal and smooth muscle interstitial progenitor cells.[6] There are also publications suggesting the occurrence of EGIST from mesenchymal cells with the Cajal interstitial cell phenotype outside the gastrointestinal tract.[2]

In the vast majority of cases, the main triggering mechanism of stromal tumors development is a mutation of the C-KIT proto-oncogene which is located on chromosome 4 (4q11-4q13) and encodes the CD117 tyrosine kinase transmembrane receptor protein.[3]

The most selective IHC marker for distinguishing stromal tumors from true smooth muscle tumors is CD117, positive in 95% of cases. Expression of the CD34 hematopoietic stem cell receptor is detected in 60%–70% of cases.[7] Other mesenchymal markers periodically detected by IHC include DOG-1, smooth muscle actin, S-100, SMA, vimentin, desmin, and keratin.[8] A very important marker is the Ki-67 proliferative activity index, the expression level of which is directly proportional to the degree of tumor aggressiveness.[4]

GIST are divided into three main types: spindle cell (70%), epithelioid (20%) and mixed cell (10%).[1] Spindle cell tumors consist of elongated cells that form beam-like structures, have a less developed fascicular pattern, and are devoid of cytoplasmic eosinophilia. Epithelioid tumors are characterized by rounded or oval cells with eosinophilic cytoplasm. Mixed-cell forms are characterized by a combination of both spindle-cell and epithelioid-cell sites.[6]

Since GIST is mostly a spindle cell proliferation tumor, it must be differentiated from leiomyoma, leiomyosarcoma, schwannoma, fibrosarcoma, fibromatosis, inflammatory fibroid polyps, and other tumors of mesenchymal origin. Differential diagnosis is made on the basis of histopathological, immunophenotypic and molecular features. Immunohistochemical study with positive CD117 (C-Kit) confirms the diagnosis of GIST.[1] Analysis of mutations in the C-Kit and PDGFRA genes can be useful in cases where CD117 is negative, and can also be used to predict the therapeutic response to imatinib.[5]

The standard method of treating patients with localized and locally advanced forms of GIST is complete surgical resection with negative microscopic edges.[7] The choice of the optimal type of resection for EGIST of the pancreas depends on the localization of the mass. Pancreatoduodenectomy is performed for tumors of the head of the pancreas, and distal pancreatectomy – for tumors of the body and tail.[9] In small tumors with clear boundaries, duodenum-sparing resection of the pancreatic head or simple excision of the tumor is acceptable.[8] Systemic regional lymphadenectomy is usually not considered, since the incidence of lymphogenic metastasis in stromal tumors does not exceed 1%–3%. It is very important to prevent the rupture of the tumor capsule during surgery, as this can significantly worsen the prognosis of the disease.[4,10]

Stromal tumors have extremely low sensitivity to traditional chemotherapeutic drugs and radiotherapy: the response rates are less than 10% and 5%, respectively.[10,11] Targeted therapy with C-Kit tyrosine kinase inhibitors is now widespread. The most commonly used drug in this group is imatinib. Adjuvant imatinib therapy has been shown to reduce the risk of recurrence and increase the five-year survival rate after surgery.[9] Adjuvant targeted therapy for a year is recommended for all GIST patients with a high risk of progression. Neoadjuvant imatinib therapy is the gold standard for treating conditionally resectable, unresectable, and metastatic forms of gist. The purpose of preoperative treatment is to reduce the tumor mass, increase the resectability and frequency of organ-preserving operations, as well as reduce the risk of recurrence.[4,11]

