

CASE REPORT

Splenic Infarction. A Rare Presentation of Anaplastic Pancreatic Carcinoma and a Review of the Literature

Manzhi Wong¹, Ju-Yaw See¹, Wajiha Sufyan², Ravishankar K Diddapur¹

Departments of ¹Surgery and ²Pathology, National University Hospital. Singapore, Singapore

ABSTRACT

Context Anaplastic carcinoma of the pancreas is a rare variant of ductal adenocarcinoma. The histogenesis and biologic behavior of these tumors are still controversial. They occur in elderly men and are associated with a very poor prognosis.

Case report We report a case of advanced anaplastic carcinoma in a 41-year-old man who presented with splenic infarction. He had a prolonged survival of 16 months from diagnosis.

Conclusion Splenic infarction is a most unusual acute presentation of pancreatic carcinoma, which may require emergency tumor resection and splenectomy.

INTRODUCTION

Anaplastic carcinoma of the pancreas makes up approximately 1-2% of all pancreatic malignancies [1]. It occurs with greater frequency in the head of the pancreas and usually in men over 60 years of age [2]. The prognosis is usually serious. However, there are reports of response to chemotherapy, with isolated cases of long term survival [3]. A few main histological subtypes have been described [4]. This paper reports a primary anaplastic spindle cell carcinoma of the pancreas, with a first presentation as acute abdomen secondary to splenic infarction. We believe this to be the first case reported in the English literature.

CASE REPORT

A 41-year-old Malay man was admitted complaining of severe left hypochondrial pain of one-day duration. He had a one-month history of weight loss (11 kg), associated with 2 weeks of vomiting and intermittent fever. He had smoked cigarettes for more than 20 years. Physical examination revealed a temperature of 38.1°C, tenderness with rebound in the left hypochondrium and a positive left renal punch.

Initial investigation revealed elevated total white cells of $17.0 \times 10^9/L$ (reference range: $4-11 \times 10^9/L$) with a predominance of polymorphs. His renal function, liver function tests and amylase were within the normal range. CEA was $11.3 \mu g/L$ (reference range: $0-5 \mu g/L$), but CA 19-9 was less than $10 U/mL$ (reference range: $0-37 U/mL$). A septic work up including urinary microscopy, chest and abdominal radiographs and blood cultures were negative.

The initial clinical impression was that of acute pyelonephritis or diverticulitis. Ultrasound of the kidneys showed an incidental finding of a well-defined lobulated solid mass measuring $8.0 \times 6.4 \times 7.9$ cm at the splenic hilum with heterogeneous hypoechogenicity. A Doppler study showed internal vascularity. An urgent computed tomography (CT) scan of the abdomen showed a large 8.9×7.6 cm heterogeneous mass in the region of the splenic hilum (Figure 1). Invasion into the spleen was noted, associated with a wedged-shaped peripheral

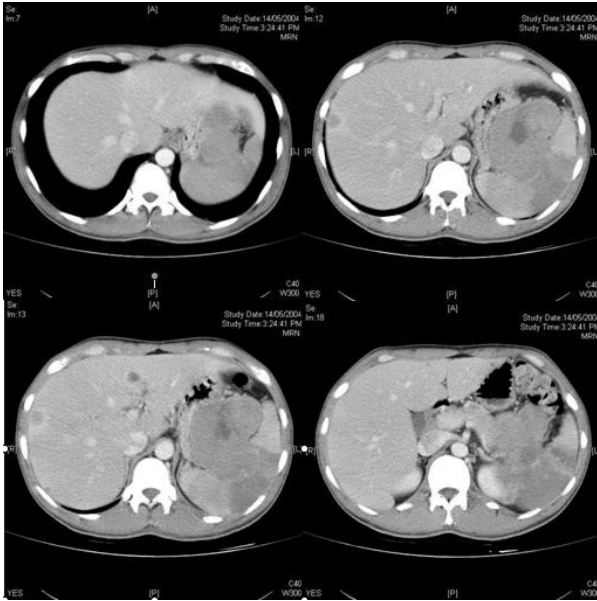


Figure 1. CT abdomen and pelvis at presentation showed a large 8.9x7.6 cm heterogeneous mass in the region of the splenic hilum. This mass displaced the stomach to the right and the pancreatic tail inferiorly. There was invasion into the spleen. A wedged-shaped peripheral hypodensity was also seen in the spleen, representing an infarct. Hepatic metastases and cysts were present. The larger metastases are located in segments 2 and 8, measuring 3.9x3.6 cm and 2.4x1.9 cm, respectively. Incidental, cysts were noted in the left kidney.

hypodensity representing a splenic infarct. Two hepatic metastases were also noted. They were located in segments II and VIII, measuring 3.9x3.6 cm and 2.4x1.9 cm, respectively. No enlarged intra-abdominal lymph nodes or ascites were detected.

