The quandary of autoimmune pancreatitis and pancreatic ductal adenocarcinoma: A case report and review of IgG4 immunostaining in a cohort of patients receiving neoadjuvant chemotherapy

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ABSTRACT

Introduction: Autoimmune pancreatitis (AIP) is an inflammatory disease whose clinical presentation can mimic that of pancreatic ductal adenocarcinoma (PDA). AIP can appear on imaging as a bulky, sausage-like pancreatic mass with biliary and pancreatic ductal obstruction, resembling the classic “double duct sign” appearance of PDA. A definitive preoperative diagnosis of AIP can be difficult because the two diseases (AIP and PDA) are similar in clinical presentation. Recent advances in serum marker evaluation such as IgG4 serum levels and immunostaining techniques have shown some promise in the differentiation of AIP from PDA. Case Report: We report the case of a patient with a preoperative diagnosis of locally advanced PDA who was treated with neoadjuvant gemcitabine based chemotherapy followed by surgical resection, but whose post-resection pathology was indicative of AIP and not PDA. To explore the possibility that the pre-resection gemcitabine-based chemotherapy had generated a complete pathological response and an inflammatory reaction of IgG4-positive plasma cells, we studied the histology features and IgG4 plasma cell immunostaining characteristics of the pathology specimens of 14 patients with a diagnosis of PDA who were treated with neoadjuvant chemotherapy and surgical resection at our institution. Conclusion: Our results indicate that none of the patients treated with neoadjuvant chemotherapy had increased IgG4-positive plasma cell immunostaining post-operatively, further supporting the diagnosis of AIP and not PDA in our patient.

Keywords: Autoimmune pancreatitis, Pancreatic tumor, Adenocarcinoma

Dervishaj O, Lavu H, Yeo CJ, Witkiewicz AK. The quandary of autoimmune pancreatitis and pancreatic ductal adenocarcinoma: A case report and review of IgG4 immunostaining in a cohort of patients receiving neoadjuvant chemotherapy. International Journal of Hepatobiliary and Pancreatic Diseases 2013;3:1–9.

Article ID: 100010IJHPDOD2013

doi:10.5348/ijhpd-2013-10-CR-1

INTRODUCTION

Autoimmune pancreatitis (AIP) is a rare form of chronic pancreatitis characterized by a lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells. It was formally recognized in 1995 when Yoshida et al. published a case report of a patient with pancreatitis and the presence of hypergammaglobulinemia [1]. However, reports of autoimmune pancreatitis may date to as early as the 1960’s, when Sarles et al. described a group of patients suffering from “primary inflammatory pancreatitis or primary noncalcifying pancreatitis with
hyper gammaglobulinemia” [1–3]. Other terms used to describe autoimmune pancreatitis in the past have included “lymphoplasmacytic sclerosing pancreatitis” [4], “non-alcoholic duct-destructive chronic pancreatitis” [2] and “chronic sclerosing pancreatitis” [5]. Autoimmune pancreatitis may be part of the autoimmune systemic disorder described as IgG4-related disease as it is often associated with a IgG4-positive plasma cell infiltrate in the biliary tree, lungs, lymph nodes, salivary glands and kidneys. Untreated IgG4-related disease often progresses from lymphoplasmacytic inflammation to extensive fibrosis. Glucocorticoids are generally the first line of treatment regardless of the organ involved [8, 39].

The typical clinical presentation of AIP i.e. painless jaundice with weight loss, often mimics that of pancreatic ductal adenocarcinoma (PDA) and there can be difficulty in distinguishing between the two diseases. In North America, nearly 2.5% of pancreatectoduodenectomies have been performed for cases of AIP that were presumed to be PDA [6]. Due to the difficulty in obtaining a definitive preoperative histologic diagnosis, it is not uncommon in the clinical setting to have cases of PDA that are not confirmed until after surgical resection and postoperative pathologic examination of the resected specimen. Given the similarity in clinical presentation between AIP and PDA, a number of published studies have offered criteria to allow for a more accurate differentiation between the two diseases [6, 9] (Table 1). While some of these criteria have sensitivity as high as 97% [7], a basic tenet for the workup of these patients calls for the exclusion of malignancy before the diagnosis of AIP can be made. IgG4-positive plasma cell immunostaining has shown some promise in distinguishing between AIP and PDA, although interpretation of IgG4-positive plasma cell immunostaining on preoperative fine needle or core needle biopsies can be challenging.

