

Distinctive Pulmonary Histopathology With Increased IgG4-positive Plasma Cells in Patients With Autoimmune Pancreatitis

Report of 6 and 12 Cases With Similar Histopathology

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Abstract: Autoimmune pancreatitis (AP) is one manifestation of a systemic, steroid-responsive disease with elevated serum IgG4 and characteristic histopathology, including increased IgG4-positive (+) plasma cells in the tissue. The histopathology of pulmonary IgG4 disease has not been well established. Six lung biopsies from patients with documented AP were studied, along with 12 additional cases showing similar pulmonary histopathology. For comparison, we examined Erdheim-Chester disease (n = 3), pulmonary Sjögren syndrome (n = 19), inflammatory myofibroblastic tumor (n = 10), various inflammatory and interstitial lung disease (n = 61), and nodal or extranodal Rosai-Dorfman disease (RD) in adults (n = 8). All cases were stained for IgG4 and scored as 1, 2, and 3 as described in AP according to the following criteria: 0, < 5 (per high power field); 1, 5 to 10; 2, 11 to 30; and 3, > 30. Five lung biopsies from AP patients showed IgG4 score of 3, and 1 had a score of 2. Consistent findings in lung biopsies of AP patients included endothelialitis of pulmonary vessels, active fibrosis, lymphangitic inflammatory infiltrates rich in plasma cells and histiocytes with or without nodule formation, and fibrinous pleuritis. Prominent lymphatic dilatation with histiocytes showing emperipolesis of lymphocytes was also seen. All 12 additional cases showing these histologic features also had the IgG4 score of 2 or 3. Among other conditions, an IgG4 score of 2 or 3 was seen in 6 of 8 RD, 4 of 10 inflammatory myofibroblastic tumors, and 8 of 61 inflammatory and interstitial lung disease, but in none of the rest. In conclusion, distinctive pulmonary histopathology

was associated with increased IgG4+ cells in both AP patients and those unknown for AP status. The significance of increased IgG4+ cells in high proportion of RD cases merits further study as does overlap of RD and IgG4 disease.

Key Words: IgG4, inflammatory and interstitial lung disease, autoimmune pancreatitis, Sjögren syndrome, Erdheim-Chester disease, Rosai-Dorfman disease, inflammatory myofibroblastic tumor

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Yoshida et al²⁹ proposed the concept of autoimmune pancreatitis (AP), and it has become the prototype of a highly steroid-responsive, systemic IgG4-related disease.^{2,6,13,29} Most patients have elevated serum IgG4⁹ and increased IgG4-positive (+) plasma cells in tissue.^{6,14,18,34} Histopathologically, AP is characterized by dense periductal lymphoplasmacytic infiltrates without duct destruction, obliterative phlebitis, interstitial fibrosis (often in storiform pattern), and IgG4+ plasma cells greater than 10 per high power field (HPF).^{15,31,34} IgG4-related systemic disease involves various extrapancreatic sites, including the gall bladder,^{6,13–15} bile duct,^{1–3,6,8,10,13–15,18} stomach,¹⁵ colonic mucosa,¹⁵ liver,^{1,26} lymph node,^{3,14,15,18,24} salivary glands,^{1,3,6,10,13–15,18,25} orbit,¹⁹ kidney,^{5,6,13,18} prostate,^{10,13,27,28,30} breast,³² aorta,²⁰ mediastinum,¹² pituitary,^{24–26} bone marrow,¹³ retroperitoneum,^{8,16,19,25,26} and lung.^{7,8,11,12,16,17,19,22–26,29,32} The list of organs involved has been even longer and includes the brain, mesentery, thyroid, mediastinum, peritoneum, and pleura according to a review by Nield et al.¹⁷

A recent study documented a successful steroid treatment of sclerosing mediastinal case with a high serum IgG4 level and IgG4+ plasma cells in the tissue.¹² AP has been postulated to be associated with Sjögren syndrome (SS) because of its systemic manifestation and occasional presentation as Sjögren-like salivary gland enlargement.

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However, the relationship between these 2 conditions has not been established.¹⁶

There have been 11 reports in the English literature of pulmonary lesions with IgG4+ plasma cell infiltration or pulmonary involvement of IgG4-related systemic disease^{6,7,10,16,21–25,28,33} (Table 1). Some of these reports were based only on radiologic findings without histopathologic examination. Various pathologic findings as purported pulmonary manifestations of IgG4 lung disease have been described, mainly in the form of single case reports. The largest series to date, by Zen et al,³³ described 9 cases of plasma cell granuloma with increased IgG4+ cells. Two of their 9 cases also had sclerosing sialadenitis or lymphadenopathy. However, serum IgG4 levels and status of systemic IgG4-related disease were not described.³³ A recent histopathologic study by Yamashita et al²⁸ described 3 cases showing lymphoplasmacytic vasculitis and interstitial fibrosis, said to be indistinguishable from grade 1 lymphomatoid granulomatosis (LYG). Serum IgG4 level was elevated in 1 of their 3 patients, normal in 1 and unknown in the third patient.²⁸

Other pulmonary manifestations of IgG4 lung disease reported in the literature include bronchiolitis obliterans with organizing pneumonia-like or organizing pneumonia (OP),^{7,16,23} interstitial pneumonia,^{6,22} non-specific interstitial pneumonia (NSIP),²¹ and peribronchiolar lymphoplasmacytic inflammation.¹⁶ However, it is still not clear whether there are any distinctive pulmonary histopathologic features associated with IgG4-related systemic disease. In addition, the specificity of increased IgG4+ cells for IgG4-related lung disease is not known.

The purposes of this study are to (1) identify consistent histologic features in the lung biopsies from 6 patients with documented AP to establish histopathologic criteria for IgG4-related lung disease; (2) study 12 cases that show similar histopathologic features but with unknown AP status; (3) assess the “baseline” levels of IgG4+ cells in various lung diseases including 3 cases of pulmonary Erdheim-Chester disease (ECD), 19 cases of pulmonary SS, 10 cases of inflammatory myofibroblastic tumors (IMTs), and 61 other assorted inflammatory and interstitial lung diseases (IILDs); and (4) examine IgG4+ cells in 8 cases of nodal or extranodal Rosai-Dorfman disease (RD) in adults given some histopathologic similarities to RD in our AP and AP-like cases.

MATERIALS AND METHODS

Case Selection

Lung Biopsies With Known AP

Five lung biopsies with the clinical diagnosis of AP were identified in consult and surgical pathology files at Mayo Clinic Rochester (MCR) during the period from 2002 to 2008. One additional case was identified from a cross search for lung biopsy in the cohort of AP patients previously studied by one author (S.T.C.) at MCR.

Lung Biopsies With Similar Histologic Features to AP Cases

Most cases without known AP status but showing the similar histopathology to those with clinically documented AP were contributed by one author (T.V.C.). Additional cases showing similar histopathologic findings were identified among cases with a diagnosis of “inflammatory pseudotumor” or “RD or RD-like changes” from the MCR diagnosis database.

Various Lung Diseases and Nodal or Extranodal RD

Surgical lung biopsies from SS patients were identified by a cross search of the cohort of SS patients at Mayo Clinic provided by one author (J.H.R.). Cases of pulmonary ECD, various IILDs, and nodal or extranodal RD were found by a search of surgical pathology files at MCR during the period of 1994 to 2008. Additional cases were retrieved from the teaching files of one of the authors (T.V.C.), which included various IILDs with well-established diagnosis encompassing lesions associated with increased IgG4+ plasma cells reported in the literature (Table 1).