The patient was initially managed conservatively for three days. However, his total white cell count continued to increase from $17.0 \times 10^9/L$ to $27.5 \times 10^9/L$, with clinical worsening of the localized peritonitis. A decision was made to perform an urgent laparotomy on clinical grounds. A distal pancreatectomy with splenectomy and left adrenalectomy was performed. Intra-operative findings were of tumor involving distal pancreas, spleen and adrenal gland with infarction of spleen and metastasis in segments II, IV, and VIII of the liver. The patient's recovery was uneventful and he was discharged on the 8th postoperative day. Postoperative TMN staging was T3N0M1 (stage IV). Following surgery, he underwent

six cycles of chemotherapy consisting of gemcitabine 1,690 mg in 500 mL of normal saline, oxaliplatin 150 mg in 250 mL of 5% dextrose, dexamethasone 8 mg, and ondansetron 8 mg. Palliative radiofrequency ablation of his stable liver metastasis was performed. However, 15 months later, he presented with an inability to retain food and breathlessness. CT scans showed local tumor recurrence indenting the stomach. He had right pleural effusion with multiple pulmonary metastases, contributing to his demise not long after.

Pathology

Gross Findings

The tumor including the pancreas measured 10x8x3.5 cm. The spleen measured 9x7x3.5 cm. A cut section showed a fleshy tan-colored tumor replacing the pancreas and invading the hilum of the spleen into the splenic substance (Figure 2). Small satellite tumor extension, 1.1 cm in maximum dimension, was present situated 0.5 cm from the splenic capsular surface.

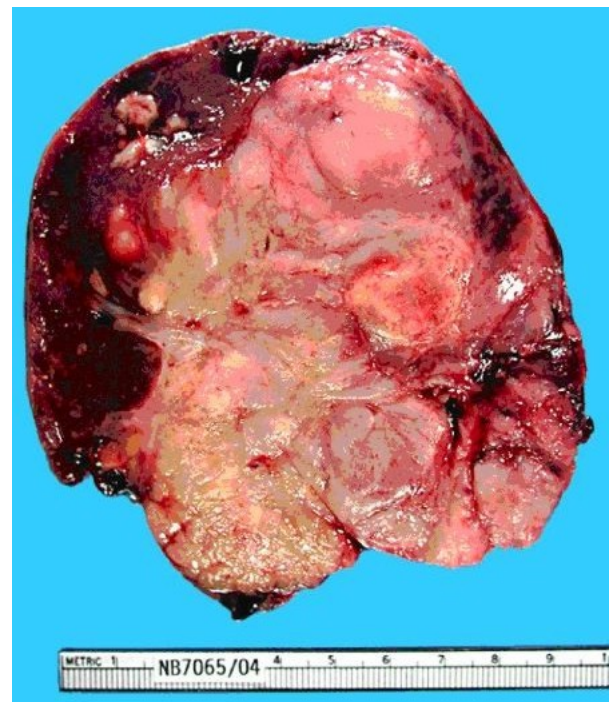


Figure 2. A fleshy tan-colored tumour replacing the pancreas and invading through the hilum of the spleen into the splenic substance. A rim of the remaining splenic parenchyma is seen at the periphery.

Histopathologic Findings

Sections showed a mixture of moderately differentiated ductal adenocarcinoma and an undifferentiated tumor predominantly involving the splenic substance (Figure 3). Areas of adenocarcinoma merging with undifferentiated tumor were present. The moderately differentiated ductal adenocarcinoma was composed of glandular structures with varying amounts of mucinous content surrounded by a fibrotic stroma. The undifferentiated component was composed of sheets of pleomorphic spindle-shaped cells with interspersed multinucleated giant cells and a patchy acute and chronic inflammatory cell collection in the vascular stroma. Mitotic activity was elevated. The rest of the splenic parenchyma showed an area of necrosis. The splenic hilar vessels appeared free of malignancy or thrombosis. The pancreatic resection margin, two peri-pancreatic lymph nodes and the omental fat were free of tumor involvement.