In this paper, we report the case of a patient who underwent neoadjuvant gemcitabine based chemotherapy for suspected locally advanced PDA. After what was assumed to be a favorable clinical response to preoperative treatment, the patient underwent surgical resection via pancreaticoduodenectomy. However, pathologic evaluation of the resected specimen showed features more consistent with AIP rather than PDA. In this study we review the important facts related to this case and describe the findings of a retrospective analysis of the pathologic specimens of fourteen other patients who underwent neoadjuvant chemotherapy and surgical resection at our institution. We immunostained the tissues of these fourteen neoadjuvant patients with a marker for AIP, the IgG4 antibody. To our knowledge this is the first such report in the English literature.

**CASE REPORT**

The patient was a 62-year-old African-American woman of blood type O Rh+, with a past medical history significant for diabetes, who presented to her primary care physician with abdominal pain and about 12 kg weight loss. The patient had also been experiencing symptoms of belching and acid reflux for one year and had recently developed dark urine and pale stools. At presentation her total and direct bilirubin levels were 10.6 mg/dl and 5 mg/dl, respectively. She was a non-smoker, social drinker and denied illicit drug use. Her family history was significant for sarcoidosis in a sister and systemic lupus erythematosus in her daughter and another sister. There was no family history of pancreatic or other malignancy.

A computerized tomography (CT) scan revealed a four centimeter pancreatic head mass with intrahepatic and extrahepatic biliary and pancreatic duct dilatation, as well as encasement of the superior mesenteric vein (SMV) (Figure 1). The CA19–9 (21 U/ml) and CEA (1.6 ng/ml) levels were within normal limits. Endoscopic retrograde cholangiopancreatography (ERCP) was done and showed a stricture within the distal common bile duct (CBD) with marked proximal biliary ductal dilatation. The bile duct brushings performed at the time were negative for neoplastic cells and a metal biliary endoprosthesis was placed within the CBD. The patient then underwent an endoscopic ultrasound (EUS) which demonstrated the mass in the head of pancreas measuring 3.8x3 cm invading the splenoportal confluence, SMV and partially encasing the hepatic artery. Enlarged hypoechoic lymph nodes adjacent to the pancreas were also noted. A fine needle aspiration of the mass was non-diagnostic and revealed a few atypical cells in a background of benign glandular cells, inflammatory cells and debris. A subsequent positron emission tomography (PET) scan showed a hypermetabolic mass in the head of the pancreas with an SUV of 7.14 and no metabolically active lymphadenopathy. The patient underwent a repeat EUS-FNA in an attempt to obtain a definitive tissue diagnosis, but this also revealed benign glandular and inflammatory cells with debris.

Despite failure to obtain a confirmatory pathologic diagnosis, given the clinical picture, the patient was given the presumptive diagnosis of PDA. The mass was initially deemed unresectable due to vascular encasement and the patient was referred for neoadjuvant chemotherapy with gemcitabine at a dose of 1000 mg/m². She tolerated the neoadjuvant treatment well, except for early myelosuppression that required a dose reduction of gemcitabine after her second infusion. The patient completed three cycles of treatment, with a total of nine infusions. Post chemotherapy restaging CT scan (Figure 2) showed a reduction in the size of the pancreatic mass and found the SMV and portal vein to be free of tumor encasement. However, there still remained an area of abnormality within the uncinate process of the pancreas. At this point, the mass was judged amendable to surgical resection and the patient underwent a pylorus-preserving pancreatectoduodenectomy. The patient tolerated the surgery well and had an uneventful postoperative course on our clinical pathway [37]. She
Table 1: Current Criteria for the diagnosis of AIP.

