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Update on respiratory lesions in patients with IgG4-related autoimmune pancreatitis

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Abstract

We previously reported respiratory involvement in 25 patients with autoimmune pancreatitis, a pancreatic manifestation of IgG4-related disease that responds well to glucocorticoid treatment. However, whether all respiratory lesions in patients with autoimmune pancreatitis have genuine respiratory involvement is unclear. This study aimed to update respiratory lesions' clinical and radiological characteristics in patients with autoimmune pancreatitis. We retrospectively reviewed the clinical and radiological data of 74 consecutive patients diagnosed with autoimmune pancreatitis at Shinshu University Hospital and treated with glucocorticoid. Clinical features and chest high-resolution computed tomography findings before and after therapy were reviewed. Fifty-one patients (68.9%) had respiratory lesions. In 65 of the 74 patients, chest high-resolution computed tomography results were evaluated before and after treatment. Patients with IgG4-related disease and respiratory lesions showed significantly higher serum IgG4 levels and hypocomplementemia than those without respiratory lesions; they also had more affected organs. While most abnormal thoracic findings improved, 4 cases of 7 with reticular opacities and all 11 cases with emphysema did not improve. Therefore, these lesions with poor response to glucocorticoid treatment should not be considered due to respiratory involvement of autoimmune pancreatitis based on the current classification criteria for IgG4-related disease. Patients with autoimmune pancreatitis and respiratory lesions exhibited higher disease activity than those without. Most chest high-resolution computed tomography lesions were responsive to glucocorticoid treatment, whereas reticular opacities and emphysema were poorly responsive.

Abbreviations: AIP = autoimmune pancreatitis, BVB = bronchovascular bundle, CT = computed tomography, GC = glucocorticoid, GGO = ground-glass opacity, HRCT = high-resolution computed tomography, Ig = immunoglobulin, IgG4-RD = immunoglobulin G4-related disease, IgG4-RRD = IgG4-related respiratory disease, IP = interstitial pneumonia.

Keywords: autoimmune pancreatitis, IgG4, IgG4-related disease, IgG4-related respiratory disease, interstitial pneumonia

1. Introduction

Immunoglobulin (Ig) G4-related disease (IgG4-RD) is a systemic disease characterized by tumefactive lesions with abundant IgG4-positive plasma cells and a high serum IgG4 concentration.[1,2] Autoimmune pancreatitis (AIP) is classified into type 1 and type 2 AIP. Histopathologically, type 1 AIP is characterized by lymphoplasmacytic sclerosing pancreatitis, and type 2 is characterized by idiopathic duct-centric pancreatitis.[3] Clinically, type 1 AIP, a pancreatic manifestation of IgG4-RD, is a unique form of chronic pancreatitis characterized by various extrapancreatic involvements, including salivary glands, lungs, kidneys, and retroperitoneum.[3,4] We previously reported 4 types of chest computed tomography (CT) findings (nodular lesions, bronchial thickening, interlobular thickening, and consolidation) in 25 patients with type 1 AIP who showed an improvement with glucocorticoid (GC) treatment.[5] Subsequently, we assessed patients with GC-responsive airway involvement in type 1 AIP and characteristic chest CT and bronchoscopic findings.[6,7] These thoracic lesions with GC responsiveness are considered IgG4-related respiratory disease (IgG4-RRD).[8] Furthermore, we assessed IgG4-RRD with extrathoracic manifestations and reported that the lesions developed through lymphatic routes associated with vascular involvement of the lungs and showed a positive response to GC treatment with benign prognoses.[9]

However, some patients with interstitial pneumonia (IP) with IgG4-positive plasma cells were reported to have a poor

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response to therapy or died from IP exacerbation.[10–12] Current guidelines[13–15] recommend that lesions with poor response to GC treatment should be evaluated for proper diagnosis. Therefore, reexamining AIP-related respiratory lesions, including their responsiveness to GC treatment, is essential. This study aimed to update respiratory lesions' clinical and radiological characteristics in type 1 AIP. Only type 1 AIP was included in this study, hereafter referred to as AIP.