Clinical information was obtained either from medical record at Mayo Clinic or provided by referring pathologists for consult cases. This study was approved by the Mayo Foundation Institutional Review Board.

Histopathology and Immunohistochemistry

All glass slides for the AP cases and AP-like cases were evaluated for the following findings: pattern of involvement, endothelialitis and mural inflammation of pulmonary vessels, fibrosis, plasma cell proportion in inflammatory infiltrates, presence of prominent lymphatic dilation, emperipolesis, pleuritis, peribronchial inflammation, presence of prominent eosinophils (> 30/HPF in areas of highest concentration of eosinophils), lymphoid hyperplasia, OP, and NSIP pattern (Tables 2, 3).

Immunostains were performed by an autostainer using DAKO dual multimer system or DAKO advance 2 stops multimer system (DAKO, Carpinteria, CA). IgG4 immunohistochemical staining was performed using monoclonal IgG4 antibody (clone HP6025, dilution 1:100; Zymed, San Francisco, CA) on formalin-fixed, paraffin-embedded tissue. IgG stain was also performed using polyclonal rabbit antihuman IgG antibody (dilution 1:10,000, DAKO, Carpinteria, CA). In all 6 AP and 12 AP-like cases, S100 protein (dilution 1:1600, DAKO, Carpinteria, CA) was also performed. In selected cases, additional immunostains were performed for κ and λ light chains (dilution 1:2500 and 1:3000, respectively, DAKO, Carpinteria, CA), CD68 (KP-1, dilution 1:3000, DAKO, Carpinteria, CA), and podoplanin (clone D2-40, dilution 1:40, Covance, Emeryville, CA). Epstein-Barr virus in situ hybridization study using Epstein-Barr virus-Encoding RNA1 probe was also performed on 1 AP case (case 6) and on 1 case with similar pathology (case 12).

Quantitation of IgG4 – and IgG+ Cells

Two methods were used.

TABLE 1. Lung Involvement in IgG4 Diseases

Reference	No. Cases	Tissue Type	Histologic Findings	Radiology	IgG or IgG4 Level in Serum	IgG4 + Cells in Tissue
Duvic et al ⁷	1	Open biopsy	BOOP-like, fibroblasts filling the airspaces	CXR: peripheral reticulo-nodular opacities in R lung CT: bilateral nodules	IgG (1800 mg/dL) IgG4 (110 mg/dL)	NA
Taniguchi et al ²²	1	Transbronchial lung biopsy	Interstitial pneumonia, marked thickening of alveolar septum with marked plasma cells and lymphocytic infiltration	CXR: reticular shadow in lower lung field CT: ground glass middle and lower lobes; honeycombing back of lower lobes	IgG (2350 mg/dL) IgG4 (1690 mg/dL)	Present (no count)
Zen et al ³³	9	Two lobectomies, 6 partial resection, 1 biopsy	Plasma cell granuloma, lymphoplasmacytic infiltrate with fibrosis, eosinophilic and giant cell infiltrate, lymph follicles, entrapped bronchioles, obliterative phlebitis and arteritis	CXR and CT: solitary nodules in the hilar region or at the periphery	IgG (3110 mg/dL) (examined in only 1 case) IgG4 not available	62-235/HPF
Deshpande et al ⁶	2	Wedge biopsy	Interstitial lymphoplasmacytic infiltrate, obliterative phlebitis	CT: mass lesion with septal thickening	NA	> 50/per 20 × objectives
Taniguchi et al ²³	1	Transbronchial lung biopsy	Organizing pneumonia	CT: consolidation adjacent to pleura in RUL, RLL and LLL	IgG (604 mg/dL) IgG4 not available	NA
Hamed et al ¹⁰	1	Open biopsy	LYG-like, vasoinvasion and destruction by polymorphic lymphoid infiltrates, alveolar fibrosis with plasmalymphocytic and macrophage infiltrate	CXR: abnormal shadow CT: solid nodule right S2, S10 segments and hilar LN	IgG (3153 mg/dL) IgG4 (499 mg/dL)	Present (no count)
Kobayashi et al ¹⁶	1	Wedge biopsy	Lymphoplasmacytic infiltration in peribronchial region and organizing pneumonia	CXR: consolidation in perihilar region CT: bilateral consolidation, in left lung interlobar pleural involvement	IgG (4400 mg/dL) IgG4 (572 mg/dL)	Present (no count)
Tsushima et al ²⁵	2	Transbronchial biopsy	Thickened interstitial septa with infiltration of IgG4+ plasma cells in first lung case; plasma cell granuloma in second lung case	Case 1: interstitial pneumonia; Case 2: mass in right lung	Case 1: "Increased IgG4" Case 2: "normal"	Present in both cases (no count)
Takato et al ²¹	1	Wedge biopsy	NSIP, a fibrosing pattern, diffuse interstitial fibrosis with moderate lymphoplasmacytic infiltration in uniform distribution	CXR: reticular shadow CT: ground-glass opacities and reticular shadows with honeycomb-like changes and reaction bronchiectasis in lower lobes	IgG (2330 mg/dL) IgG4 (325 mg/dL)	Numerous (no count)
Yamashita et al ²⁸	3	Wedge biopsy	LYG like, expansion of the interstitium by dense lymphoplasmacytic infiltrate with prominent vascular involvement which are indistinguishable from lymphomatoid granulomatosis (LYG-G1)	CT: ill-defined mass-like spiculation, ill-defined subpleural consolidation, pleural effusion	Case 1: IgG4 (196 mg/dL), no IgG Case 2: IgG (1329 mg/dL), no IgG4 Case 3: no IgG or IgG4 levels	IgG4/IgG ratio: 85%, 47%, and 46%, each
Tsuboi et al ²⁴	1	Wedge biopsy	Pseudotumor containing IgG4+ plasmacytes, fibrosis and obliterative vasculitis both in arterioles and venules, noncaseating granulomas	CT: bilateral pulmonary infiltrate and mediastinal and hilar lymph node swelling	IgG (1990 mg/dL); IgG4 (292 mg/dL)	IgG4/IgG ratio: 23%

BOOP indicates bronchiolitis obliterans with organizing pneumonia; CT, computed tomography; CXR, chest x-ray; HPF, high power field; LLL, left lower lobe; LN, lymph node; LYG, lymphomatoid granulomatosis; NA, not available; NSIP, nonspecific interstitial pneumonia; RLL, right lower lobe; RUL, right upper lobe.

