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Case Report

Diffuse Neuroendocrine Tumor of the Pancreas: A Diagnostic and Therapeutic Challenge

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Abstract

A Neuroendocrine Tumor (NET) diffusely infiltrating and replacing most of the pancreas is a rare entity and requires a high index of suspicion for diagnosis. This report discusses the presentation, findings on computed tomography scan and key aspects of management of a patient with a non-functioning diffuse pancreatic NET.

Keywords: Pancreatic neuroendocrine tumor; Diffuse; Splenic vein thrombosis; Computed tomography; Distal pancreatectomy; Adjuvant therapy

Abbreviations

CT: Computed Tomography; PET: Positron Emission Tomography; AIP: Autoimmune Pancreatitis; NET: Neuroendocrine Tumor

Case Presentation

A 59-year-old man presented with history of upper abdominal pain of one month duration. The pain was dull aching and had become severe for 5 days for which he sought medical attention. He was referred with a diagnosis of acute pancreatitis based on a Computed Tomography (CT) scan which had shown a bulky pancreas with mild peripancreatic stranding and splenic vein thrombosis. He recalled 3-4 such episodes over the last 3 years which did not require hospital admission. There was a significant history of weight loss of 15 kg over the past one year. There was no vomiting, malena, jaundice or fever. Patient had hypertension and diabetes mellitus which was well controlled, with no recent worsening of glycemic control. There was history suggestive of pancreatic exocrine insufficiency in the form of greasy, bulky stools. Patient was a non-smoker and did not consume alcohol. Examination was remarkable only for muscle wasting (body mass index 17.8 kg/m^2). There was no lymphadenopathy or abdominal findings.

Hemoglobin was 14 g%; liver function tests were normal with albumin of 4.2 g/dL. Serum Amylase and lipase were within normal limits. There were no gallstones on abdominal ultrasonography. A contrast enhanced CT scan was done (Figure 1). The pancreas was bulky with loss of lobulations. There were no calcifications and pancreatic duct was not dilated. On the pancreatic parenchymal phase (Figure 1b), the pancreas enhanced uniformly (120 HU) with slight decrease in enhancement (116 HU) in the portal venous phase (Figure 1c). Splenic vein thrombosis with multiple perigastric collaterals was seen. CA 19-9 levels was 1.4 U/mL (normal up to 37); serum IgG4 levels was 0.53 g/L (normal 0.03-2.0). Serum Chromogranin A level was done which showed an elevated value of 356.8 ng/ml (normal <108). Following this, a Ga-68 DOTANOC Positron Emission Tomography (PET) scan was done. It showed diffuse uptake of radiotracer involving the body and tail of the pancreas with sparing of the head and uncinate process (Figure 1d); there was no uptake in the splenic vein thrombus or evidence of any extra-pancreatic disease.

Patient underwent laparotomy, "extended" distal pancreatectomy and splenectomy (Figure 2a). The transection of the pancreas was to the right of the superior mesenteric vein (Figure 2b) where the pancreas appeared grossly normal on visual inspection and texture. The histopathology showed a well differentiated neuroendocrine tumor (Figure 2c) which was diffusely positive for synaptophysin (Figure 2d) and focally positive for chromogranin. The Ki-67 index was 7%. The transected pancreatic margin was positive (R1 resection). One out of 13 lymph nodes retrieved was positive for tumor. There was microvascular invasion but no perineural invasion. Patient also had an incidental gastrointestinal stromal tumor of the jejunum which was resected (1.8 cm in diameter, strongly positive for CD 117, DOG1 and CD 34. The Ki67 index was 3% and mitoses were <5/50 high power fields).

Discussion

A patient presenting with non-specific pain, weight loss and a bulky pancreas on CT scan can be a diagnostic challenge. The differential diagnoses considered were acute on chronic pancreatitis, auto-immune pancreatitis and pancreatic tumor. Careful examination of the CT scan as discussed below led us to the right diagnosis. There were no changes of chronic pancreatitis- no ductal dilatation or calcifications. Type I Autoimmune Pancreatitis (AIP) was an important consideration (age, male sex, diffuse involvement of the pancreas with loss of lobulations). However, in type I AIP, IgG4

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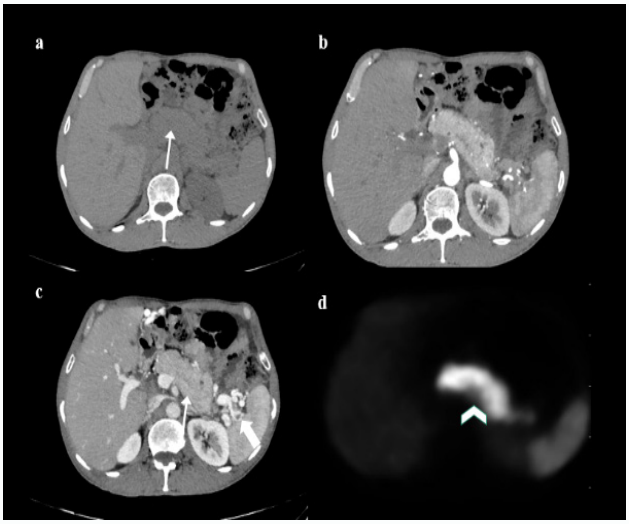

Figure 1: Panel a depicts a plain section computed tomography scan showing unenhanced pancreas (arrow). Panel b depicts the pancreatic parenchymal (arrow) phase showing a bulky pancreas with uniform enhancement. In panel c, portal venous phase, there is slight reduction in enhancement compared to the arterial phase. The thin arrow points to the thrombosed splenic vein. The thick arrow points to perisplenic collaterals. Panel d depicts a section of DOTANOC positron emission tomorgraphy scan in which the body and tail of pancreas show diffuse uptake (arrow head).

