Immunoglobulin G4-Negative Inflammatory Pseudotumors of the Pancreas

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Abstract

Inflammatory pseudotumor (IPT) can occur in any organ, but rarely shows pancreatic involvement. While surgical excision has been recommended as the primary treatment for IPT of the pancreas in the past, some authors suggest observation while medical management often results in regression. Corticosteroids, nonsteroidal anti-inflammatory drugs and immunosuppressive therapy have been used to treat IPTs. Spontaneous regression has also been reported in IPT managed without surgical intervention. A 62-year-old female was evaluated for worsening abdominal pain and a mass in the neck of the pancreas that was identified on ultrasound. Further imaging with magnetic resonance imaging revealed a pancreatic mass with dilated pancreatic duct and an atrophic parenchyma of the pancreatic neck. Her serum tumor markers were not elevated. As this lesion appeared to be resectable pancreatic cancer based on cross-sectional imaging, no biopsy was performed prior to surgical resection. Distal pancreatectomy and splenectomy was recommended and the patient desired to proceed. Her recovery was uneventful with no postoperative complications, including pancreatic fistula. Final pathology revealed a lesion consistent with the diagnosis of immunoglobulin G4 (IgG4)-negative IPT without neoplasm. IPT of the pancreas is a difficult entity to diagnose and treat due to clinical and imaging characteristics closely resembling pancreatic adenocarcinoma. Biopsy with immunohistochemical analysis can be useful in diagnosing IPT; however, symptomatic lesions and concerning findings on cross-sectional imaging may warrant more definitive surgical intervention.

Keywords: Inflammatory pseudotumor; Pancreas; Normal IgG4

Introduction

An inflammatory pseudotumor (IPT) is a benign, mass-forming lesion composed of inflammatory infiltrate surrounding myofibroblastic and fibroblastic proliferation [1]. The etiology of IPT is not well understood, but has been associated with chronic inflammatory conditions, trauma, and lymphoproliferative processes [2]. IPT was first described after a tumor was resected from the lung parenchyma of a child by Brunn in 1939 [3]. It was named due to its radiological and clinical similarities to malignant tumors [4]. It has since been observed in nearly every organ in the body, including the pancreas [4-7], although it is rather rare in the pancreas [6, 8-11]. Unfortunately, this entity can clinically and radiographically mimic both pancreatic carcinoma and chronic pancreatitis [9]. Previous literature suggests pancreatic IPT in adults is more common in women and that the pancreatic head is most commonly involved (60% of cases) as opposed to the body and tail [12]. About 5-10% of pancreatectomies performed with the suspicion of malignancy reveal non-malignant IPTs [2, 13, 14]. IPT of the pancreas poses a diagnostic challenge, as it is difficult to rule out malignancy of the pancreas in a safe and accurate fashion prior to resection [2]. Even with negative preoperative biopsy via endoscopic ultrasound, given dismal prognosis of pancreatic cancer, surgical intervention is often recommended for those with reasonable perioperative risks.

We have recently experienced a case of immunoglobulin G4 (IgG4)-negative IPT of the pancreatic neck successfully managed with distal pancreatectomy and splenectomy, and herein present a case report with literature review.

Case Report

A 62-year-old female without any significant past medical his-
tory was referred to the surgical oncology department with a newly identified pancreatic neck mass. It was discovered during her workup of worsening right upper quadrant pain that had been present for several years. The pain was intermittent, stabbing, radiating to her mid back, exacerbated by food and associated with nausea, bloating, constipation and loss of appetite. An abdominal ultrasound demonstrated a hypoechoic lesion in the pancreatic body region measuring 2.2 × 1.8 × 1.9 cm. Subsequent magnetic resonance imaging (MRI) found a hypoenhancing mass in the pancreatic body which was moderate intensity on T2 sequence, measuring 2.4 × 1.9 × 3.2 cm, causing mild upstream dilation of the pancreatic duct in the body and tail (Fig. 1a, b). The lesion abutted the portal confluence and there was no arterial involvement. Interestingly, there was additional downstream pancreatic ductal dilation up to 4 mm and the pancreatic neck was atrophic as well. The cross-sectional imaging findings were highly concerning for pancreatic adenocarcinoma. After discussion in a multidisciplinary tumor board, surgical resection without tissue diagnosis was considered reasonable given the tumor location and distinct imaging characteristics. Neoadjuvant chemotherapy with tissue diagnosis was considered but forgone, as a potential tumor growth during the neoadjuvant treatment would possibly make this tumor unresectable. Her serum carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9) and IgG4 level were within normal limits.