TABLE 2. Pulmonary Histopathology and IgG4+ Cells in AP Patients

Case	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age/sex	74/M	58/F	72/M	55/M	86/M	69/M
Interval between AP diagnosis and lung biopsy	2 y	8 y	4 y	2 mo*	1 y*	2 y
Specimen type	Wedge biopsy	Wedge biopsy	Needle biopsy	Lobectomy	Wedge biopsy	Wedge biopsy
Pattern of involvement	Infiltrative	Infiltrative	Mass-like	Infiltrative	Infiltrative	Infiltrative and mass-like
Lymphangitic distribution	+	+	NA	+	+	+
Endothelialitis/intimitis	+	+	NA	+	+	+
Vascular mural inflammation	+	+	NA	+	—	+
Active fibrosis	—	+	+	+	+	+
Plasma cells in inflammatory infiltrate (%)	> 50	> 50	> 50	> 50	> 50	> 50
Prominent lymphatic dilatation	+	+	NA	+	+	+
S100 + histiocytes with emperipolesis	—	+	—	—	—	+
Fibrinous/fibrous pleuritis	+	+	+	+	+	+
Peribronchial inflammation	+	+	NA	+	+	+
Prominent eosinophils	—	—	—	+	—	—
Lymphoid hyperplasia	—	+	—	+	—	—
OP	—	—	NA	—	+	+
NSIP-pattern	—	+ (c)	NA	—	+ (c)	+ (c)
IgG/HPF	284	301	164	197	81	323
IgG4/HPF	29	112	53	115	69	231
IgG4 score	2	3	3	3	3	3
IgG4/IgG (%)	10	37	32	58	85	72

*Lung biopsy performed before the diagnosis of AP.

AP indicates autoimmune pancreatitis; c, cellular; F, female; HPF, high power field; M, male; NA, not applicable because of the lack of sufficient evaluable lung parenchymal tissue; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia.

Mayo Clinic Rochester

All AP and AP-like cases and 8 cases RD and 34 control IILD cases were assessed for IgG+ and IgG4+ cells at MCR. Areas with the highest density of IgG4+ plasma cells were found by scanning at low power in each case. Three HPFs in the high-density area were selected in each case and photographed under the 40 × objective lens (Nikon Eclipse E400 microscope, field diameter 0.55 mm and Olympus DP 70 camera, 0.0645 mm²). The corresponding areas were also photographed for counting IgG+ plasma cells. Averages of IgG and IgG4+ cells in the 3 HPFs were calculated by manually counting the cells using the printed photographs, for IgG4 score and for IgG4/IgG percentage in each case. IgG4 score was assigned using the scale system as described earlier: 0, < 5 (per HPF); 1, 5 to 10; 2, 11 to 30; and 3, > 30.^{15,34}

Mayo Clinic Arizona

For 59 IILD cases from Mayo Clinic Arizona (MCA), the number of IgG4+ plasma cells and IgG+ plasma cells were counted on the glass slides in the regions of highest density, and the average of the 3 most cellular HPFs was taken as the count as was percentage of IgG4+ plasma cells among all plasma cells in the same regions. The score (0 to 3) and percentage of IgG4+ plasma cells were taken from the average of the 2 observers' IgG and IgG4 counts. The cases were studied with an Olympus microscope with wide field oculars and 40 × HPF (area of a HPF = 0.196 mm²). All cases were

evaluated independently by 2 observers. Reliability of IgG4+ and IgG+ cell counts and IgG4/IgG ratios and the averaging of these values across 2 observers was assessed using the intraclass correlation coefficient on the basis of a 2-way analysis of variance model.

RESULTS

Lung Biopsies From AP Patients

Pertinent findings are summarized in Table 2.

Clinical Summaries

Case 1

A 74-year-old man was initially suspected to have pancreatic cancer and underwent Whipple procedure in 2000, which revealed an ill-defined mass-like lesion in the head of pancreas with features of AP. No evidence of malignancy was present. In 2002, he was referred to Mayo Clinic again for persistent chronic nonproductive cough. The chest computed tomography (CT) scan showed moderate right upper lobe consolidation and right pleural thickening with a small amount of right pleural effusion. The pleural fluid cytology was negative for malignant cells. Right upper lobe wedge biopsy was performed for the evaluation of persistent lung infiltrate with nondiagnostic findings on bronchoscopic lung biopsy performed 1 month before.

TABLE 3. Pulmonary Histopathology and IgG4-positive Cells in Patients With AP-like Changes and Unknown AP Status

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12
Age/sex	79/M	40/F	66/M	56/F	73/M	67/M	71/M	77/M	76/M	77/M	50/F	63/F
Other organ involvement	Unknown	RD in LN*	RD in LNs†	Orbit (IgG4 score 3)	Unknown	Prostate (IgG4 score 3)	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
Specimen type	Wedge biopsy	Lobectomy	Wedge biopsy	Lobectomy	Wedge biopsy	Lobectomy	Wedge biopsy	Wedge biopsy	Lobectomy	Wedge biopsy	Lobectomy	Wedge biopsy
Pattern of involvement	Infiltrative	Mass-like	Infiltrative	Infiltrative	Mass-like	Mass-like	Infiltrative	Infiltrative	Mass-like	Infiltrative	Infiltrative	Mass-like
Lymphangitic distribution	+	NA	+	+	+	+	+	+	+	+	+	+
Endothelialitis/intimitis	+	+‡	+	+	—	+	+	+	+	+	+	+
Vascular mural inflammation	—	+‡	—	+	+	+	+	—	+	+	—	—
Active fibrosis	+	+	+	+	+	+	+	+	+	+	+	+
Plasma cells in inflammatory infiltrate (%)	> 50	< 50	> 50	> 50	< 50	> 50	> 50	< 50	> 50	> 50	> 50	> 50
Prominent lymphatic dilatation	+	—	+	—	—	+	+	+	+	—	—	—
S100 + histiocytes with emperipolesis	+	+	+	+	—	+	+	—	—	—	—	—
Fibrinous/fibrous pleuritis	+	+	+	+	—	—	+	+	+	+	—	+
Peribronchial inflammation	+	+	+	+	—	+	—	—	+	+	+	+
Prominent eosinophils	—	—	—	—	—	+	+	—	—	—	—	—
Lymphoid hyperplasia	+	—	—	+	+	+	—	—	+	—	+	+
OP	—	NA	—	—	—	—	+	—	+	—	—	—
NSIP-pattern	+ (c)	NA	+ (c)	+ (m)	+ (c)	+ (c)	+ (m)	+ (c)	+ (c)	+ (c)	—	+ (f)
IgG/HPF	226	187	NA	373	NA	90	200	177	97	280	112	206
IgG4/HPF	159	29	24	229	30	28	105	72	63	160	20	66
IgG4 Score	3	2	2	3	2	2	3	3	3	3	2	3
IgG4/IgG (%)	71	16	NA	61	NA	31	53	41	65	57	18	32

*Peribronchial LN involvement of RD by direct extension from the lung lesion.

†An intrathoracic LN biopsy showing classic features of RD, 1 year before lung involvement and another involved peribronchial LN discovered at the time of lung biopsy.

‡Evaluation based on a single elastic pulmonary artery present on the section.

c indicates cellular; f, fibrosing; F, female; HPF, high power field; LN, lymph node; M, male; m, mixed cellular and fibrosing; NA, not applicable because of lack of sufficient tissue; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; RD, Rosai-Dorfman disease.

Case 2

A 58-year-old woman presented with bilateral pulmonary infiltrates with subpleural nodules on CT scan, 8 years after the diagnosis of AP. Wedge biopsies from the lingula and right lower lobe were performed.

