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

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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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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).

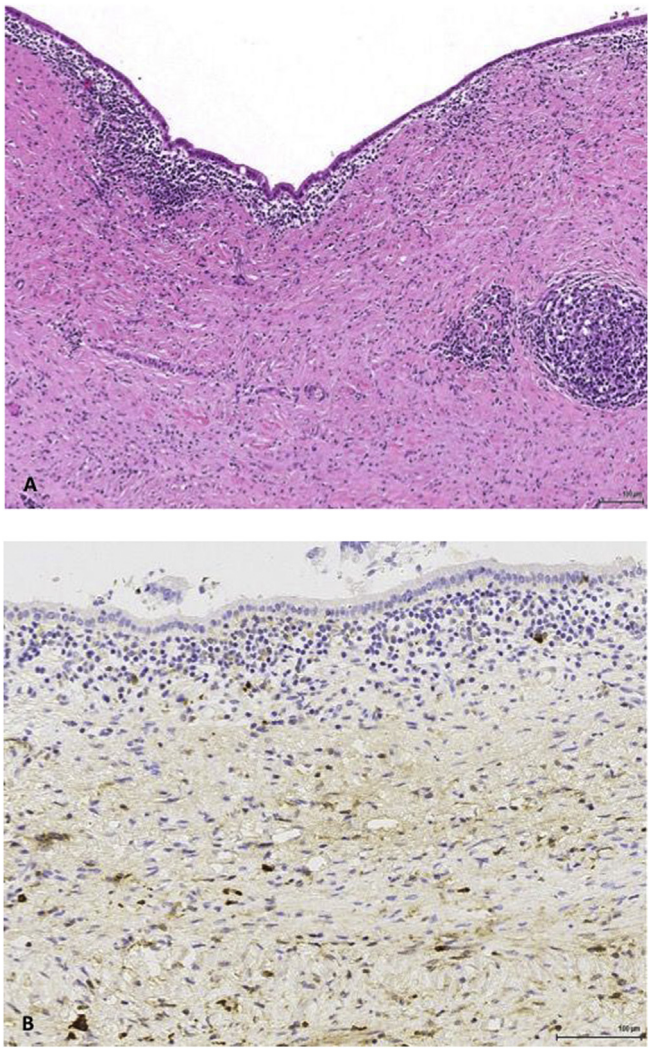

Fig. 1. A) low power H&E, 200X, demonstrates epithelial lining with increased lymphoplasmacytic infiltration in the wall of the IPMN. B), IgG4 immunostaining, 200X, highlights the IgG4 positive plasma cells. This area was not part of a "hot spot".

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 μm^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.

Histologically, the cysts were lined by tall columnar cells with eosinophilic cytoplasm, abundant intracellular and extracellular mucin and basally located nuclei resembling gastric foveolar-type epithelium. The main pancreatic duct was not involved. Stroma was paucicellular with no evidence of invasion. Thirty-four lymph nodes were free of malignancy. The diagnosis was low grade, branch duct-type intraductal papillary mucinous neoplasm.

One year later a lymph node excision was performed at an outside institution and showed reactive lymphoid hyperplasia with progressive transformation of germinal center and markedly increased IgG4 positive cells in the germinal centers (>100/HPF and IgG4/IgG >40%). Serum IgG was 1276 mg/dL (normal range 791–1643) and serum IgG4 was 275 mg/dL (normal range 7–89 mg/dL). Serum IgM, IgA, CBC, CRP, viral, ANA, ANCA, anti-centromere antibody and rheumatoid factor were within normal range. The lymph node findings were consistent with IgG4-related lymphadenopathy, type IV.

Pathologic review of the previously performed subtotal-pancreatectomy revealed fibrosis with focal storiform pattern and periductal lymphoplasmacytic inflammation with frequent eosinophils and multiple reactive lymphoid follicles. A medium-sized artery revealed focal vasculitis with fibrosis, abundant lymphoplasmacytic cells, and lymphoid follicle formation. Immunohistochemistry for CD138 and IgG showed increased plasma cells in multiple areas. IgG4 showed >50 cells/HPF in >3 areas with an IgG4/IgG ratio >40%. The final histopathologic diagnosis was IgG4-related autoimmune pancreatitis, in addition to low-grade intraductal papillary mucinous neoplasm.

