

Adenosquamous carcinoma of the uncinate process of the pancreas with synchronous gastrointestinal stromal tumor of the stomach: Case report and review of the literature

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Received June 11, 2012; Accepted August 29, 2012

DOI: 10.3892/ol.2012.902

Abstract. Recently, the coexistence of gastrointestinal stromal tumors (GISTs) with other neoplasms has been studied with increasing frequency. Coexistence of pancreatic cancer with GISTs remains a rarity; however, here, we report a very rare case of adenosquamous carcinoma (ASC) of the uncinate process of the pancreas with synchronous GISTs of the stomach in a 62-year-old female. The patient presented with epigastric discomfort and vomiting. Radiographic imaging revealed two masses; one located at the body of the stomach and the other located at the uncinate process of the pancreas. Intraoperatively, a fine needle aspiration biopsy was conducted in the uncinate process of the pancreas, which revealed the malignancy of the masses. A pancreaticoduodenectomy and partial gastrectomy were then conducted, and subsequent pathological examinations identified an ASC of the pancreas and a GIST of the stomach. In our case, contrary to the majority of previous cases of synchronous GISTs and other malignancies, GIST was not an incidental finding. The initial suspicion on the GIST as the underlying cause of clinical symptoms led to the discovery of the ASC of the uncinate process of the pancreas.

Introduction

Recently, the synchronous occurrence of primary neoplasms has been studied with increasing frequency, which may be due to the improved preoperative imaging capabilities. The coexistence of gastrointestinal stromal tumors (GISTs) with other gastrointestinal or non-gastrointestinal malignancies has also been studied with increasing frequency, although the occurrence remains rare (1). It has been identified that the overall frequency of second tumors in different sites among patients with GISTs ranges between 4.5 and 18.6%, with a mean of 13% (2).

GISTs are the most common type of mesenchymal tumor of the gastrointestinal tract, which most likely arise from precursor interstitial cells of Cajal. The majority of GISTs occur as a single lesion. They are common in the stomach (60-70% of all cases) and small intestine (30%), while they rarely occur in the rectum (5%), esophagus, colon, pancreas, appendix, omentum, mesentery and retroperitoneum (3). The best survival predictors are the size, location and mitotic rate of the tumor.

Pancreatic cancer is a common gastrointestinal malignancy. Ductal adenocarcinoma accounts for 80-85% of pancreatic tumors, while adenosquamous carcinoma (ASC) of the pancreas is a rare, aggressive variant of pancreatic carcinoma with a worse prognosis. Its exact incidence is not known; however, autopsy and surgical specimen findings suggest that this lesion accounts for 1-4% of all exocrine malignancies of the pancreas (4).

The uncinate process is a hook-like extension of the lower part of the pancreatic head that projects medially and wraps around the superior mesenteric vessels. Carcinoma in the uncinate process of the pancreas (CUPP) appears to be less common than that in other parts of the pancreas. Previous studies identify an incidence rate of 2.5% (3/119) (5), 7.7% (39/506) (6) and 10.7% (6/56) (7) of pancreatic malignancies.

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Key words: adenosquamous carcinoma, gastrointestinal stromal tumor, synchronous cancer, uncinate process of the pancreas

To the best of our knowledge, only one case in the literature demonstrated coexistence of ASC of the head of the pancreas with GIST (8), and the small GIST in this patient was only incidentally identified following surgery. With approved patient consent, we report a case of ASC of the uncinate process of the pancreas with the synchronous occurrence of large symptomatic GIST. 1. The study was approved by the Ethics Committee of The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China.

Case report

A 62-year-old female presented with a chief complaint of recurrent epigastric discomfort and progressively worsening vomiting for two weeks. The patient had experienced anorexia and weight loss for several months, but had no significant past medical history. The patient's family history was significant for pancreatic cancer from her mother, but no other malignancies were present in her other immediate family members. On admission, the patient's vital signs were stable and a mass of approximately 10 cm was palpated in the upper quadrant area of the abdomen. The remainder of the examination was unremarkable.