| Criteria/Parameter | Japanese (2006)                                                                 | Korean                                                                 | HISORt (Mayo Clinic)                                                                 |
|--------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Imaging            | US, CT or MRI showing narrowing (diffuse/focal) of MPD with pancreas enlargement (diffuse/focal) | US, CT or MRI showing enlarged gland with mass or hypoattenuation rim and ERCP or MRCP of pancreaticobiliary duct showing ductal narrowing. | Enlargement (diffuse or focal) of gland with rim enhancement, ductal stricture (diffuse or focal), pancreatic atrophy, pancreatic calcification or pancreatitis. |
| Serology           | Increased levels of F-globulin, IgG or IgG4 or presence of autoantibodies (ANA and RF) | Increased levels of IgG or IgG4 and/or presence of autoantibodies     | Increased levels of IgG4 (>140 mg/dL)                                               |
| Histology          | Interlobular fibrosis and lymphoplasmacytic periductal infiltrates              | Lymphoplasmacytic infiltration and fibrosis with obliterative phlebitis and/or >10 IgG4-positive plasma cells/HPF. | Lymphoplasmacytic infiltrate and storiform fibrosis with either obliterative phlebitis and/or >10 IgG4-positive plasma cells/HPF                                    |
| Other organ involvement | NUD                                                                             | NUD                                                                     | Hilar/intrahepatic/distal biliary stricture, salivary gland involvement, mediastinal lymphadenopathy, retroperitoneal fibrosis |
| Steroid response   | NUD                                                                             | Marked improvement of pancreatic/extrapancreatic lesion                | Marked improvement of pancreatic/extrapancreatic manifestation                      |
| Diagnosis          | Imaging + Serology and/or Histology                                            | Definite:                                                             | Patients that satisfy criteria for at least one of the following groups:             |
|                    |                                                                                 | 1. Imaging + serology and/or steroid response                         | 1. Group A. Diagnostic pancreatic histology                                           |
|                    |                                                                                 | 2. Pancreatic resection specimen showing histology + IgG4-positive plasma cells | 2. Group B. Imaging + Serology                                                       |
|                    |                                                                                 | Probable:                                                             | 3. Group C. Steroid treatment response.                                               |
|                    |                                                                                 | Unexplained pancreatic disease without pancreatic enlargement, associated with other organ involvement or increased levels of IgG4. |                                                                                       |

MPD - Main pancreatic duct; US - Ultrasonography; CT - Computed tomography, MRI - Magnetic resonance imaging, ERCP - Endoscopic retrograde cholangiopancreatography, MRCP - Magnetic resonance cholangiopancreatography, HPF - High power field, ANA - Antinjen trophil antibody, RF- Rheumatoid factor
NUD- Criteria/parameter not used for diagnosis

was discharged to home six days after surgery. At eight months post surgery, the patient was symptom and disease free with no signs of recurrent AIP and no requirement for steroid treatment.

On pathologic examination of the patient’s resected pancreas specimen no PDA was identified. However, there was a marked ductocentric lymphoplasmacytic infiltrate consistent with AIP. Plasma cells present in the inflammatory infiltrate had expression of CD138 (plasma cell marker) and 90% of them were IgG4 positive (43 IgG4-positive plasma cells/HPF). Venulitis was present and granulocytic epithelial lesions were absent. The entire pancreas specimen was submitted for microscopic evaluation and there was no tumor present and no evidence of metastasis in the 15 harvested lymph nodes (figure 3).
To study the possibility that neoadjuvant chemotherapy elicited a complete tumor response with a IgG4-positive plasma cell infiltrate, we immunostained with IgG4 antibody fourteen other cases of PDA that were treated preoperatively with either gemcitabine alone or another chemotherapeutic agent and were surgically resected at our institution. Informed patient consent was obtained preoperatively via an IRB approved protocol for the use of resected tissues for scholarly activity. The clinicopathologic characteristics of each case and the results of IgG4 staining are shown in Table 2. The age range for the PDA patients treated with neoadjuvant chemotherapy was 49–69 years with a median age of 57 years. All patients except one were treated with gemcitabine based neoadjuvant chemotherapy and ten patients were also treated with radiation preoperatively. All patients had proven PDA on pathology after surgery, and no patient had a complete pathologic response. None of the patients had histologic features of AIP or a high number of IgG4-positive plasma cells on analysis of their resection specimens (figure 4).