Case 3

A 72-year-old man initially presented with nephrotic syndrome in 2000, which was completely resolved by prednisone treatment at a dose of 60 mg per day. In 2003, he developed painless jaundice and underwent pancreaticoduodenectomy 6 months after the manifestation of jaundice, under the clinical impression of adenocarcinoma in the pancreatic head. A diagnosis of lymphoplasmacytic sclerosing pancreatitis was made by histopathologic examination. Incidentally, he was also found to have an abdominal aortic aneurysm with plasma cell-rich chronic fibrosing inflammation on periaortic biopsy performed in 2004. In 2008, he was readmitted for progressive renal dysfunction with rising creatinine and proteinuria with global sclerosis involving 20 of 25 glomeruli and acute interstitial nephritis on renal biopsy. In 2008, a left lung mass measuring $6 \times 3.3 \times 1.6$ cm was discovered incidentally on a follow-up abdominal CT scan for the evaluation of his abdominal aortic aneurysm. A CT-guided needle biopsy was performed for an evaluation of this lung mass.

Case 4

A 55-year-old man underwent a left lower lobe lobectomy in 2005, which was initially diagnosed as ECD based on lymphangitic distribution of fibrosis and histiocytic infiltrates and lymphoplasmacytic pulmonary inflammation. Two months later, he was diagnosed to have IgG4-related sclerosing disease involving the pancreas, gallbladder, and common bile duct by histopathologic examination.

Case 5

An 86-year-old man underwent transbronchial biopsy after by surgical lung biopsy in 2007 for the evaluation of bilateral pulmonary infiltrates. He responded to corticosteroid therapy with the resolution of these infiltrates. Approximately a year later in 2008, he developed an obstructive jaundice with a strictured common bile duct found on endoscopic retrograde cholangiopancreatography (ERCP). A subsequent laparotomy revealed enlarged, diffusely firm pancreas. Surgical biopsy from the pancreas showed a benign fibroinflammatory lesion with increased IgG4+ plasma cells (25/HPF, score 2). Serum IgG4 level was 380 mg/dL (normal, 8 to 140 mg/dL) with normal IgG level at that time.

Case 6

A 69-year-old man initially presented with acute epigastric pain accompanied by fever, jaundice, and elevated liver pancreatic enzyme levels in 2001. ERCP at that time revealed common bile duct dilation with an abrupt cutoff, for which a stent was placed. CT scan

showed a mass at the pancreatic head suspicious for adenocarcinoma. However, 2 ERCP-guided biopsies performed over 2 months were negative for malignancy. He underwent biliary drainage and cholecystectomy with a resolution of abdominal symptoms until 2006, when he presented with the recurrence of jaundice, epigastric pain, and elevated liver and pancreatic enzymes. At that point, serum IgG4 level was measured under the impression of AP and was 2490 mg/dL. He was treated successfully with corticosteroids but had an episode of relapse in 2007 with the IgG4 level of 2330 mg/dL. His IgG4 level decreased to 349 mg/dL after the completion of corticosteroid therapy. In 2008, he was readmitted for a treatment of diverticulitis, when bilateral ground glass opacities in the lung bases were incidentally discovered in an abdominal CT scan. A follow-up CT scan revealed persistent left lower lobe infiltrate with an area of consolidation and adjacent linear densities (Fig. 1). Initial transbronchial biopsy was nondiagnostic and pulmonary infiltrates did not improve on 30 days of sulfamethoxazole/trimethoprim treatment. Wedge biopsy by video-assisted thoracoscopic surgery was performed for the evaluation of this mass-like density. Serum IgG4 level was 1150 mg/dL at the time of wedge biopsy.

Pathology and IgG4+ Cell Assessment

Specimens included 1 lobectomy, 4 wedge biopsies, and 1 needle biopsy. Five cases showed infiltrative pattern, 1 of which also revealed a mass-like density well demonstrated by chest CT scan (Fig. 1A). One case showed a mass lesion, which was subjected to a needle biopsy. All surgical biopsies revealed fibrosis and inflammatory infiltrates in prominent lymphangitic distribution involving the visceral pleura and interlobular septa (Fig. 2A).

All but 1 case showed chronic pleuritis with fibrinous exudates and reactive changes (Fig. 2B). Plasma cells comprised the main cell type among the inflammatory infiltrates, followed by lymphocytes and histiocytes. Two cases showed marked lymphoid follicular hyperplasia and 1 case had prominent eosinophils greater than 30 per HPF in some areas. Histiocytes were often localized within the dilated lymphatics (Fig. 2B) lined with D2-40-positive lymphatic endothelial cells and formed loose aggregates, well demonstrated by CD68 immunostain. Some intralymphatic histiocytes were mixed with profuse fibrinous materials. Immunostain with S100 antibody highlighted readily identifiable emperipolesis in 2 cases (Figs. 2C, D).

Both pulmonary arteries and veins were infiltrated by lymphocytes and plasma cells that were mainly localized to the intima (Fig. 2E). Many vessels also revealed endothelialitis characterized by lifted endothelial cells with subendothelial edema and intimal and mural inflammation (Figs. 2E, F). However, no necrotizing vasculitis was found in any case. Inflammatory infiltrates were present within the media in some vessels (Fig. 2F).

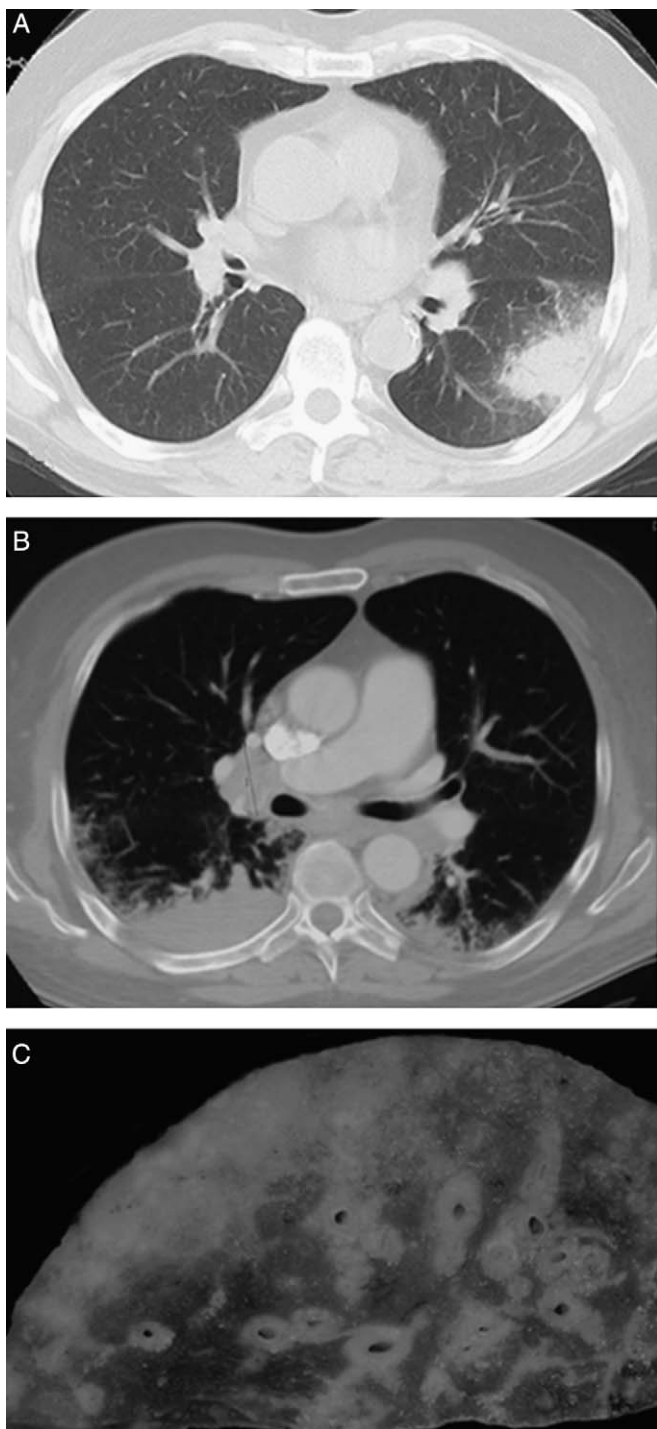


FIGURE 1. A, Chest CT scan of an AP patient showing left lower lobe infiltrates with an area of consolidation and adjacent linear densities that persisted despite antibiotic treatment. B and C, Chest CT scan and gross photograph of an AP-like patient, revealing similar changes as seen in AP patient shown in A. AP indicates autoimmune pancreatitis; CT, computed tomography.