Special Studies and Immunohistochemical Findings

Mucin positivity (DPAS and mucicarmine) was demonstrable in the glandular, as well as, in some undifferentiated tumor cells. The entire adenocarcinoma component and focal undifferentiated tumor cells were positive for cytokeratin (AE1/3) (Figure 4), CEA and tumor-associated glycoprotein 72 (TAG72; also known as B72.3 or CA 72-4). The

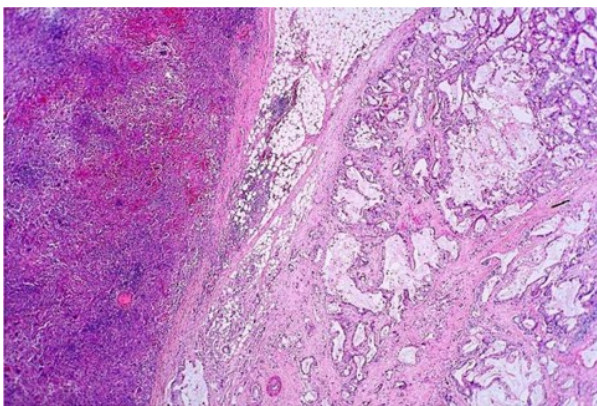


Figure 3. Moderately differentiated adenocarcinoma (left) with an undifferentiated tumour component (right). Hematoxylin and eosin staining; original magnification (x40).

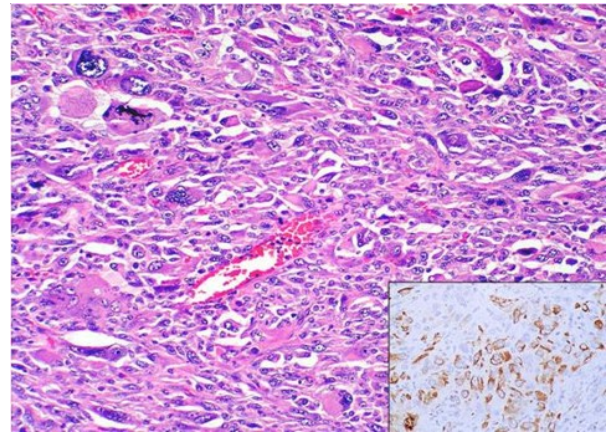


Figure 4. Sheets of pleomorphic spindle shaped cells with scattered multinucleated giant cells. Hematoxylin and eosin staining; original magnification (x400). The inset shows undifferentiated spindle cells staining for cytokeratin (AE1/3); original magnification (x100)

pleomorphic stromal and giant cells were positive for CD68. Factor 8, CD34 and CD31 were positive in the endothelial cells of the stromal blood vessels. Both components were negative for CD21 and desmin.

DISCUSSION

We present a case of anaplastic pancreatic carcinoma presenting acutely as splenic infarction. The surgery performed was minimal and essential in the form of a distal pancreatectomy and splenectomy, debulking the major portion of the tumor and infarcted spleen. On hindsight, this helped in providing a full histological assessment of the specimen and probably reduced the tumor load for further chemotherapy thus allowing the patient to survive for 16 months following diagnosis.

A variety of terms have been used to describe these tumors, including undifferentiated or pleomorphic carcinoma, pleomorphic giant cell carcinoma, small cell carcinoma and sarcomatoid carcinoma [5, 6]. Ductal adenocarcinoma of the pancreas is subdivided into the following types: 1) mucinous noncystic carcinoma; 2) signet ring cell carcinoma; 3) adenosquamous carcinoma; 4) undifferentiated (anaplastic) carcinoma (the present case); 5) undifferentiated carcinoma with osteoclast-like giant cells; 6) mixed ductal-endocrine carcinoma [7]. Small round cell tumors of the pancreas have been

described but may often represent metastatic small cell carcinomas of the lung, malignant lymphomas or islet cell tumors [8]. Hence, true anaplastic carcinomas are rare, representing about 2% of all pancreatic ductal adenocarcinomas.

Paal *et al.* [8] described 35 anaplastic carcinomas of the pancreas, of which 31 were described as being typically composed of large, round to polygonal, pleomorphic cells. Atypical giant cells appeared to be a feature, exhibiting engulfment of the surrounding tumor/inflammatory cells. Four spindle cell carcinomas were also included in this case series, only one of which contained an infiltrating ductal adenocarcinoma. Other case reports have also presented mucinous cystadenocarcinomas combined with anaplastic components [9].