DISCUSSION

We present the case of a patient who had a presumptive diagnosis of locally advanced pancreatic ductal adenocarcinoma (PDA) and received neoadjuvant gemcitabine based chemotherapy and subsequent surgical resection. However, postoperative pathologic examination of the pancreas revealed evidence of autoimmune pancreatitis (AIP) and no sign of PDA. AIP and PDA can be difficult to distinguish clinically. The average age of AIP patients is 68 years with a range noted in the literature between 51–87 years, which coincides with the typical age range for PDA [6, 9, 12, 13]. The symptom cluster of AIP coincides with that of PDA, including obstructive jaundice, abdominal pain and elevated liver enzymes [9, 12, 15]. More than 50% AIP patients present with weight loss [9, 12] and some may also report new onset diabetes or worsening glycemic control, all of which are also common findings in patients with PDA [12]. Despite the similarities in presentation between these two diseases, it is essential to differentiate between them in order to devise a proper treatment strategy.

Although the pathogenesis of AIP is still uncertain, our understanding of this disease entity has increased in the recent years. Two forms of AIP are recognized: type 1 and type 2. Type 1 AIP is histologically characterized by lymphoplasmacytic inflammation in a storiform pattern around medium sized and large pancreatic ducts and is associated with acinar atrophy, obliterative venulitis and a mild-to-moderate eosinophil infiltrate [2, 4, 5, 8, 15]. The periductal nature of the inflammatory infiltrate is particularly distinctive and helps separate AIP from other types of pancreatitis. This form of AIP is more likely to be systemic and is characterized by IgG4-positive plasma cell infiltrates and elevated serum levels of IgG4. Associated systemic or extrapancreatic manifestations of type 1 AIP can include lymphoplasmacytic sclerosing cholecystitis, as well as lymphoplasmacyctic infiltrates in the lungs, salivary glands and kidneys [2, 4, 8]. The inflammatory lesion frequently forms a tumefactive mass that may destroy the involved organ [8]. Interestingly, all of the extrapancreatic lesions in patients with type 1 AIP will show an infiltration of abundant IgG4-positive plasma cells, but such an infiltration is not detected in patients with PDA [16]. Based upon this observation some authors have recommended IgG4-immunostaining of extrapancreatic lesions (salivary glands, gallbladder etc.) in addition to Japanese criteria to diagnose AIP [6] (Table 1).

Figure 1: Pre-neoadjuvant chemotherapy abdominal CT scan demonstrating tumor mass (m). The superior mesenteric vein (SMV, black arrow) appears to be completely encased by the tumor at this cross-sectional level.

Figure 2: Post-neoadjuvant chemotherapy CT scan illustrating marked decrease in pancreatic mass. The metallic biliary endoprosthesis is seen (white arrowhead) and the Superior mesenteric vein (SMV, black arrow) is no longer encased by tumor.
venulitis and absent granulocytic epithelial lesions, she appears to be best classified as type 1 AIP.