There was myointimal remodeling with areas of web-like recanalizing thrombi or cellular intimal thickening with luminal occlusion (Fig. 2F).

Fibroblast-rich, active fibrosis was present in all except 1 case that showed only mild, mostly collagen deposition without fibroblastic component (Fig. 2G). Fibrosis was generally associated with inflammatory infiltrates but some fibrotic areas were paucicellular. The visceral pleura was thickened with some fibrosis in all cases. Peribronchial inflammation was present in all, except in 1 needle biopsy case in which it was not applicable, with a relative sparing of bronchial epithelium and architecture (Fig. 2H). OP was seen in 2 of 6 cases and mild-to-moderate cellular NSIP was noted in 2 and 1 case, respectively, in the alveolar tissue.

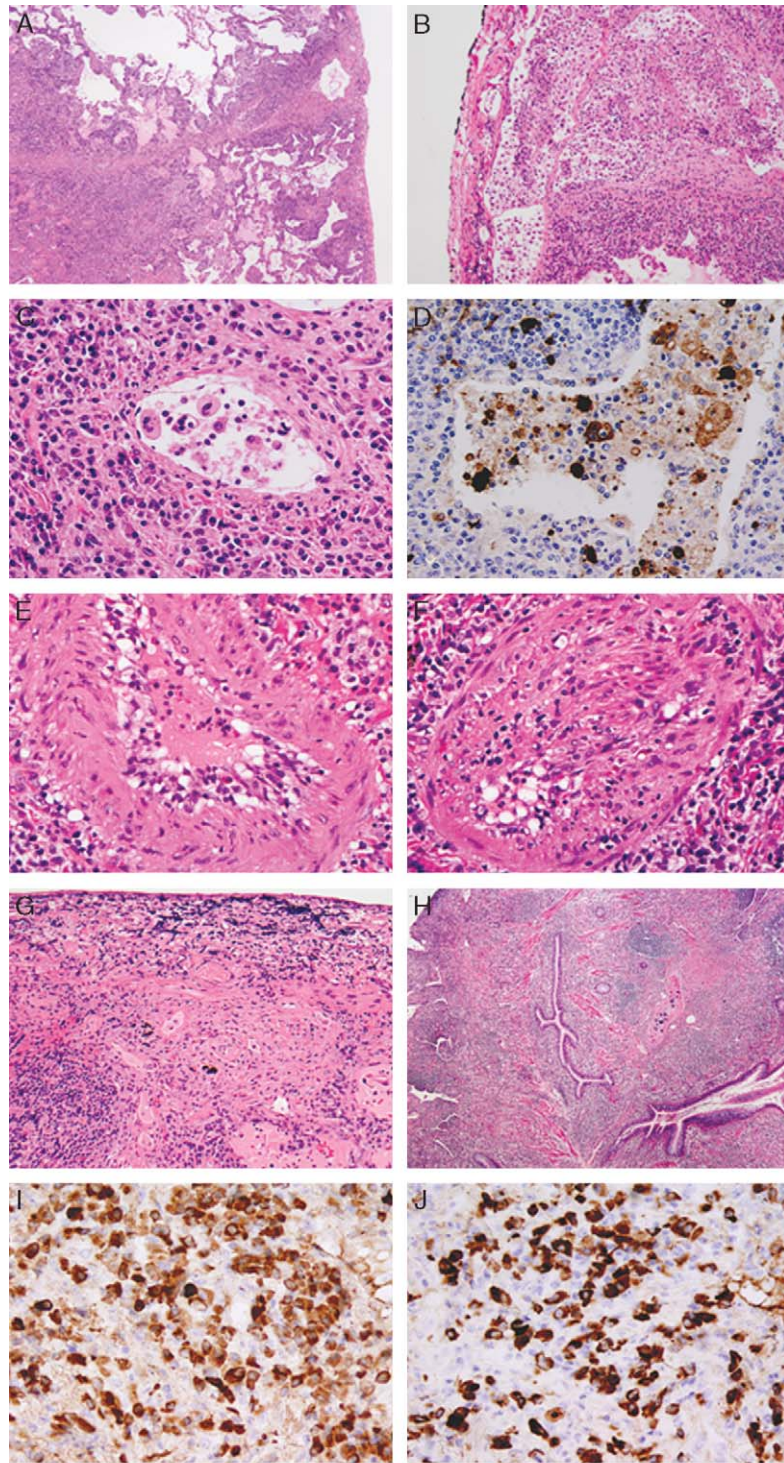
Five cases had IgG4 score of 3 (count ranging from 53 to 231/HPF) with the IgG4/IgG ratio ranging from 32% to 85% (Figs. 2I, J). The remaining 1 case had IgG4 score of 2 (29/HPF) with the IgG4/IgG ratio of 10% (Table 2).

Pathology and IgG4+ Cell Assessment in 12 Lung Biopsies With Similar Pathologic Features to AP Cases

Pertinent findings are summarized in Table 3. Two carried a diagnosis of RD involving the peribronchial lymph nodes as well as the lung (Table 3, cases 2 and 3). Seven of 12 cases had infiltrative growth pattern and 5 cases presented as mass-like density, 2 of which were in central location with mediastinal involvement (Table 3, cases 2 and 9). All but 1 cases had appreciable lymphangitic distribution of fibrosis and inflammation (Fig. 3A) that was apparent chest CT scan and gross examination (Figs. 1B, C). Prominent lymphatic dilatation (Fig. 3B) was seen in 6 cases and emperipolesis with positive S100 staining was seen in 6 cases, resulting in the histologic features reminiscent of RD (Fig. 3C). In addition, there were prominent intimitis/endothelialitis of pulmonary vessels in 11 cases and mural vascular inflammation in 7 cases (Figs. 3D, E). Marked fibrosis was seen in all 12 cases (Fig. 3F). Two of 12 cases showed prominent eosinophils and 1 of these 2 cases had a prostate biopsy, which also revealed the similar histopathology including prominent eosinophils and increased plasma cells and active fibrosis (Table 3, case 6). One of 12 cases (Table 3, case 4) had ocular involvement by plasma cell-rich fibroinflammatory lesion suggesting a possibility of systemic IgG4 sclerosing disease despite the lack of known clinical history of AP. Marked lymphoid hyperplasia with germinal center was seen in 7 cases. All cases were stained for IgG4 and also with IgG except 2 cases that had insufficient material (Table 3) (Figs. 3G, H). All 12 cases demonstrated an IgG4 score of 2 or 3 with the IgG4/IgG ratio ranging from 16% to 71% (Table 3).