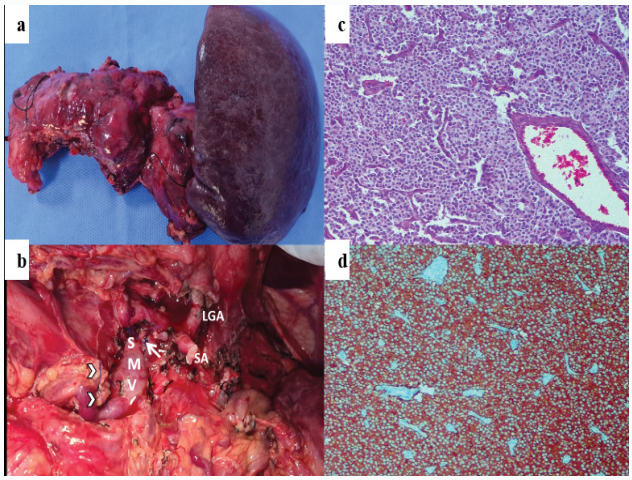

Figure 2: Panel a shows the distal pancreatectomy, splenectomy specimen. Panel b shows the surgical bed after resection. Arrow heads depict the transection margin of the pancreas. SMV-superior mesenteric vein; SA-splenic artery; LGA- left gastric artery. The arrow points to the splenic vein divided flush with the SMV. Panel c depicts a low power histopathology slide of the tumor. There are no pancreatic acinar structures seen. The entire gland is replaced by tumor cells. Panel d shows the tumor cells showing diffuse synaphtophysin positivity.

is usually elevated- in this instance it was normal. Also, in AIP, the enhancement increases on portal venous phase [1] where as in this case, there was a mild fall in the attenuation values from the pancreatic parenchymal to the portal venous phase. Due to significant weight loss and splenic vein thrombosis, pancreatic malignancy was a possibility. Diffuse adenocarcinoma and lymphoma were considered; however, both are hypo-attenuating on CT. In this patient the enhancement pattern was normal- increased on arterial phase with a slight fall in portal venous phase, but the attenuation values were slightly more than that of a normal pancreas. On a high index of suspicion, a serum Chromogranin A was done, which showed significantly elevated values. This led to the DOTANOC scan and the correct diagnosis of a diffuse Neuroendocrine Tumor (NET) of the pancreas.

Diffuse NET is a rare entity and only case reports of this condition exist [2]. Pancreatic NETs due to their slow growing nature are well known to present with sinistral portal hypertension due to splenic vein thrombosis [3].The index patient did not present with history of overt or occult bleeding. An upper gastrointestinal endoscopy and endoscopic ultrasound guided biopsy would have been the logical step; had not the DOTANOC scan provided an unambiguous diagnosis. An important learning point here is to consider NET in the differential diagnosis of a diffusely enlarged pancreas. Portal vein thrombus has also been reported in the setting of a pancreatic NET and the DOTANOC scan also differentiate a tumor thrombus from a bland thrombus based on radiotracer uptake [4]. Multiple mesenteric tumor thrombi in a patient with pancreatic NET presenting with abdominal pain have been reported [5].

Surgical resection remains the cornerstone of treatment of NET confined to the pancreas. In this patient open "extended" distal pancreatectomy with splenectomy was done with the transection margin extended to the right of the superior mesenteric vein where there was no gross tumor visible or palpable. Intra-operative frozen section was not done. There is no consensus for managing a patient with R1 resection. The options available to this patient were observation, adjuvant somatostatin analogues, adjuvant chemotherapy and completion surgery (total pancreatectomy/ pancreaticoduodenectomy). There is a case report of completion pancreaticoduodenectomy for low grade diffuse pancreatic NET initially treated with distal pancreatectomy [6]. However recent data from the United States Neuroendocrine Tumor Study Group [7] suggests that re-resection after intra-operative frozen section to achieve R0 resection in non-functioning pancreatic NETs does not confer any advantage in terms of overall survival. Ten-year recurrence free survival also remains similar to that of R1 resection (~45%) and does not compare to patients who have primary R0 resection (~63%). The index patient is at high risk for recurrent disease not just because of R1 status but due to the higher tumor burden, node positivity and microvascular invasion. R1 resection is not a driver of mortality and the fact that it is a well differentiated, grade II tumor may well be a good prognostic factor for overall survival. The patient is one year from the initial surgery and remains well with a weight gain of 6 kg. A DOTANOC PET-CT scan is planned with maintenance Octreotide therapy. This strategy of use of long-acting Octreotide after resection of a grade II pancreatic NET has been shown recently to improve 3-year disease free survival [8]. Role of adjuvant cytotoxic chemotherapy is limited in this setting.

To summarize, the salient and instructive points of this case report are the challenge in arriving at the correct diagnosis based on the clinical presentation and CT scan findings, the rare presentation of diffuse involvement of the pancreas with a non-functioning NET, decision making about the extent of surgery and management of R1 resection based on available evidence.

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