The complete blood count identified a white cell count of 6,900 cells/mm³ (73.4% neutrophils), hemoglobin count of 135 g/dl and a platelet count of 181,000 platelets/mm³. The blood chemistry examination revealed 23.0 μ mol/l total bilirubin, 9.6 μ mol/l direct bilirubin, 74 U/l aspartate transaminase (AST) and 102 U/l alanine aminotransferase (ALT). The carbohydrate antigen 19-9 (CA19-9) was slightly elevated to 78.4 U/l (normal range, 0-37 U/l), while carcinoembryonic antigen (CEA), α -fetoprotein (AFP), carbohydrate antigen 24-2 (CA24-2), blood glucose, calcium and amylase levels were within normal ranges.

Computed tomography (CT) revealed a discrete mass measuring 8x7 cm with notable enhancement in the body of stomach (Fig. 1). It also revealed a 4x3-cm lesion with an unclear boundary and mild enhancement in the uncinate process of pancreas and close to the horizontal part of the duodenum (Fig. 2). Ultrasonography of the liver, pancreas, spleen and gallbladder revealed no abnormality.

The initial impression from the CT scan was emphasized on the gastric mass as the lesion in the uncinate process of the pancreas was not well-defined. The gastric mass was suspected to be a GIST (Fig. 1), and the symptoms of bowel obstruction were suggested to be caused by the presumed GIST in the patient's stomach. However, an upper gastrointestinal series with meglumine diatrizoate was consistent with a partial bowel obstruction at the level of the third portion of duodenum. Therefore, the case was discussed at the multi-disciplinary team (MDT) conference, and it was recommended to intraoperatively explore the pancreas in addition to the resection of the gastric mass.

Intraoperatively, no liver metastasis or peritoneal dissemination was identified. A solid, partially capsulated mass, measuring approximately 8x7x7 cm, was identified in the body of the stomach near the lesser curvature. Another solid mass was also revealed in the uncinate process of the pancreas, which had horizontally infiltrated part of duodenum and closely adhered to the inferior vena cava for ~4 cm (Fig. 2).



Figure 1. Abdominal CT scan revealing a tumor in the body of stomach (arrow). CT, computed tomography.

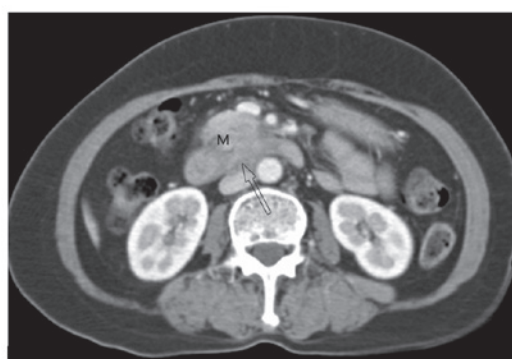


Figure 2. Abdominal CT scan revealing a tumor in the uncinate process of pancreas with an unclear boundary, which had horizontally infiltrated part of the duodenum and closely adhered to the inferior vena cava (arrow). CT, computed tomography.

A fine needle aspiration biopsy was conducted in the uncinate process of the pancreas and revealed the adenocarcinoma. Therefore, a pancreaticoduodenectomy (PD) was conducted, which included resection of the gastric mass and partial resection of the inferior vena cava.

The pathological specimen was composed of the head of the pancreas, distal portion of the stomach, common bile duct, duodenum and gallbladder. Microscopically, the gastric tumor tissue was comprised of spindle cells with coagulative necrosis and a mitotic rate of $\leq 5/50$ within a high power field (HPF; Fig. 3A). The tumor cells were immunoreactive for CD117 (Fig. 3B), supporting the diagnosis of GIST. The Union for International Cancer Control tumor-node-metastasis (UICC TNM) pathological staging of this GIST was pT3 (stage IB), and its National Institute of Health (NIH) risk stratification was intermediate. The pancreatic tumor was comprised of poorly differentiated cells with vascular and perineural invasion and infiltrating submucosa of duodenum (Fig. 4A). The tumor cells in the pancreas were immunoreactive for cytokeratin 5/6 (CK5/6), p63 and CAM5.2, supporting the diagnosis of ASC (Fig. 4B-D). None of the nine peripancreatic lymph nodes were involved. Ultimately, the pathological TNM staging was pT3N0M0.