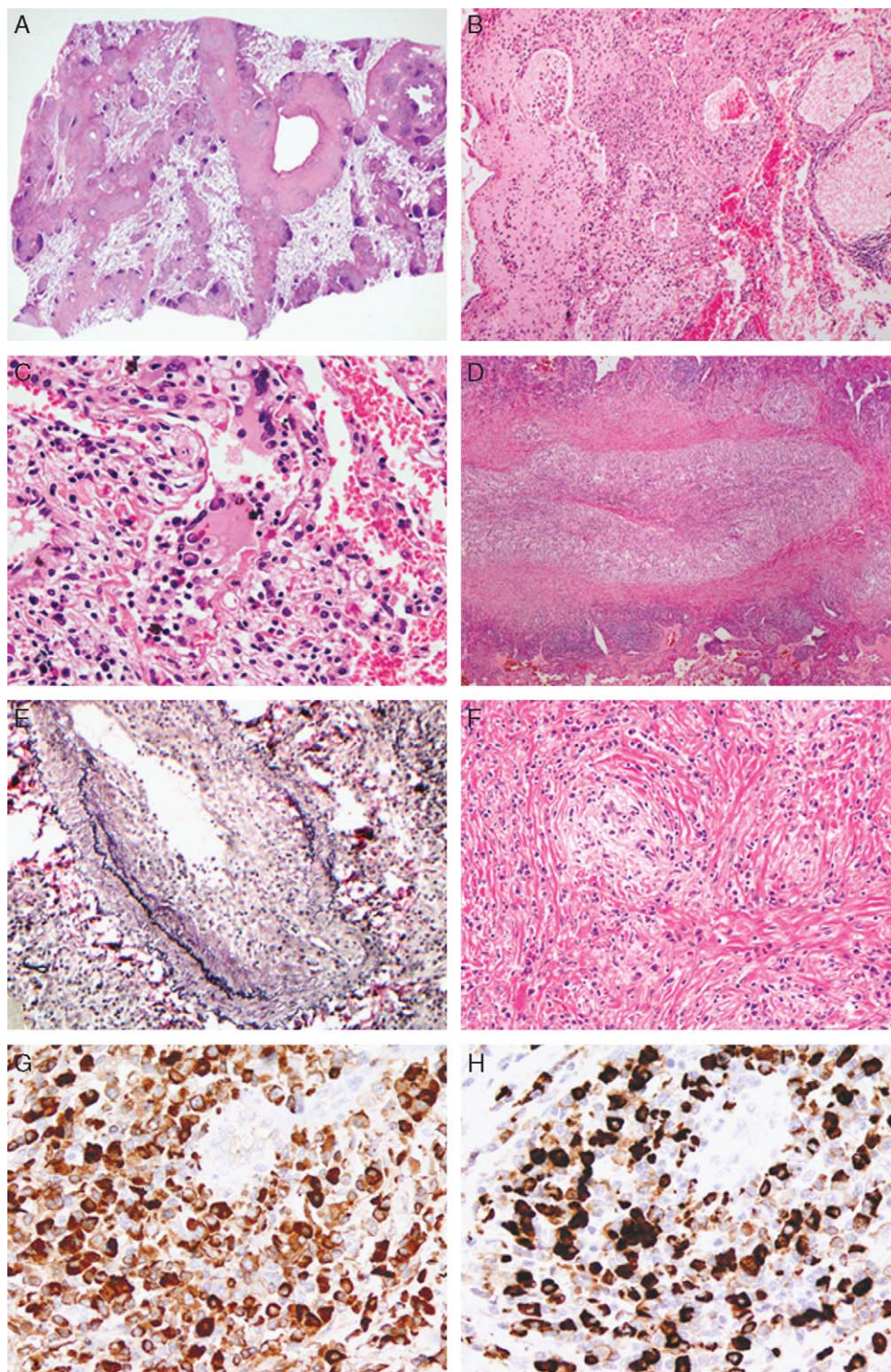
IgG4+ Cell Assessment in Other Conditions

Six of 8 RD cases involving nodal or extranodal sites showed IgG4 score of 2 or 3, with the IgG4/IgG ratio ranging from 10% to 70% (Table 4). None of the 3



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FIGURE 2. A, Lower power view of the lung biopsy showing a lymphangitic distribution of fibroinflammatory changes with focal consolidation shown in the lower field (HE, 40 × original magnification). B, Dilated lymphatic spaces filled with histiocytes seen in the visceral pleura, which shows mild fibrinous pleuritis (HE, 100 ×). C and D, Emperipolesis in S100-positive histiocytes (HE and S100, 400 ×). E, Endothelialitis characterized by subendothelial mixed inflammatory infiltrates with reactive endothelial cell changes (HE, 400 ×). F, Intimal and mural inflammatory infiltrates accompanied by luminal occlusion owing to cellular myointimal proliferation (HE, 400 ×). G, Fibroblastic proliferation in the center surrounded by mononuclear infiltrates at the periphery of field (HE, 100 ×). H, Peribronchial inflammation without structural alteration of the involved airways (HE, 40 ×). I and J, A marked increase in IgG – and IgG4+ plasma cells among the inflammatory infiltrates showing a high IgG4/IgG ratio (IgG and IgG4, 400 ×). HE indicates hematoxylin and eosin.



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FIGURE 3. A, Prominent lymphangitic pattern shown in whole mount section (HE, 1 ×). B, Dilated lymphatic spaces adjacent to the visceral pleura showing fibrinous pleuritis (HE, 100 ×). C, Two histiocytes showing emperipolesis within a dilated lymphatic space (HE, 400 ×). D, A large septal vein involved by a marked intimal and mural inflammation (HE, 40 ×). E, Intimal inflammation in a muscular pulmonary artery with distinct internal and external elastin layers (Verhoeff Van Gieson, 200 ×). F, Fibroblast-rich active fibrosis with storiform pattern (HE, 100 ×). G and H, A marked increase in IgG – and IgG4+ plasma cells among the inflammatory infiltrates showing a high IgG4/IgG ratio (IgG and IgG4, 400 ×). HE indicates hematoxylin and eosin.

TABLE 4. IgG4+ Cell in Nodal/Extranodal Rosai-Dorfman Disease

Case	Age	Sex	Site	IgG/HPF	IgG4/HPF	IgG4 Score	IgG4/IgG %
1	51	M	Cervical LN	318	224	3	70
2	55	F	Mediastinal LN	330	131	3	40
3	56	F	Axillary LN	49	0	0	0
4	65	F	Abdominal wall	187	91	3	49
5	73	F	Thigh	109	37	3	34
6	56	F	Spleen	92	4	0	4
7	37	F	Hip	328	32	3	10
8	43	F	Orbit	122	16	2	13

F indicates female; HPF, high power field; LN, lymph node; M, male.

ECD cases or 19 pulmonary SD cases had IgG4 score of 2 or 3. Four of 10 IMTs showed an IgG4 score of 2 or 3 with the IgG4/IgG ratio ranging from 21% to 58%. Various lung diseases included in this study are listed by clinical/clinical pathologic diagnosis (Table 5). Details of the cases with increased IgG+ plasma cells (score 2 or 3) are summarized in Table 6. IgG4 scores according to the different histologic patterns seen in the various lung diseases are listed in Table 7.

