Pancreatology xxx (2017) 1–4

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

# Association of IgG4 response and autoimmune pancreatitis with intraductal papillary-mucinous neoplasms

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ARTICLE INFO

*Article history:*
Received 4 October 2016
Received in revised form
14 January 2017
Accepted 6 February 2017
Available online xxx

*Keywords:*
Intraductal papillary-mucinous neoplasm
IPMN
Autoimmune pancreatitis
AIP
IgG4

ABSTRACT

*Objectives:* Concurrent intraductal papillary-mucinous neoplasm (IPMN) and autoimmune pancreatitis (AIP) was observed in a patient (index case) at our institution. Cases of coincidental IPMN and type 1 AIP and concurrent ductal adenocarcinoma (PDAC) and AIP have been previously reported. In this study we evaluate the hypothesis that IPMN elicits an IgG4 response.
*Methods:* Twenty-one pancreases (including the index case) with IPMN resected at our institution were studied. H&E stained slides were reviewed and blocks of peritumoral pancreas were immunostained with IgG4 to look for IgG4-positive plasma cells.
*Results:* We found evidence of variable IgG4 overexpression in 4/21 (19%) of IPMN. These included the index case and three others without stigmata of AIP.
*Conclusion:* A small subset of pancreatic neoplasms including intraductal papillary-mucinous neoplasms (IPMN) is associated with an IgG4 autoimmune response that sometimes progresses to peritumoral type 1 AIP and less often to diffuse AIP and IgG4-related systemic disease.


## 1. Introduction

In 2011, we diagnosed a pancreas resected at DHMC as having both an intraductal papillary mucinous neoplasm (IPMN) and autoimmune pancreatitis (AIP). The AIP was localized around the IPMN and did not involve pancreas remote from the IPMN. This localization raised two questions: (1) is this situation reflective of an association between the diseases, or (2) is an autoimmune response to the IPMN causing or being misinterpreted as AIP. Beginning in 2013, reports of seven cases of IPMN associated with AIP were published from other centers [1–5]. Tabata et al. concluded "the association of an IPMN with AIP type 1-like changes seems to be exceptional and coincidental." [4] Whereas Vaquero et al. concluded that "Common risk factors to IPMN and AIP may facilitate its coincidental generation." [5].

In one of the published cases, imaging studies documented the presence of cysts (presumably IPMN) for 3 years before changes of AIP were noted [2]. In five cases, the AIP was type 1, a form of AIP that is associated with elevation of serum IgG4 and infiltrates of IgG4 positive plasma cells in involved tissues. Separately, it had been reported that pancreatic ductal adenocarcinomas without AIP were sometimes found to have peritumoral infiltrates with conspicuous IgG4-positive plasma cells when there were no other stigmata of AIP [6]. However, the counts of IgG4-positive cells were lower in the peritumoral infiltrates than in type 1 AIP. These observations suggest the possibility (hypothesis) that some pancreatic neoplasms including IPMN elaborate an antigenic epitope that elicits an IgG4 response. The current project is undertaken to evaluate the relationship between an autoimmune IgG4 response, IPMN and AIP. One possible outcome is that peritumoral AIP is a new and previously unrecognized subset of type 1 AIP. In our patient and in two of the previously reported cases there is evidence supporting a diagnosis of IgG4-related systemic disease. This raises the additional question of whether a tumor associated-IgG4 response may sometimes progress to systemic IgG4-related disease with AIP.

## 2. Materials and methods

We systematically searched the Dartmouth-Hitchcock Medical Center (DHMC) pathology database for diagnoses of IPMN between 2000 and 2014, and 21 surgical pathology specimens (including the index case) were retrieved from the files of DHMC. Our series was consecutive except that it was necessary to eliminate 36 cases

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http://dx.doi.org/10.1016/j.pan.2017.02.004
1424-3903/

because they were referred (outside) cases and we did not have the blocks in our files. Slides from these cases were reviewed to choose areas of the IPMN wall with well preserved epithelial lining and adjacent stroma with a leukocytic infiltrate if this was present. We searched for ductal or stromal changes with stigmata of autoimmune pancreatitis but found none in either the tumor wall or the remote pancreas except in the index case. One and sometimes two blocks of tumor wall were chosen from each case for immunostaining with antibody to IgG4.

Entire sections immunostained using anti-IgG4 antibody were scanned at 40X magnification using a Leica SNC 400 scanner. Counts of IgG4-positive plasma cells were made independently by two observers (AH and DSL) using printouts of 450,886 μm2 fields. The average of the three highest counts is reported and was used for calculations. In the event that it was difficult to find fields with more than 2 positive cells, we photographed 1 or 2 fields and counted additional fields online.

## 3. Results

Although the response is variable and graded, 4/21 IPMN (19%) showed infiltrates of IgG4-positive plasma cells (Fig. 1) that are clearly above background levels [7] (Table 1). Cases were re-graded based on the revised classification system and recommendations from the Baltimore consensus meeting for neoplastic precursor lesions in the pancreas [8]. These included the index case (Case 9).