The postoperative course was uneventful. The patient declined any further adjuvant therapy, and 6 months following

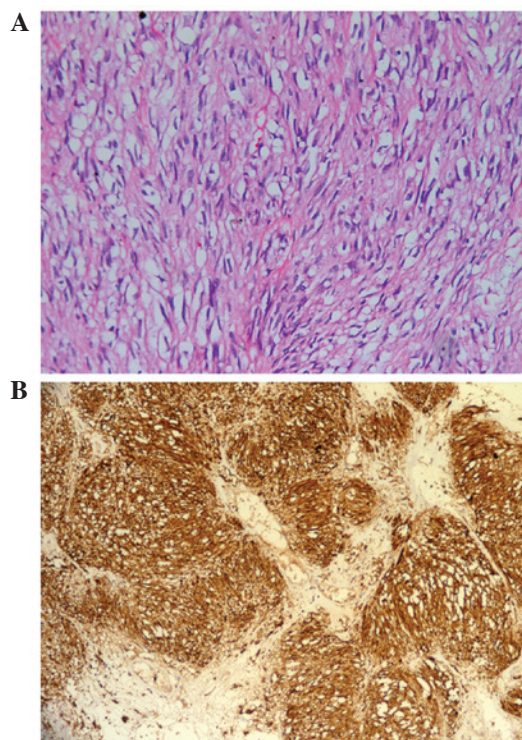


Figure 3. (A) Medium-power review of the gastric biopsy specimen identifying a soft tissue mass consisting of a spindle cell neoplasm. (B) Positive immunohistochemistry staining for c-kit (CD117) was consistent with the diagnosis of GIST (magnification, x20). GIST, gastrointestinal stromal tumor.

therapy the patient remains healthy and has experienced no tumor recurrence.

Discussion

GISTs are the most common type of mesenchymal neoplasm of the gastrointestinal tract. Primary GISTs are usually solitary, but may occur in groups, e.g. Carney's triad or when associated with neurofibromatosis. Without the presence of Carney's triad or neurofibromatosis syndromes, synchronous occurrence of a GIST with a tumor of different histological type is rare and has been documented in the literature mainly in the form of case reports. Malignancies of the gastrointestinal tract are the most commonly accompanied neoplasms; however, there are few previous studies concerning synchronous pancreatic cancer and GIST in the stomach (8,9). Liu *et al* reported that the most common epithelial tumors associated with GIST in their series were esophageal squamous cell carcinomas (1.13%), followed by gastric (0.53%), pancreatic (0.38%) and colorectal (0.03%) adenocarcinomas (9).

Compared with a GIST alone, synchronous GISTs have various clinical manifestations. Agaimy and Wuensch analyzed a series of 97 cases of surgically resected GIST and revealed that the majority of GISTs in their series were benign or low-risk and appeared to be innocent bystanders (2). Liska *et al* identified that these GISTs tended to be an incidental findings during surgery, and were most commonly localized in the small intestine (10). In our case, the GIST was associated with an intermediate risk and located in the stomach.