A number of serum diagnostic markers for AIP have been studied. Given the inflammatory nature of the disease, antinuclear antibody (ANA) and rheumatoid factor (RF) have been examined and found to be positive in 43% to 75% of AIP patients. Neither of these possess adequate sensitivity or specificity to be deemed reliable clinical diagnostic tests [3, 6, 14, 18]. To date, serum IgG4 levels have shown the most promise as a diagnostic marker for AIP with 80% of patients having elevated serum levels (above 140 mg/dL) [6, 18]. In comparison, PDA patients rarely have elevated values of serum IgG4. Ghazale et al. found that 10% of PDA patients had serum IgG4 values above 140 mg/dL, as compared with 76% of AIP patients. If a higher level (greater than 280 mg/dL) of serum IgG4 is used as a cutoff only 1% of PDA patients will have values above this threshold, compared to 53% AIP patients [7, 18]. To increase the diagnostic value of serum IgG4 in AIP, some authors have recommended combining serum IgG4 with ANA and RF. The combined sensitivity of these three tests may be as high as 97% [6, 7, 14].

On cross-sectional imaging, AIP has the characteristic appearance of diffuse enlargement of the pancreas with a capsule-like rim and without ductal dilatation or cut-off [17], though Manfredi et al. found that on review of CT scan imaging, 67% of their patients with AIP had focal enlargement of the pancreas while 33% patients had diffuse enlargement [21]. A capsule-like rim of contrast enhancement was seen in 46% patients where delayed phase scanning was performed and the main pancreatic duct (MPD) was dilated upstream in 57% patients with focal enlargement of the pancreas. Recently it has been suggested that a 2-week trial of steroids may help to distinguish AIP from PDA as there can be a dramatic imaging response in cases of AIP and typically no response in the setting of malignancy [16, 39]. AIP patients do not have elevated values of serum tumor marker CA19-9, which are usually elevated in cases of PDA. A diagnosis of AIP is one of exclusion and can only be concluded when the work-up for malignancy is negative and there is strong clinical evidence for AIP. As a cautionary note, our group recently reported on the case of a patient with simultaneous AIP and PDA [32], an unusual and problematic event.

Type 2 AIP differs from type 1 in that it is not associated with infiltrates of IgG4-positive plasma cells in the pancreas or other organs nor increased serum levels of IgG4. Histopathologically, type 2 AIP is characterized by granulocytic epithelial lesions in association with destruction and obliteration of the pancreatic duct, which are absent in type 1 AIP. Clinically, the disease tends to be confined to the pancreas, though a few studies have linked type 2 AIP to ulcerative colitis. It has been suggested that type 2 AIP may have a higher likelihood of recurrence [16]. AIP is sometimes referred to as lymphoplasmacytic sclerosing pancreatitis (LPSFP) for type 1 AIP and idiopathic duct-centric pancreatitis (IDCP) for type 2 AIP. Given that our patient had an IgG4 inflammatory infiltrate with
Table 2: PDA patients treated with neoadjuvant chemotherapy, radiation and resection (n=14).

