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CASE REPORT

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Liver metastasis from pancreatic gastrointestinal stromal tumor presenting 5 years after resection: a rare case with management challenges

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Abstract

Gastrointestinal stromal tumors (GISTs) are rare mesenchymal tumors arising from the gastrointestinal tract. Stromal tumors arising outside the gastrointestinal tract are called extra-gastrointestinal stromal tumors, usually found in omentum, mesentery, retroperitoneum and gallbladder. We report a case of 31 years old male with 3-month history of painless jaundice and undocumented weight loss. Computerized tomography scan showed a well-defined, rounded enhancing lesion in the uncinate process of pancreas measuring 53x49mm compressing the distal common bile duct. Percutaneous biopsy confirmed gastrointestinal stromal tumor. He underwent Whipple's procedure followed by adjuvant imatinib due to high-risk features. He remained well for a long time and developed oligo-metastasis in liver 5 years after resection while he was still on imatinib. The patient underwent hepatic resection and remains well one year after the second resection on adjuvant treatment. Pancreatic extra-gastrointestinal stromal tumor involving uncinate process is a rare disease entity. First line of management is negative margin resection followed by adjuvant therapy with imatinib for high-risk tumors. In case of resectable liver metastasis, resection of metastasis followed by multimodal therapy seems to prolong the disease free and overall survival.

Keywords: *pancreas, gastrointestinal stromal tumor, Whipple's procedure*

Introduction

Gastrointestinal stromal tumors (GISTs) are rare mesenchymal tumors arising from gastrointestinal tract. The most common location is the stomach (50-60%), followed by small bowel (20-30%), large bowel (10%), and esophagus (5%) [1]. Stromal tumors arising outside the gastrointestinal tract are called extra-gastrointestinal stromal tumors (EGISTs), and are usually found in omentum, mesentery, retroperitoneum and gallbladder [2]. Pancreatic EGIST is extremely rare and only 45 cases have been reported in literature [3]. We report a case of 31 years old male, who had Whipple's procedure done for pancreatic head GIST at our institution, developed liver metastasis after five years and underwent liver resection.

Case

AA 31 years old male presented to our outpatient clinic in 2012 with three-month history of painless jaundice and undocumented weight loss. Physical examination revealed icterus and a palpable gallbladder. Laboratory investigations revealed normal blood counts and coagulation profile, but liver function tests were deranged with a total bilirubin of 12.1mg/dl, direct component of 7.4mg/dl, alkaline phosphatase of 435IU/L and serum CA 19-9 level of 217U/ml. Ultrasound abdomen showed a large mass in head of pancreas with dilated intra and extra hepatic bile duct. Pancreatic protocol computerized tomography scan (CT) showed a well-defined, rounded enhancing lesion in the uncinate process of pancreas measuring 53x49 mm compressing duodenum and common bile duct with resultant biliary dilatation (Figure 1). Considering the imaging features atypical for a primary pancreatic adenocarcinoma, the patient underwent image-guided biopsy of the lesion. Histopathology showed spindle cells with abundant eosinophilic cytoplasm and hyperchromatic to vesicular nuclei strongly reactive for CD117 and CD 34 consistent with GIST. The Patient underwent a standard Whipple's procedure; intra-operatively tumor was involving the uncinate process of pancreas. Final histopathology of the resected specimen revealed pancreatic GIST with high-risk features including size of 6.5x6x5cm and mitotic index of 43/50 on high power fields (HPF) (Figure 2). All tumor margins were negative and this was considered an R0 resection. After uneventful postoperative course, patients was discharged on 8th postoperative day and referred to oncology clinic for adjuvant treatment considering the high-risk features. Patient was started on Imatinib and had regular follow-ups including surveillance CT scans. His CT scan done at 5 years showed a lesion in segment VII of liver, which was biopsied, and histopathology was consistent with metastatic GIST. Case was discussed in the institutional tumor board meeting and resection was advised. Patient underwent segment VII hepatectomy and final histopathology confirmed negative margin resection of metastatic GIST. Patient was discharged on 5th postoperative day on adjuvant Imatinib. He is asymptomatic with no evidence of disease recurrence at one year after the second surgery.