4. Discussion

Table 2 lists five reports that include seven patients with peritumoral AIP associated with IPMN. Naitoh et al. noted that detection of the pancreatitis and cyst was coincidental in a patient with a normal serum IgG4 level [1]. Bateman et al. reported two cases with AIP that both showed stigmata of IgG4-related systemic disease, but concluded that most chronic pancreatitis associated with IPMN is not AIP [3]. Urata et al. reported that cystic masses preceded AIP by three years in their patient and concluded that the IPMN may be influencing the pathogenesis of AIP [2]. Although they designated their IPMN as branch duct type they were probably gastric type since they were MUC2 negative, and MUC5AC positive. Tabata et al. reported elevated serum IgG4 levels in 2/54 patients with IPMN (4%), and found significant infiltration by IgG4 positive plasma cells in 4/23 resected IPMN (17%) [4]. Vaquero et al. report two cases of coincidental IPMN and AIP [5]. One patient, a 74-year-old woman, exhibits several features of interest. (1) She was found to harbor a CFTR gene mutation. (2) Her IPMN was classed as pancreatobiliary type on the basis of mucin stains. (3) AIP involved her pancreas diffusely.

Vaquero's second patient, a 79 year old male, is also of interest because of these features: (1) The patient had an IPMN designated as “branch duct type” resected 6 years earlier and the resected specimen showed no stigmata of AIP and sparse IgG4 positive plasma cells. (2) The IPMN associated with AIP was designated as intestinal phenotype. (3) The AIP was type 1 with extrapancreatic involvement and diffuse involvement of the pancreas. As noted above, the authors conclude “common risk factors to IPMN and AIP may facilitate its (sic) coincidental generation.” [5].

Table 2
Reports of simultaneous IPMN and AIP.

Author	Year	IPMN type	AIP type
Naitoh	2013	gastric	Type 1
Bateman	2013		Type 1 (2 cases)
Tabata	2013		Type 1
Urata	2013	Branch duct	Type 1
Vaquero	2014	Pancreatobiliary (case 1)	Type 1
		Intestinal (case 2)	Type 1

There are four major subtypes of IPMN: gastric type, intestinal type, oncocytic, and pancreatobiliary. Our case and most coincidental occurrences of IPMN and AIP have been with gastric type IPMN, however, the cases reported by Vaquero et al. indicate that other types of IPMN may be involved [5]. To date we have found no examples of IPMN associated with type 2 AIP.

The finding by Dhall et al. of varying numbers of IgG4-positive plasma cells in the vicinity of pancreatic ductal adenocarcinomas suggests that these carcinomas may also produce an epitope that elicits an IgG4 response [6]. There are also reports of coincidental occurrence of AIP and pancreatic ductal adenocarcinomas (PDAC) [9–11], and a report of a patient with a mucinous cystic neoplasm and stigmata of AIP [12]. The latter authors speculated that their case reflected “an anti-inflammatory antitumor response driven by Th2 cytokines” rather than a typical type 1 AIP (IgG4-related disease).

The incidence of AIP in Japan is estimated to be 1/100,000[13,14] and is predominately type 1. No such data are available for the US, but we note that the fraction of AIP that is type 1 vs. type 2 is lower in the US than in Japan [15]. Using insurance claims and SEER data, Klibansky et al. estimated that the rate of all IPMN in 2005 (4.35 per 100,000 person years), was 68.5 fold higher than that of malignant IPMN (0.06 per 100,000 person years) [16]. Although it has been estimated that one third of IPMN are malignant [17], Klibansky suggests that studies of surgical specimens tend to oversample larger, symptomatic lesions and exaggerate the proportion of malignant lesions among all IPMN [16,18,19]. Even so, the incidence of simultaneous AIP and IPMN, malignant or not, in a patient would be extremely low if their occurrence were purely sporadic (the product of independent probabilities). This seems at odds with the growing number of reports of coincidental type 1 AIP and IPMN (Table 2 plus our index case). The data reported here and by Tabata et al. [4] suggest that the association of these diseases is more than coincidental.

Overall, our data and that in the literature are consistent with these conclusions: a small subset of IPMN, MCN and PDAC elicit an IgG4 autoimmune response that may progress to peritumoral AIP, and less often to diffuse AIP and other manifestations of IgG4-related systemic disease. The data and literature also raise the question: should peritumoral AIP be regarded as an established subset of type 1 AIP that is characterized by the close association of the AIP with a neoplasm?

Ethical adherence

The protocol for this study was approved by the institutional committee for protection of human subjects of Dartmouth-Hitchcock Medical Center and the Geisel School of Medicine at Dartmouth. The IRB study number is: STUDY 00028629. Date of approval: 2/13/2015.

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Statement of authorship

Each of the authors listed in the manuscript contributed to its preparation and is their original work.

Conflicts of interest

None declared.

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