| Patients | Age | Gender | Diagnosis | Reason for Neoadjuvant Treatment | Chemotherapy Type | Radiati on (Y/N) | pTNM | IgG4/HPF |
|----------|-----|--------|-----------|----------------------------------|------------------|-----------------|------|---------|
| 1        | 56  | F      | PDA       | SMV involvement                  | gemcitabine      | Y               | pT3NxMx | <1/50 HPF |
| 2        | 56  | M      | PDA       | Visceral Vessel involvement      | gemcitabine + cisplatin | Y               | pT1NoMx | None     |
| 3        | 49  | M      | PDA       | Liver lesions                    | gemcitabine + erlotinib | N               | pT3N1bM1 | None     |
| 4        | 50  | M      | PDA       | Liver lesions                    | gemcitabine + fluorouracil + oxaliplatin | N               | pT3N1aMx | <1/50 HPF |
| 5        | 67  | M      | PDA       | Celiac axis involvement and oblitera tion of SMV/PV confluence | gemcitabine + erlotinib | Y               | pT2NoMx | None     |
| 6        | 53  | F      | PDA       | SMA and portal vein encasement   | gemcitabine + fluorouracil + erlotinib + paclitaxel | N               | pT4N1bMx | None     |
| 7        | 54  | M      | PDA       | SMV encasement                   | gemcitabine      | Y               | pT1NoMx | 16/HPF (focal) |
| 8        | 66  | F      | PDA       | Celiac axis encasement           | Isacoff regimen (fluorouracil + leucovorin + calci um + mitomycin C + dipyridamol) | N               | pT1NoMx | <1/50 HPF |
| 9        | 53  | F      | PDA       | SMA and SMV encasement           | gemcitabine + fluorouracil | Y               | pT3N1bMx | None     |
| 10       | 49  | M      | PDA       | Celiac axis and Proximal Splenic artery encasement | fluorouracil + gemcitabine + bevacizumab + oxaliplatin | Y               | pT2NoMx | None     |
| 11       | 60  | M      | PDA       | Celiac axis involvement          | capecitabine + erlotinib + gemcitabine | Y               | pT1NoMx | None     |
| 12       | 69  | M      | PDA       | Visceral vessels, including SMA and SMV involvement | gemcitabine + erlotinib | Y               | pT3N0Mx | None     |
| 13       | 67  | F      | PDA       | Visceral vessel invasion         | gemcitabine      | Y               | pT3N0Mx | None     |
| 14       | 56  | M      | PDA       | SMA encasement                   | bevacizumab + oxaliplatin + gemcitabine | Y               | pT3N0Mx | None     |

PDA - Pancreatic Ductal Adenocarcinoma, SMA - Superior Mesenteric Artery, SMV - Superior Mesenteric Vein, HPF - High Power Field, Radiation - Administration of radiation post-chemotherapy and pre-resection
Histopathologic examination of our 14 neoadjuvant-treated PDA patients did not reveal any of the previously mentioned histologic features of AIP (lymphoplasmacytic inflammation, obliterative venulitis, or elevated IgG4-positive plasma cells). Only one of our 14 patients had more than 10 IgG4-positive plasma cells/HPF (Table 2), which is still much lower than the typical cutoff value of 50 cells/HPF seen on histologic examination of AIP patients. Based upon these results it appears that neoadjuvant chemotherapy does not result in an AIP-like IgG4-positive plasma cell inflammatory reaction within the pancreatic parenchyma.

The only curative treatment for PDA involves surgical resection. Hence, the recommended practice for localized disease is surgery followed by adjuvant chemotherapy with or without radiation [28]. Neoadjuvant chemotherapy is used to downstage patients who present with locally advanced unresectable disease or, in some centers, as an upfront treatment in patients with operable PDA. Although there are studies demonstrating decreased margin positivity and local failure, as well as increased survival in the subset of patients who undergo neoadjuvant therapy followed by surgical resection for operable PDA, much of the existing evidence is in the form of single-institution experience. Although gemcitabine [25] or gemcitabine based combination chemotherapy [26–27] is considered the standard of care, only 30% of patients treated in the neoadjuvant setting will exhibit conversion to resectable disease [19, 20], and to date no pathologic complete responses to gemcitabine neoadjuvant therapy has been reported.

CONCLUSION

In conclusion, we report the case of AIP in a patient who was originally considered to have PDA and underwent neoadjuvant chemotherapy and subsequent surgical resection. Post-operative pathologic examination of the specimen revealed the presence of abundant IgG4-positive plasma cells and ductocentric inflammation, characteristic of AIP. Neither a complete pathologic response, nor histologic features of AIP, nor an increased number of IgG4-positive plasma cells were seen in any of the other 14 specimens from PDA patients treated with neoadjuvant chemotherapy examined in this study. To the best of our knowledge this is the first time that these results are being reported in the English literature. We conclude that neoadjuvant chemotherapy does not result in an IgG4-positive plasma cell infiltrate in the pancreas, and we additionally have concluded that our patient had an initial diagnosis of AIP and not PDA.

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Author Contributions

Ornella Dervishaj – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Harish Lavu – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Charles J Yeo – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Agnieszka K Witkiewicz – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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