Discussion

Extra-intestinal GISTs account for 5% to 10% of all GISTs and commonly located in omentum, mesentery or retroperitoneum. EGISTS arising from pancreas constitute only 5% of all EGISTs [4]. The concept of GIST has recently been established, due to the progress in immunohistochemical analyses. The tumor cells are presumed to originate from interstitial cells of Cajal, which are pacemaker cells to regulate motility, and present throughout the wall of gastrointestinal tract. Interstitial cells of Cajal share many characteristics with EGISTs, including expression of CD117

and CD34. The most selective immunohistochemical markers differentiating GISTs from true smooth muscle tumors is the expression of the c-Kit receptor tyrosine kinase (CD117 antigen), present in about 95% of GISTs [5]. The KIT mutation leads to kinase activation, and experimental studies have demonstrated that the mutation is capable of causing Cajal cells hyperplasia and GIST-like tumors in mice [6]. In addition, GISTs are generally (40 to 70% of the time) positive for CD34. These may also show associated variablepositivity for other mesenchymal markers, such asvimentin, myoid (smooth muscle actin anddesmin) and neural (S100) markers [7].

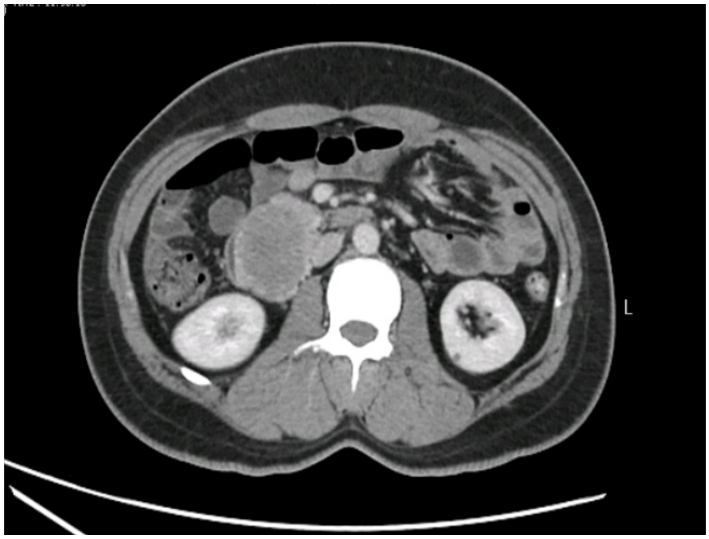

Figure 1. *Axial section of CT scan showing a well-defined, rounded enhancing lesion in the uncinate process of pancreas measuring 53x49mm.*

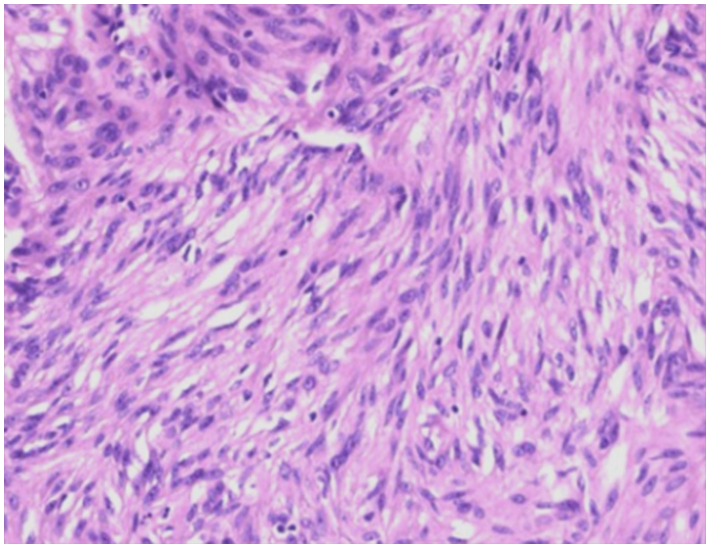

Figure 1. *Axial section of CT scan showing a well-defined, rounded enhancing lesion in the uncinate process of pancreas measuring 53x49mm.*