She underwent a diagnostic laparoscopy, and open subtotal distal pancreatectomy and splenectomy. There was no peritoneal disease or liver metastasis on the diagnostic laparoscopy. A firm mass was identified in the inferomedial margin of the pancreatic neck, the body was dissected and the pancreas was elevated from the retroperitoneum. The pancreatic neck was then transected with good margins and complete lymphadenectomy along the celiac axis were performed. A Jackson Pratt drain was placed in the pancreatic bed.

Her postoperative course was overall unremarkable. Her diet was gradually advanced and she was discharged on postoperative day 6. And the drain was removed in the office.

Pathological evaluation revealed a firm, white, bulky mass near the medial margin measuring 3.5 × 3.6 × 2.1 cm. Histologic evaluation showed an intact architecture with a tumefactive-forming chronic pancreatitis. There are exuberant lymphocytic infiltrate and copious multinucleated giant cells involving lobules and periductal regions. There was no evidence of carcinoma in the pancreas specimen as well as in all 16 resected lymph nodes (Fig. 2a, b). While IgG was focally positive on immunohistochemistry (IHC) staining, IgG4 stain was negative (Fig. 3a, b). Also, cytokeratin 7 (CK-7) stain was localized to the epithelial cells (Fig. 4). Immunostain for anaplastic lymphoma kinase-1 (ALK-1) was negative. While autoimmune pancreatitis could not be fully excluded, the lesion is suggestive of an inflammatory pseudotumor without any evidence of carcinoma.

Discussion

Pancreatic cancer is a calamitous diagnosis, as nearly 94% of diagnosed cases worldwide resulted in death in 2020. It is the seventh leading cause of cancer death in both males and fe-

![Figure 1. Representative images from MRI. (a) Abrupt cut off of the main pancreatic duct on the T2 sequence. (b) Hypoenhancing mass, measuring 2.4 × 1.9 × 3.2 cm, on the contrast study. MRI: magnetic resonance imaging.](image-url)
IPT is described as an uncommon, benign and tumefactive lesion composed of a variety of infiltrative inflammatory and mesenchymal cells. IPT has been defined as a benign mimicker of malignant processes and must be considered in the evaluation of any neoplasm, as successful treatment may be achieved without radical surgical intervention [19]. While the origin of IPT remains unclear, some literature suggests trauma, surgery, and autoimmune mechanisms as possible etiologies [2, 4]. IPT arising from the pancreas is extraordinarily rare, with only a few cases reports in the English literature [2, 20-22]. The radiographic appearance of pancreatic IPT is highly variable, requiring histological evaluation for definitive diagnosis [2]. Contrast CT of intra-abdominal IPT demonstrates a variety of patterns including early peripheral with delayed central filling, heterogenous, homogenous, as well as non-enhancing lesions [4, 23, 24]. MRI demonstrates hypointensity on T1-weighted images [4, 25-27], and hyper- [4, 27] or hypointensity [25, 26] on T2-weighted images. However, these highly variable findings cannot distinguish IPT from other conditions such as pancreatic carcinoma and chronic pancreatitis on imaging characteristics alone [2, 4].