2. Methods

2.1. Study subjects

The Institutional Review Board of Shinshu University approved this retrospective, single-center study (approval number: 5795). This study was conducted in accordance with the principles of the amended Declaration of Helsinki. The Institutional Review Board waived the need for informed consent owing to the retrospective study design; the opportunity to opt out was provided.

We reviewed the medical records of consecutive patients newly diagnosed with AIP at Shinshu University Hospital between January 2000 and December 2020. AIP was diagnosed according to the International Consensus Diagnostic Criteria for AIP[16]; accordingly, 107 patients were diagnosed with definitive type 1 AIP and 14 were diagnosed with probable type 1 AIP by gastroenterologists (A.N. and T.O.).

Patients with AIP for whom high-resolution chest CT (HRCT) images could be evaluated (n = 74) were initially screened for inclusion in this study. We analyzed the presence of extrapancreatic organ involvement and evaluated these patients' detailed chest HRCT findings.

Additionally, we reviewed patients treated using GC and reevaluated their chest HRCT findings within 180 days of GC treatment initiation. Nine patients who could not undergo chest HRCT within 180 days of GC treatment initiation were excluded. Thus, the CT finding analysis included 65 patients with AIP for whom pre- and post-treatment chest HRCT findings were available.

2.2. Clinical, physiological, and radiological findings

Baseline clinical and physiological data and medication for AIP were obtained from patient medical records. CT images at the active stage of AIP before the GC therapy initiation were also reviewed.

The involvement of affected extrapancreatic organs was evaluated based on systemic CT image analysis. In cases where decision-making was difficult, multidisciplinary discussions with physicians and radiologists were held to reach a consensus. Even in patients without specific symptoms, extrapancreatic lesions consistent with IgG4-RD were considered because organs found to be affected on images are not always associated with symptoms.[17]

Additionally, a detailed review of chest HRCT images was independently conducted. Abnormalities were described as follows: consolidation, reticular opacities, linear opacities, traction bronchiectasis, honeycombing, ground-glass opacities (GGO), interlobular septal thickening, bronchovascular bundle (BVB) thickening, bronchial wall thickening, solid nodules, centrilobular nodules, mass, cyst, emphysema, hilar and/or mediastinal lymph node swelling, paravertebral band-like lesions, and pleural abnormalities.

To evaluate the GC responsiveness of thoracic lesions at baseline and post-GC treatment HRCT images were compared. Responsiveness was assessed using the first HRCT image obtained within 180 days of GC treatment initiation and was classified as either improved, stable, or deteriorated.

All chest HRCT images were independently reviewed by 2 experienced radiologists blinded to the clinical information (K.T. and S.K.). Any disagreements between radiologists were resolved through discussion.

Twenty of the 74 patients had undergone pathological pulmonary evaluation. Histopathological sections of surgical or transbronchial lung biopsy specimens were stained with hematoxylin and eosin and also for IgG and IgG4. Specimens were reviewed for the involvement of IgG4-RD by an experienced pathologist (T.U.).

2.3. Statistical analysis

Multivariate logistic regression analysis was performed to verify the relevance of variables for specific imaging findings. Continuous variables are expressed as mean and standard deviation or median and range values. Categorical variables are expressed as numbers, proportions, and percentages. Differences between groups were compared using the chi-square or Fisher's exact tests for continuous variables and the Mann–Whitney *U* test for categorical variables. Statistical significance was set at $P < .05$. StatFlex® version 7.0 (Artech, Osaka, Japan) was used for all statistical analyses.

3. Results

3.1. Patient characteristics

The clinical characteristics of patients with AIP are summarized in Table 1. The median age at AIP diagnosis was 67 years, and 57 of 74 patients (77.0%) were male. All 74 patients were diagnosed with definitive type 1 AIP. Forty-nine patients (66.2%) had a history of smoking, and 27 patients (36.5%) had allergies. Nineteen patients (25.7%) had respiratory symptoms. The median serum IgG and IgG4 levels were 2243 (range, 1228–6319) and 651 (range, 3–270) mg/dL, respectively.