Most authors have supported an epithelial derivation for the mononuclear undifferentiated cells. This tumor was made up of a significant infiltrating ductal adenocarcinoma merging with the undifferentiated component. The spindle cells were also reactive with epithelial markers such as CEA, supporting the studies in the literature. However, there is still controversy regarding the origin of the giant cells often seen in association with anaplastic pancreatic carcinoma. The osteoclast-like giant cells seen in our patient probably had a histiocytic origin, as evidenced by their bland nuclear features and CD68 reactivity. Osteoclast cells may occur in a variety of benign conditions too, such as abscess or necrosis. In contrast, malignant 'giant cells' have also previously been described but were not identified in our patient. These are large, bizarre, multinucleated, tumor giant cells of possible epithelial origin. These may represent phagocytosis of erythrocytes or tumor cells.

In terms of clinical features, a male:female ratio of up to 2.5:1 has been reported in the literature [8]. These tumors, like other pancreatic ductal adenocarcinoma variants, occur predominantly in elderly patients with a peak age incidence over 60 years of age. Patients under 40 years of age make up only 0.2% of all pancreatic ductal adenocarcinomas.

Clinicopathological features and survival data in this subgroup appear comparable to those in patients over 40 years of age [2]. However, the relative frequency of variants such as anaplastic carcinoma may be greater. Hereditary tumor syndromes, such as Peutz-Jegher's syndrome or hereditary pancreatic cancer syndrome, account for 1/3 of pancreatic ductal adenocarcinomas in patients under 40 years of age. In a relatively young patient without any clinical or family background, the genetic alterations were found to be similar to those in patients over 60 years of age. These commonly include the *K-ras* oncogene [10] and tumor suppressor genes *p16*, *p53* and *SMAD family member 4* (*SMAD4*; also known as *DPC4*). The alteration of adhesion molecules, such as the loss of E-cadherin expression, may help account for the aggressiveness of the tumor.

About half of the patients with pancreatic cancer have stage IV disease at diagnosis. They usually present late with anorexia and weight loss, abdominal pain and vomiting. The duration of symptoms is particularly short in patients with the undifferentiated variant, averaging 3 months [8]. The location of the tumor (in the head, body or tail) may be variable. Our patient had a pancreatic tail anaplastic adenocarcinoma presenting as acute abdomen due to splenic infarction, which we believe may be the first such case reported in the English literature. Görg *et al.* [11] presented a case series of 10 patients with splenic infarction secondary to cancer, including two patients with pancreatic carcinoma and one patient with pancreatic neuroendocrine tumor. The sudden onset of left hypochondrium pain is the pathognomic feature of splenic infarction. However, all 10 patients were asymptomatic, with splenic infarction diagnosed on routine ultrasound carried out for staging.

Splenic infarctions typically occur in patients with myeloproliferative diseases, sickle cell anemia and endocarditis. However, malignancy-associated arterial thrombosis is rare. The hypercoagulable state is the main pathophysiological mechanism proposed which may be evidenced by the coexistence

of migratory superficial thrombophlebitis, disseminated intravascular coagulation or venous thrombosis in some patients. Sepsis and the presence of metastases may also be predisposing factors. Interestingly, the splenic vessels were grossly uninvolved in our patient, and we could not ascertain any other discrete factor to explain this acute event. When cancer is the underlying etiology, complete infarctions are more common, resulting in a small hypodense spleen. Our patient had a wedged-shaped partial infarct, producing a moderately enlarged spleen on ultrasound. Such lesions may heal spontaneously. In contrast, complete acute infarction is associated with a survival of less than one month [11].

Large tumor size, local invasion and lymph node metastasis are typical of the anaplastic variant, leading to a significantly worse prognosis compared to that of pancreatic adenocarcinoma. A 3-year survival of 3% has been quoted [8]. Limited evidence shows that the large cell subtype may be associated with a slightly better prognosis of 6 months as compared to a reported 3.5 months, on average, for the spindle cell type. Our patient's response to surgery and adjunctive treatment, though limited, could have contributed to his relatively prolonged survival of 16 months from diagnosis.

CONCLUSION

We believe this to be the first case report in the English literature of an anaplastic pancreatic carcinoma presenting as an acute abdomen due to splenic infarction. The patient required emergency palliative resection and subsequently received chemotherapy and radiofrequency ablation for his liver metastasis. He showed relatively prolonged survival. A review of the literature regarding the histogenesis and behavior of this rare variant is presented.

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Correspondence

Ravishankar K Diddapur
Division of Hepatobiliary Surgery
Department of Surgery
National University Hospital
5 Lower Kent Ridge Road
Singapore 119074
Singapore
Tel: +65-9181.7293
Fax: +65-6779.5678
E-mail: ravi_diddapur@hotmail.com

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