Origin of extra-intestinal GISTs still remains controversial. One of the hypothesis suggests that they may be the result of extensive extramural growth of mural GISTs resulting in minimal or complete loss of contact with the muscularis propria [8]. Other school of thought is that interstitial cells of Cajal may not be the actual cells of origin, but that GISTs actually arise from a common precursor cell of the interstitial cells of Cajal and smooth muscle, which accounts for their growth within and outside the gastrointestinal tract. Popescu et al. have recently shown the existence of interstitial cells of Cajal in the human exocrine pancreas, which have a phenotype similar to that of the enteric interstitial cells of Cajal [9]. Although the exact function of these cells is not clear, the discovery of exocrine pancreatic interstitial cells of Cajal supports the diagnosis of EGISTs arising from the pancreas.

Clinical presentation of EGISTs is variable depending on the location and size of tumor in pancreas. Unfortunately the diagnostic accuracy of CT scan in detecting EGISTs is not very high. In 50% of reported cases in literature showed heterogeneous mass with necrotic areas or solid cum cystic appearance that could raise the possibility of cystic neoplasm of pancreas. The diagnostic accuracy of CT for cystic pancreatic lesion is less than 50% [10,11]. Tissue diagnosis is the only way to diagnose EGIST in preoperative setting, which can be either done with endoscopic ultrasound or percutaneous image guided. Our patient had CT guided percutaneous biopsy and the histopathology confirmed EGIST with strong immunohistochemical positivity of CD117 and CD 34.

First line of treatment for EGIST is negative margin resection for resectable disease with no metastasis and the procedure depends on location and extent of disease [12]. Our patient underwent a standard Whipple's procedure because of the location of tumor. Routine lymph node dissection is not indicated in pancreatic EGIST cases because of rare regional lymph node metastases[13]. Clinical behavior of EGISTs is broad spectrum ranging from low risk with stable disease for years or high risk with metastatic disease. National Institute of Health (NIH) consensus criteria (Fletcher's criteria) proposed risk stratification of tumor behavior into risk categories of very low, low, intermediate, and high risk of metastasis, based on its size and mitotic activity. Tumors larger than 10 cm in size and with more than 10 mitoses per 50 HPF are at high risk of aggressive behavior [14]. Our patients final histopathology revealed pancreatic EGIST with high risk features, tumor size of 6.5x6x5cm with mitotic index of 43/50 high power fields (HPF).

Imatinib, which is an inhibitor of the tyrosine kinase activity of C-Kit, has been recommended as a treatment of EGISTs with high-risk features [15]. According to European Society for Medical Oncology 2017 report, long-term results from a trial comparing adjuvant imatinib treatment to observation after R0/R1 resection for GIST support the recommendation to administer imatinib only in patients with high-risk features [16]. Considering the high risk features on final histopathology, our patient was started on adjuvant imatinib 400mg twice daily. There is no consensus on the duration of imatinib for these patients. One phase II trial studying five-year imatinib therapy for high-risk patients showed five-year recurrence free survival rate of 90% and overall survival rate of 95% [17]. DeMattero et al. [15] have reported that most recurrence of GIST occurred within 24 months after resection, with liver and peritoneum being the most common site of recurrence. Reith et al reported that 39% of patients with EGIST developed metastatic

disease or died from tumors within a short period, suggesting that EGIST was an aggressive type of stromal tumor [18].

Our patient presented 5 years after resection of the primary EGIST with oligo-metastasis of the liver and underwent a second major resection. Management of patients with liver metastasis after resection is multimodal. A study by Shi YNet al showed that patients who received combination therapy with tyrosine kinase inhibitors and hepatic resection had more favorable outcomes with increased median survival time when compared with those who just received imatinib (89 vs 53 months) which indicated better overall survival in patients with combined therapy [19]. Our patient remains symptom free at one year after second resection.

Conclusion

Pancreatic EGIST involving uncinate process is a rare disease entity. First line of management is negative margin resection followed by adjuvant therapy with imatinib for high-risk tumors. In case of resectable liver metastasis, resection of metastasis followed by multimodal therapy seems to prolong the disease free and overall survival.

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