The median corticosteroid dose at initiating AIP treatment was 0.60 (range, 0.30–1.0) mg/kg/d. The median period from GC treatment initiation to the first HRCT assessment was 33 (range, 23–2056) d.

The median number of affected organs was 5 (range, 1–10). A total of 51 patients (68.9%) had respiratory lesions, 30 (40.5%) had salivary gland lesions, 26 (35.1%) had lacrimal gland lesions, and 25 (33.8%) had kidney lesions.

3.2. Chest HRCT and pathological findings in patients with AIP

Chest HRCT findings in patients with AIP are summarized in Table 2, and typical chest HRCT images are shown in Figure 1. Thickening of the bronchial wall (33.8%), solid nodules (24.3%), centrilobular nodules (20.3%), GGO (17.6%), BVB thickening (10.8%), hilar and/or mediastinal lymph node swelling (85.1%), paravertebral band-like lesions (6.8%), reticular opacities (24.3%), emphysema (18.9%), and cysts (4.1%) were observed on chest HRCT.

We focused on the centrilobular nodules because it was found more frequently than in previous studies.[5,18,19] Considering chest HRCT findings associated with centrilobular nodules, multivariate logistic regression analysis revealed an association only between centrilobular nodules and bronchial wall thickening (Table 3).

Twelve of the 74 patients were evaluated for pathological lesions with transbronchial biopsy, and bronchial lesions were evaluable in 16 of the 20 patients. Of them, there were 12 cases of bronchiolitis with infiltration with lymphoplasmacytic infiltration. On the other hand, there was no evidence of obliterative phlebitis in the small specimen with transbronchial biopsy. Figure 2 demonstrates the typical pathological findings of transbronchial biopsy samples from patients with AIP and centrilobular nodules. Infiltration of lymphocytes and plasma cells was

Table 1

Clinical characteristics of patients with autoimmune pancreatitis.

Characteristic	n = 74
Median age at diagnosis, years	67.0 (46.0–92.0)
Male/female, n (%)	57 (77.0)/17 (23.0)
Respiratory symptoms	19 (25.7)
Smoking history, n (%)	49 (66.2)
Allergy, n (%)	27 (36.5)
Laboratory findings	
IgG, mg/dL	2243 (1228–6913)
IgG4, mg/dL	651 (3–2970)
C3, mg/dL	96 (28–218)
C4, mg/dL	17.5 (0.70–49.30)
CH50, U/mL	6.2 (2.0–317.0)
sIL-2R, U/mL	869 (356–4695)
Steroid dose, mg/kg/d	0.60 (0.30–1.0)
≦0.50 mg/kg, n (%)	15 (20.3)
0.50–0.80 mg/kg, n (%)	47 (63.5)
0.80–1.0 mg/kg, n (%)	12 (16.2)
Time to first HRCT assessment, days	33 (23–2056)
Within 180 d, n (%)	65 (87.8)
Over 180 d, n (%)	9 (12.2)
Affected organs	
Number of affected organs	5 (1–10)
Pancreas	74 (100)
Lung	51 (68.9)
Salivary gland	30 (40.5)
Lymph node	63 (85.1)
Lacrimal gland	26 (35.1)
Kidney	25 (33.8)
Liver	3 (4.1)
Nasal sinus	9 (12.2)
Bile duct	51 (68.9)
Retroperitoneum	1 (12.0)
Pituitary	2 (2.7)
Thyroid gland	1 (1.4)
Pericardium	1 (1.4)
Blood vessel	6 (8.1)
Prostate (in men [n = 57])	12 (21.1)

Data are presented as medians (ranges) or numbers (%).
HRCT = high-resolution computed tomography.