The reliability of IgG4+ and IgG+ cell counting for IILD cases performed by 2 observers at MCA (T.V.C. and P.G.) was estimated to be 0.97 [95% confidence interval (CI): 0.955, 0.985] and 0.795 (95% CI: 0.665, 0.877), respectively. The reliability of the IgG4+/IgG+ cell ratio was estimated to be 0.90 (95% CI: 0.817, 0.945). When averaging across the 2 observers, the reliability for the 3 measures increased to 0.99 (95% CI: 0.977, 0.992), 0.89 (95% CI: 0.798, 0.935), and 0.95 (95% CI: 0.899, 0.972) for IgG4+ count, IgG+ count, and IgG4+/IgG+ cell ratio, respectively. As estimates may be artificially high given the large number of cases with zero IgG4+ cells, we additionally estimated reliability

using only the cases with at least 1 IgG4+ cell by either observer. The estimates of reliability decreased only slightly (by < 0.04 in all point estimates; data not shown).

DISCUSSION

In this study, we report the clinicopathologic features of the lung biopsies from 6 patients with documented AP, which, to our knowledge, is the largest series on IgG4-related lung disease in AP patients. Two of these patients underwent the lung biopsies before the diagnosis of AP was established. Thus, a better characterization of pulmonary pathologic findings in IgG4 disease would be crucial for the diagnosis and appropriate treatment. We did observe a constellation of distinctive histopathologic features and increased IgG4+ cells in all cases although no individual finding was entirely specific.

The most notable and consistent histopathologic findings were a lymphangitic distribution of plasma cell-rich inflammatory infiltrates, active fibrosis, and remarkable intimal inflammation involving both pulmonary veins and arteries without associated necrosis. Other common findings were fibrinous pleuritis and dense peribronchial inflammation. In addition, we observed prominent lymphatic dilation with increased histiocytes and emperipolesis of lymphocytes in some cases, a unique finding reminiscent of RD that has not been described earlier either in the lung or in the pancreas. Prominent eosinophils and lymphoid hyperplasia with germinal centers were seen cases in 1 and 2, respectively. Features of OP and/or cellular NSIP comprised miscellaneous, usually minor, histologic findings present in these cases.

Pulmonary histopathologic features in our 6 AP cases were generally similar to the features in the pancreas of AP. However, there also seem to be some differences between the histopathologic manifestation of the lung and the pancreas in AP patients. The characteristic storiform fibrosis seen in pancreatic biopsies was not as apparent in the lung biopsies, which often had prominent collagenized fibrosis and active fibroblastic proliferation. Both pulmonary arteries and veins were involved by intimal and mural inflammation, distinct from the features in pancreatic biopsies of AP, which mostly show obliterative phlebitis and usually spare arteries.

TABLE 5. Other Lung Diseases by Clinical/Clinicopathologic Diagnosis

Clinical/Clinicopathologic Diagnosis	MCR	MCA	Total
Erdheim-Chester disease	3	0	3
Sjögren's syndrome	11	8	19
Inflammatory myofibroblastic tumor	0	10	10
Nonspecific interstitial pneumonia	4	7	11
Rheumatoid arthritis	0	9	9
Systemic lupus erythematosus	0	8	8
Hypersensitivity pneumonia	8	0	8
Suspected drug reaction	1	5	6
Cryptogenic organizing pneumonia	0	4	4
Polymyositis/dermatomyositis	0	3	3
Idiopathic pulmonary fibrosis	3	0	3
Mixed connective tissue disease	0	2	2
Non-necrotizing granulomas unknown etiology	1	1	2
Necrotizing granulomatous inflammation	1	0	1
Nodular lymphoid hyperplasia	1	0	1
Desquamate interstitial pneumonia	1	0	1
Scleroderma	0	1	1
Cytomegalovirus pneumonitis	0	1	1
Total numbers	34	59	93

MCA indicates Mayo Clinic Arizona; MCR, Mayo Clinic Rochester.

TABLE 6. Details of 12 Cases With Increased IgG4+ Cells (Score 2 or 3)

Case Description	IgG/HPF	IgG4/HPF	Score	% IgG4
NSIP	72	19	2	26
NSIP	35	17	2	49
Necrotizing granulomatous inflammation	138	69	3	50
UIP	38	11	2	29
Rheumatoid arthritis NSIP/pleuritis	69	20	2	29
Rheumatoid arthritis UIP	54	23	2	43
Rheumatoid arthritis nodules	90	13	2	14
SLE with diffuse alveolar damage	66	47	3	71
IMT (plasma cell granuloma)	170	99	3	58
IMT (plasma cell granuloma)	97	41	3	42
IMT (plasma cell granuloma)	154	33	3	21
IMT (plasma cell granuloma)	87	27	2	31

HPF indicates high power field; IMT, inflammatory myofibroblastic tumor; NSIP, nonspecific interstitial pneumonia; SLE, systemic lupus erythematosus; UIP, usual interstitial pneumonia.

The presence of increased IgG4+ plasma cells was a consistent finding in the lung biopsies of patients with AP. All 6 AP cases had increased IgG4+ cells; 5 cases had the IgG4 score of 3 and the remaining 1 case was at the upper limit of score 2 with the IgG4 count of 29 per HPF. In the pancreas, the count greater than 10 IgG4+ plasma cells per HPF was considered characteristic in a large series from the Mayo Clinic.³⁴ However, other reports have suggested different values as > 20, > 30, or > 50 IgG4+ plasma cells per HPF.³ In our pulmonary cases with AP, the IgG4+ cells ranged from 29 to 231 per HPF. Among our other “control” cases studied, only 12 of 93 (13%) lung biopsies showed IgG4 score of 2 or 3. Furthermore, these cases with a mere increase in IgG4+ cells can be distinguished from the pulmonary infiltrates associated with AP-based on the distinctive morphologic findings in AP patients.

The 12 cases showing similar histopathology to the AP cases also demonstrated increased IgG4+ cells with a

score of 2 or 3 (Table 3). These 12 cases were originally labeled with a variety of diagnoses, including RD, RD-like inflammatory disease, inflammatory pseudotumor, and some had been a purely descriptive diagnosis. Even with the limited available clinical information, 2 of these 12 cases had histologically documented involvement of other sites: orbit and prostate. In both sites, IgG4 score was 3. Two cases (Table 3, cases 2 and 9) had associated fibrosis extending to the mediastinum, reminiscent of sclerosing mediastinitis. There has been a case report of sclerosing mediastinitis that had high serum IgG4 level and was successfully treated with corticosteroids.¹² In light of limited medical and surgical option for most sclerosing mediastinitis, further study would be important to identify a potential subset of steroid-responsive, IgG4-related fibrosing mediastinal disease. A study is in progress to evaluate this aspect.