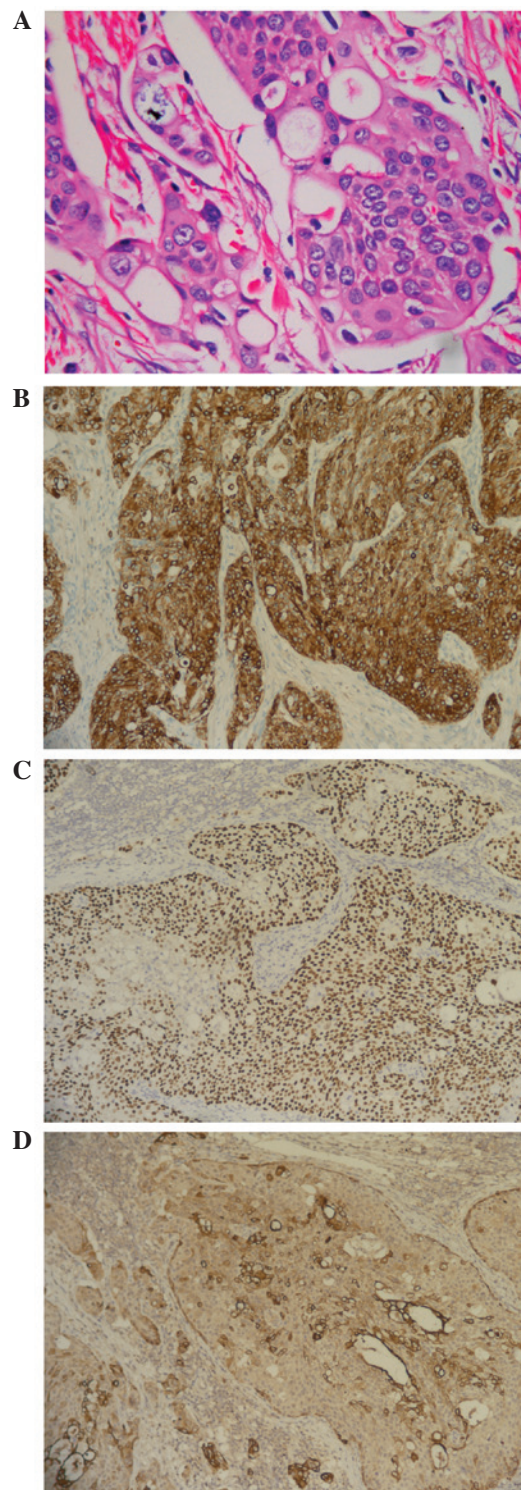


Figure 4. (A) Microphotograph of CUPP identifying the intercellular bridge (the feature of squamous carcinoma) and mucus (magnification, x40). Subsequent images show positive immunohistochemistry staining for (B) CK5/6, (C) P63 and (D) CAM5.2, consistent with the diagnosis of adeno-squamous carcinoma (magnification, x20). CUPP, carcinoma in the uncinate process of the pancreas.

ASC of the pancreas is also referred to as adenoacanthoma, mixed squamous adenocarcinoma and mucoepidermoid carcinoma. Radiographically, ASC cannot be distinguished from adenocarcinoma (11); thus, a pathological diagnosis may be made through biopsy or during surgery. Few patients undergo

surgical resection as the majority of patients have stage IV disease at the time of presentation. When resected, ASC is frequently associated with positive lymph nodes, vascular and perineural invasion and poor tumor cell differentiation (12).

Patients with ASC have a worse survival rate compared with those with adenocarcinoma. Smit *et al* demonstrated that the average survival of 72 patients with ASC of the pancreas was 5.7 months, and only five patients survived for longer than one year (13). Kardon *et al* identified that the overall survival was 12.5 months in patients treated with curative resection and adjuvant chemotherapy, and was 3.0 months in patients who received no chemotherapy or received palliative chemotherapy (14). To date, surgical resection offers the only chance for a cure. Boyd *et al* recently revealed that the resectability is the strongest predictor of survival in ASC (15). Katz *et al* demonstrated an improvement in survival with the use of palliative radiation and chemotherapy; however, the benefit of adjuvant chemoradiation was not supported by this study (16). There is no current standard of chemotherapy regimens for patients with ASC, but it has been suggested that ASC of the pancreas is sensitive to platinum-containing chemotherapy regimens (17,18).

The preoperative pathological diagnosis of ASC is often difficult. The carcinoma arising from the uncinate process has unique clinical manifestations due to its anatomical location, and the clinical presentation of CUPP is often late as a result of the lack of obstructive jaundice as a presenting feature. More common symptoms including abdominal pain and weight loss occur in up to 70% of all cases. Due to its tendency to cause duodenal obstruction, vomiting, as observed in our patient, is also a common clinical presentation. Due to the anatomical position of the uncinate process, ultrasound imaging of this area is likely to be obscured by the overlying bowel; therefore, CT is the main diagnostic method (6). Additionally, CUPP commonly involves superior mesentery vessels, making it unresectable or leading to margin-positive resection.

The overall survival in CUPP is less than that of the adenocarcinoma in the head of the pancreas. Ye *et al* identified a one-year survival rate of 37.7% and a 5-year survival rate of 5.6% for all stages of CUPP (19). Li *et al* revealed that resected CUPPs had a median survival of 17 months. Those patients who did not have venous resection had a median survival of 19 months, while those with venous resection had a median survival of 13 months (20). Thus, a delay in clinical presentation and the anatomical location of CUPP in relation to the retroperitoneum and mesenteric vessels appears to account for lower resection rates and reduced overall survival.

Contrary to the majority of previous cases of synchronous GISTs and other malignancies (9,10), and the other case report of synchronous GIST and pancreatic adenocarcinoma (8), in our case, GIST was not an incidental finding. Our initial impression was a symptomatic GIST; however, following reevaluation via a CT scan with a multidisciplinary approach, a pancreatic adenocarcinoma was suspected. Thus, the intraoperative exploration of the pancreas and the pancreatoduodectomy was preoperatively planned.

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