The prognosis in patients with GIST depends on the biological behavior of the tumor. Fletcher et al. developed criteria for assessing the risk of aggressive behavior and GIST metastasis based on tumor size (cm) and the number of mitoses (50 in the field of view) according to histological examination. According to these criteria, GIST are divided into categories of very low (<2 cm, <5/50 per field of vision), low (2-5 cm, <5/50 per field of vision), intermediate (<5 cm, 6-10/50 per field of vision or 5-10 cm, <5/50 per field of vision), and high (>5 cm, >5/50 per field of vision or >10 cm, any number of mitoses) risk of metastasis.[5,10] Predictors of poor prognosis may also include a Ki-67 expression proliferation index greater than 10%, the presence of a tumor capsule rupture before or during surgery, vascular invasion, and the presence of foci of necrosis. GIST is more likely to metastasize by hematogenous means, with up to 90% of metastases found in the liver. Implantation metastases into the peritoneum and into the greater omentum are also possible.[4]

EGIST of the pancreas is an extremely rare tumor and requires careful differential diagnosis with other large tumors of the abdominal cavity. Diagnostic modalities such as CT with intravenous contrast and ultrasound of the abdominal organs, make it possible to visualize the tumor. Nevertheless, the diagnosis must be confirmed on the basis of a morphological examination of the removed specimen with immunohistochemical analysis for specific markers.

It is impossible not to pay attention to the discrepancy between the general satisfactory condition of the patient and the severity of the disease. The patient presented with extremely scarce, nonspecific clinical symptoms with no signs of biliary obstruction or deviations of laboratory tests. There is no doubt that the patient belongs to the group of high risk of recurrence, taking into account the large size of the tumor (15 cm), invasive growth in the mesentery of the transverse colon, the proliferation index of Ki-67 expression – 15%, the presence of foci of necrosis. In this regard, the patient is required to undergo adjuvant targeted therapy with imatinib for a year and intensive follow-up.

CONCLUSIONS

The presented clinical observation clearly demonstrates the importance of timely diagnosis of an extra-gastrointestinal pancreatic tumor, often characterized by an aggressive course, and the use of modern treatment algorithms, which makes it possible to avoid further progression of the disease, as well as to reduce mortality and improve the quality of life of patients.

Ethics

Written informed consent was obtained from the patient to publish the cases report.

Author contributions

S.A., B.Z., T.M., D.D., A.I., Sh.T., I.N., F.A., Ch.Z., and C.S. conceived and designed the analysis; S.A., B.Z., T.M., D.D., A.I., Sh.T., I.N., F.A., Ch.Z., and C.S. collected the data; A.I., Ch.Z., and C.S. contributed data or analysis tools; Ch.Z. and C.S. drafted the manuscript; S.A., B.Z., T.M., D.D., A.I., Sh.T., I.N., F.A., Ch.Z., and C.S. edited the final version of the manuscript.

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Competing Interests

The authors have declared that no competing interests exist.

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Редкий клинический случай экстрагастроинтестинальной стромальной опухоли поджелудочной железы

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Резюме

Внегастроинтестинальные стромальные опухоли, возникающие из поджелудочной железы, встречаются крайне редко. На сегодняшний день в мировой литературе описано чуть более 30 случаев. Представлено клиническое наблюдение больного 67 лет с тупыми болями в эпигастрии и крупным кистозным солидным новообразованием, инструментально идентифицированным как внегастроинтестинальная стромальная опухоль головки поджелудочной железы. Объём оперативного вмешательства включил панкреатогастродуоденэктомию и правостороннюю гемиколэктомию, поскольку интраоперационно была выявлена инвазия опухоли в поперечно-ободочную кишку. На основании результатов гистопатологии и иммуногистохимии установлен окончательный диагноз: экстрагастроинтестинальная стромальная саркома головки поджелудочной железы с инвазией в среднетолстую кишку pT4N0M0, стадия III b.

Внегастроинтестинальные стромальные опухоли поджелудочной железы требуют тщательной дифференциальной диагностики с другими крупными образованиями брюшной полости. Своевременная диагностика и использование современных алгоритмов лечения позволяют избежать дальнейшего прогрессирования заболевания.

Ключевые слова

CD117, внегастроинтестинальная стромальная опухоль, иммуногистохимия, поджелудочная железа, таргетная терапия.