Similar to our case, Kroft et al described a case of IPT arising in the pancreatic body in a young female. Although this lesion was initially observed several years due to benign findings on needle aspiration of the mass, a subsequent distal pancreatectomy was eventually performed due to significant increase of the tumor size and the patient symptomatology, such as significant weight loss, abdominal pain and microcytic anemia. Following resection, her symptoms were resolved completely, and final

Figure 2. (a) Pancreas parenchyma with intact lobular architecture and exuberant chronic inflammation (low power, × 10). (b) Chronic inflammatory infiltrate (black arrow) and giant cell (black arrowhead) (medium power, × 20).

Figure 3. (a) Focally positive immunostain for IgG (medium power, × 20). (b) Negative immunostain for IgG4 (medium power, × 20). IgG4: immunoglobulin G4.
IgG4+ and > 10 cells/high powered field of biopsy sample [32].

| Serum IgG4 concentration > 135 mg/dL, and 2) > 40% of IgG+ plasma cells being | the diagnosis of IgG4-related disease: 1) serum IgG4 concentration had been established for IgG4-related disease [31]. Until 2012, no comprehensive diagnostic criteria had been established for IgG4-related disease [31].

Epithelioid cell granulomas and neutrophilic infiltration suggest eosinophilia can be present, histopathologic features such as characteristic findings such as non-necrotizing arteritis and tissue eosinophilia can be present, histopathologic features such as epithelioid cell granulomas and neutrophilic infiltration suggest non-IgG4-related disease [31]. While less characteristic findings such as non-necrotizing arteritis and tissue eosinophilia can be present, histopathologic features such as epithelioid cell granulomas and neutrophilic infiltration suggest non-IgG4-related disease [31].

Upon diagnosis, two of the following three major findings should be present: dense lymphoplasmacytic infiltrate, storiform fibrosis and obliterative phlebitis [31]. While less characteristic findings such as non-necrotizing arteritis and tissue eosinophilia can be present, histopathologic features such as epithelioid cell granulomas and neutrophilic infiltration suggest non-IgG4-related disease [31].

IPT has been found to be a feature of IgG4-positive sclerosing disease [19]. This condition exhibits IgG4-positive T-cell and plasma cell invasion of various tissues, resulting in chronic pathologies such as autoimmune pancreatitis and sclerosing cholangitis [19, 28]. The condition was discovered in 2003 and is currently poorly understood [30]. Upon diagnosis, two of the following three major findings should be present: dense lymphoplasmacytic infiltrate, storiform fibrosis and obliterative phlebitis [31]. While less characteristic findings such as non-necrotizing arteritis and tissue eosinophilia can be present, histopathologic features such as epithelioid cell granulomas and neutrophilic infiltration suggest non-IgG4-related disease [31].

As with any suspicious lesion, a definitive diagnosis is achieved via biopsy and histopathologic analysis. Regarding IPTs of the pancreas, surgical resection is often performed as there are significant concerns for malignancy, which was in our case. Since pancreatic resection portends significant morbidity and possible mortality to the patients, some authors reported their experience of observation with non-operative therapies resulting in regression. Nonsteroidal anti-inflammatory medications and corticosteroids have been previously used to treat IPTs for palliation [9, 32, 36] or to make the mass a more resectable size and configuration [6, 12, 19, 37, 38] in confirmed cases of IPTs. While rare, spontaneous regression of lesions has been reported [2, 19, 39-41].

In conclusion, we presented a rare case of IPT in the pancreas in a 62-year-old female, with vague, worsening abdominal pain. Due to strong suspicion for malignancy on cross-sectional imaging, she underwent distal pancreatectomy and splenectomy without major postoperative complications. Definitive diagnosis required histopathological analysis and IHC.

Acknowledgments

None to declare.

Financial Disclosure

Authors have no financial disclosure or funding related to the current study.

Conflict of Interest

Authors have no conflict of interest.

Figure 4. CK-7 was positive in epithelial cells (medium power, × 20). CK-7: cytokeratin 7.
Informed Consent

Informed consent was obtained from the patient.

Author Contributions

Study concept: MTG, DJA, JM, GG, HT. Writing - draft: MTG, DJA, JM, FA, HT. Writing - review and editing: KT, ES, RD, GG, HT. Supervision: ES, RD, GG, HT.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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