One of the most prominent pulmonary histopathologic features in AP patients was a lymphangitic

TABLE 7. IgG4 Score by Histologic Pattern Present in Other Lung Diseases

Histologic Pattern	Cases	IgG4 Score 0	IgG4 Score 1	IgG4 Score 2	IgG4 Score 3
Erdheim-Chester disease	3	3			
Extranodal marginal zone lymphoma/atypical lymphoid infiltrate	3	3			
Alveolar hemorrhage (acute, chronic)	3	3			
Desquamative interstitial pneumonia	2	2			
Lymphoid hyperplasia	5	4	1		
Lymphocytic interstitial pneumonia	3	1	2		
Non-necrotizing granulomas	3	2	1		
Bronchiolitis/follicular bronchiolitis	11	10	1		
Hypersensitivity pneumonitis	8	7	1		
Usual interstitial pneumonia	8	3	3	2	
Nonspecific interstitial pneumonia	29	22	4	3	
Pleuritis, fibrinous, and fibrous	5	4		1	
Rheumatoid arthritis nodules	1			1	
Inflammatory myofibroblastic tumor	10	4	2	1	3
Organizing pneumonia	13	10	2		1
Diffuse alveolar damage	5	4			1
Necrotizing granulomatous inflammation	1				1
Metastatic calcification	1	1			
Cytomegalovirus pneumonitis	1	1			

All patterns seen in each case are included; more than one pattern could be present in a given case.

distribution of the inflammatory infiltrates and fibrosis. There are only a few fibroinflammatory lung diseases that display such a prominent lymphangitic pattern and include sarcoidosis and ECD. In contrast to sarcoidosis, AP cases do not show well-formed epithelioid, non-necrotizing granulomas. However, ECD can pose a difficulty in the differential diagnosis with AP-associated pulmonary pathology. Indeed, 1 of our 6 AP cases (Table 2, case 4) was initially diagnosed as ECD. Lack of characteristic radiologic findings for ECD in long bones and the presence of vascular inflammation and marked inflammatory background with numerous plasma cells would argue against ECD. Furthermore, IgG4 staining would be also helpful as all of our 3 ECD cases were completely negative for IgG4+ cells (score 0). This finding also suggests that ECD is not an IgG4-related disease.

The most challenging differential diagnosis was with RD, which also can show prominent lymphangitic distribution involving the pleura, interlobular septa, and along the bronchovascular bundles as seen in our AP and AP-like cases. Four of our 6 AP cases revealed prominent lymphatic dilatation with emperipolesis in 2 cases highlighted by S100 stain, reminiscent of RD. Indeed, 2 of 12 cases showing AP-like features carried the diagnosis of pulmonary RD with the lymph node involvement showing collections of histiocytes with emperipolesis: 1 patient (case 2) with peribronchial lymph node involvement by a direct extension; another patient (case 3) with classic histologic features of RD shown on an intra-thoracic lymph node biopsy obtained 1 year before the lung biopsy, when another peribronchial lymph node involvement was also documented. Additional 4 cases among these 12 AP-like cases showed emperipolesis with a strong diagnostic consideration of RD as well.

We also studied 8 cases of nodal ($n = 3$) and extranodal (extrapulmonary; $n = 5$) RD; 6 of 8 RD cases showed increased IgG4+ cells (Table 4). Our results differ from the study by Cheuk et al³ in that 2 of our 3 nodal RD cases had an IgG4 score of 3 with the IgG4/IgG ratio of 40% and 70%. Two cases of nodal RD included in their study had an IgG4/IgG ratio of 17.3% and 29.4%, which did not meet their cutoff value of 40%. Four of our 5 extranodal RD cases showed increased IgG4+ cells with a score of 2 or 3 with the ratio ranging from 10% to 49% (Table 4). Further study with more cases would be needed to determine the biologic significance of these findings and possible overlap with IgG4 disease and RD.

Several authors have reported the AP occurring in patients who also had SS and postulated the possible relationship between the 2 diseases.¹⁶ In our study, none of the 19 lung biopsies from SS patients had increased IgG4+ cells, which challenges this concept. Similarly, Kamisawa et al¹⁴ did not find increased number of IgG4+ plasma cells in salivary glands of 5 patients with SS. In addition, it has been argued that the sicca syndrome observed in AP is distinctive from classical SS with positive anti-SS-A or anti-SS-B antibodies although

AP can produce Sjögren-like salivary gland enlargement. Rather, salivary gland pathology associated with IgG4 disease seems to resemble the so-called Kuttner tumor rather than SS.

The prominent vascular involvement seen in the lung biopsies of AP patients can mimic a vasculitis. However, the pulmonary vascular inflammatory infiltrates predominantly involved the intima and were not accompanied by necrosis when present in the media. Yamashita et al²⁸ described IgG4-related lymphoplasma-cytic vasculitis as similar to grade 1 lesion of LYG without Epstein-Barr virus-Encoding RNA-positive cells. Other than the presence of some vascular infiltration, the histopathology in our cases did not strongly resemble LYG. Our cases were not only negative for Epstein-Barr virus but also lacked characteristic findings of LYG such as well-defined nodule formation, necrosis, and atypical lymphoid infiltrates. Furthermore, lymphangitic distribution of pulmonary infiltrates or fibrosclerosis would not be prominent in LYG, unlike our AP and AP-like cases.

The study by Zen et al³³ of 9 cases of plasma cell granuloma showing increased IgG4+ plasma cells led us to include 10 cases of IMT for this study. By current World Health Organization classification, plasma cell granuloma of the lung is included under the heading of IMT, along with inflammatory pseudotumor and inflammatory fibrosarcoma.⁴ Four of our 10 IMT cases had an IgG4 score of 2 or 3. All of our 4 IMT cases with increased IgG4+ cells also showed plasma cell granuloma type of IMT. This finding would support the data in the study by Zen et al³³ that IgG4-related disease may encompass some cases of IMT showing the plasma cell granuloma pattern.

We examined both IgG4 score and IgG4/IgG ratio for the assessment of IgG4+ cells. In the AP cases and AP-like cases, IgG4+ cells were enumerated using the printed photographs to ensure the accuracy and consistency of counting in deriving the IgG4 score. The subset of assorted control lung cases contributed from MCA was quantitated using the glass slides by 2 observers (T.C.V. and P.G.). We think either method could be used in practice. Most earlier studies on AP have used IgG4 score based on the counting by microscopic examination of glass slides without IgG count for IgG4/IgG ratio. We also used the IgG4 score as the primary method to assess the increase in IgG4+ cells. In our study, IgG4 score generally correlated with the IgG4/IgG ratio. An earlier study on IgG4-related lymphadenopathy by Cheuk et al³ adopted “> 40% of IgG4+ cells among IgG positive cells” as the criterion for a significant increase of IgG4+ cells. However, using such a cutoff point based on the IgG4/IgG ratio may not be appropriate in extra nodal sites, which typically contain fewer plasma cells than lymph nodes; in addition, a minor change in IgG4 or IgG cell count results in a significant shift of the ratio in the cases with low level of IgG4+ and IgG+ cells per HPF.

In summary, we observed increased IgG4+ cells with characteristic and distinctive histopathologic findings in the lung biopsies from AP patients and the cases

with the similar histopathology, which could be helpful in recognizing the IgG4-related lung disease. Lung biopsies of ECD and SS did not show increased IgG4+ cells. Four of 10 IMT cases showed increased IgG4+ cells, which suggested a subset of IMT in the lung may represent IgG4 lung disease. Six of 8 nodal and extranodal RD cases showed increased IgG4+ cells, which coincided with the histopathologic resemblance to RD observed in the lung biopsies of AP and AP-like cases.

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