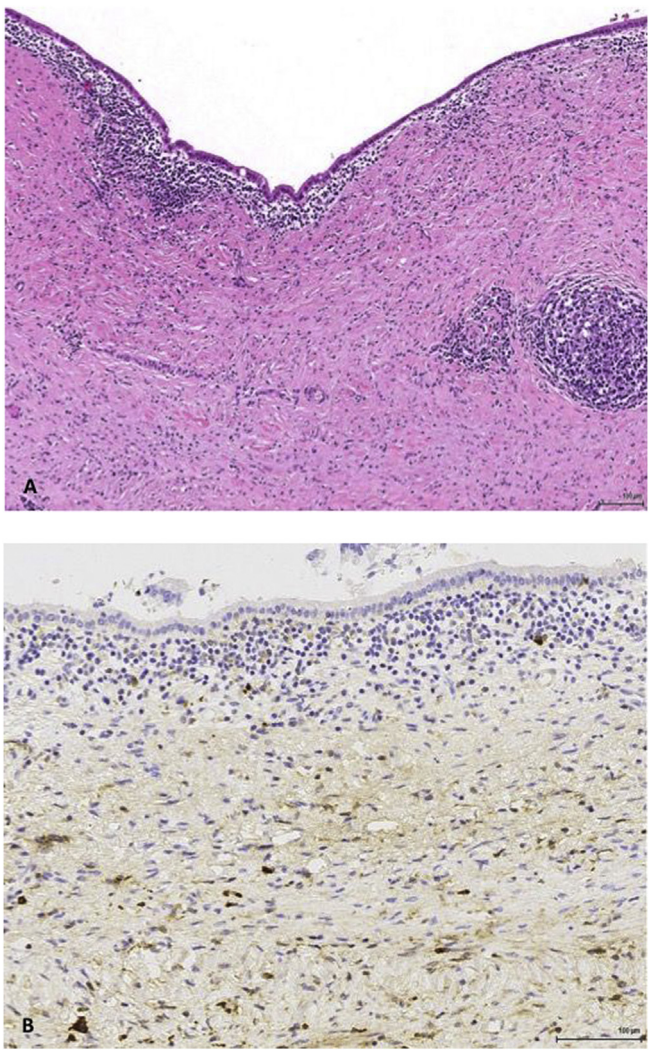


**Fig. 1.** A) low power H&E, 200X, demonstrates epithelial lining with increased lymphoplasmacytic infiltration in the wall of the IPMN. B), IgG4 immunostaining, 200X, highlights the IgG4 positive plasma cells. This area was not part of a "hot spot".

Additional detail is provided for our index case because of its importance in stimulating our study. The index case was a 53-year-old man, with past medical history significant for allergy and depression, who presented to an outside hospital with severe bloody diarrhea after a foreign trip. Infectious etiology work-up was negative. Symptoms temporarily subsided but did not resolve completely. Further work-up continued at DHMC, where a CAT scan of the abdomen showed a pancreatic cyst measuring 4.5 cm in diameter with a thick wall in the tail of the pancreas and a splenic artery aneurysm measuring 1.2 cm. No mural nodules, septations, calcifications or adenopathy were noted in the imaging studies. Diagnosis of cystadenoma or cystadenocarcinoma was suggested. No history of trauma to the abdomen, pancreatitis, or weight loss, was reported.

Preoperative endoscopic ultrasound showed a 3.3 cm thick-walled single-compartment cyst without septae in the pancreatic tail. The outer wall of the lesion was asymmetrically thick measuring up to 9 mm. Fine needle aspiration was significant for 5 ml of clear and viscous fluid. Fluid amylase and CEA were markedly elevated (amylase: >5250 unit/L; CEA: 297.9 ng/ml). Cytology showed clusters and strips of generally bland ductal epithelial cells, stroma and connective tissue with chronic inflammatory cells, fibrosis, a small amount of mucin, and abundant debris. These findings were suspicious for a cystic mucinous neoplasm. The patient underwent open distal subtotal pancreatectomy with en-bloc splenectomy, mobilization of the splenic flexure, and retroperitoneal exploration for metastasis.

Macroscopically, the resection specimen showed a 3.1 cm oligolocular cyst with fibrous septae, containing mucoid fluid and a 0.5 × 0.4 x 0.3-cm, pink, fleshy excrescence within the cyst wall. The spleen was grossly unremarkable.

**Table 1**
Cases indicating number of IGg4-positive cells and grading.

| Case Number | Average count | Avg count per HPF[a] | Grade |
|---|---|---|---|
| 1 | 7.5 | 3.7 | Low grade |
| 2 | 0.33 | 0.2 | Low grade |
| 3 | 1.33 | 0.7 | Low grade |
| 4 | 0 | 0 | Low grade |
| 5 | 13.33 | 6.6 | High grade |
| 6 | 0 | 0 | Low grade |
| 7 | 0.33 | 0 | Low grade |
| 8 | 40.67 | 20.1 | High grade |
| 9a[b] | 72 | 35.6 | Low grade |
| 9b | 118.33 | 216.5 | Low grade |
| 9c | 66.57 | 33 | Low grade |
| 10 | 13.67 | 6.8 | High grade |
| 11 | 31.33 | 15.5 | High grade |
| 12 | 11.33 | 5.6 | High grade |
| 13 | 2.5 | 1.2 | High grade |
| 14 | 0.67 | 0.3 | Low grade |
| 15 | 4.5 | 2.2 | High grade |
| 16 | 19.33 | 9.6 | High grade |
| 17 | 191.67 | 94.9 | Low grade |
| 18 | 3.67 | 1.8 | Low grade |
| 19 | 3.17 | 1.6 | Low grade |
| 20 | 0 | 0 | Low grade |
| 21 | 1 | 0.5 | Low grade |

[a] This is a calculated count per 40X field. The area of the rectangular field we used for counting IgG4-positive cells is about twice that of an average circular 40X high power field that we calculate to be 223,100 $\mu m^2$.

[b] Serum IgG and IgG4 level were elevated in this patient as noted below. Serum IgG level was also determined in patients 6 and 7 and was 530 and 531 mg/dL respectively (normal range 7–89 mg/dL) Immunoglobulin levels were not determined in other patients.

Please cite this article in press as: Hedayat AA, et al., Association of IgG4 response and autoimmune pancreatitis with intraductal papillary-mucinous neoplasms, Pancreatology (2017), http://dx.doi.org/10.1016/j.pan.2017.02.004