Table 2

Chest high-resolution computed tomography findings in patients with autoimmune pancreatitis.

Chest HRCT findings	n = 74
Consolidation	4 (5.4)
Reticular opacities	18 (24.3)
Linear opacities	6 (8.1)
Traction bronchiectasis	1 (1.4)
Honeycombing	0 (0.0)
Ground glass opacities	13 (17.6)
Interlobular septal thickening	6 (8.1)
Bronchovascular bundle thickening	8 (10.8)
Bronchial wall thickening	25 (33.8)
Solid nodules	18 (24.3)
Centrilobular nodules	15 (20.3)
Mass	3 (4.1)
Cyst	3 (4.1)
Emphysema	14 (18.9)
Hilar and/or mediastinal lymph node swelling	63 (85.1)
Paravertebral band-like lesion	5 (6.8)
Pleural abnormality	4 (5.4)

Data are presented as medians (ranges) or numbers (%).
HRCT= high-resolution computed tomography.

found in the submucosal area of the bronchus. IgG4 immunohistochemical staining revealed that the plasma cells infiltrating the bronchioles were positive for IgG4.

3.3. Comparison of clinical characteristics of patients with AIP and with or without respiratory lesions

Fifty-one patients (68.9%) were diagnosed with AIP and respiratory lesions. The characteristics of patients in groups with or without respiratory lesions are summarized in Table 4. No significant differences were observed in sex and age at the time of diagnosis, smoking history, or respiratory symptoms between the groups. In contrast, serum IgG and IgG4 levels were significantly higher in patients with AIP and respiratory lesions. Serum level of soluble interleukin-2 receptor, a potential biomarker for IgG4-RD,[20] also tended to be higher in these patients with respiratory lesions. Conversely, C3 and C4 levels were significantly lower in patients with AIP and respiratory lesions.

The median number of affected organs was significantly higher in AIP patients with respiratory lesions than in those without respiratory lesions (5 [range, 2–10] vs 4 [range, 1–6], respectively; $P < .01$). Additionally, involvement of the kidneys and lymph nodes was significantly higher in patients with AIP and respiratory lesions than in those without respiratory lesions.

3.4. Comparison of chest HRCT findings before and after GC treatment

Data regarding chest HRCT findings before and after GC treatment are summarized in Table 5. No deterioration was observed in any patient. Most findings, such as consolidation, GGO, BVB thickening, bronchial wall thickening, solid nodules, and centrilobular nodules, improved with GC treatment. However, reticular opacities, traction bronchiectasis, cysts, and emphysema showed less improvement after GC treatment.

4. Discussion

To the best of our knowledge, this is the most extensive study to focus on the responsiveness of AIP thoracic lesions to GC. In this study, almost 70% of patients with AIP had abnormalities on chest HRCT, and its 3 main findings are as follows.

First, patients with AIP and respiratory lesions may have higher disease activity than those without. Second, centrilobular nodules were frequent findings on HRCT in patients with AIP and were associated with bronchial wall thickening. Third, most lesions on chest HRCT responded well to GC treatment, whereas reticular opacities and emphysema were poorly responsive to GC treatment.

Generally, thoracic abnormalities on HRCT are reported in 14% to 52.9% of patients with IgG4-RD.[19,21,22] In contrast, fewer patients with IgG4-RRD have respiratory symptoms.[9] In our previous study, 25 of 46 patients with AIP had abnormalities in CT findings.[5] This study revealed that only 27.5% of patients with AIP and respiratory lesions complained of respiratory symptoms. In summary, many patients with AIP have respiratory lesions, but only a few complain of respiratory symptoms. In general, thoracic lesions are often detected on screening CT.[23]

However, patients with AIP and respiratory lesions had higher multiorgan involvement and were more likely to have hypocomplementemia than patients without respiratory lesions. Patients with respiratory lesions also tended to have higher serum levels of soluble interleukin-2 receptors. In other words, patients with respiratory lesions had more active stages of IgG4-RD than those without them.

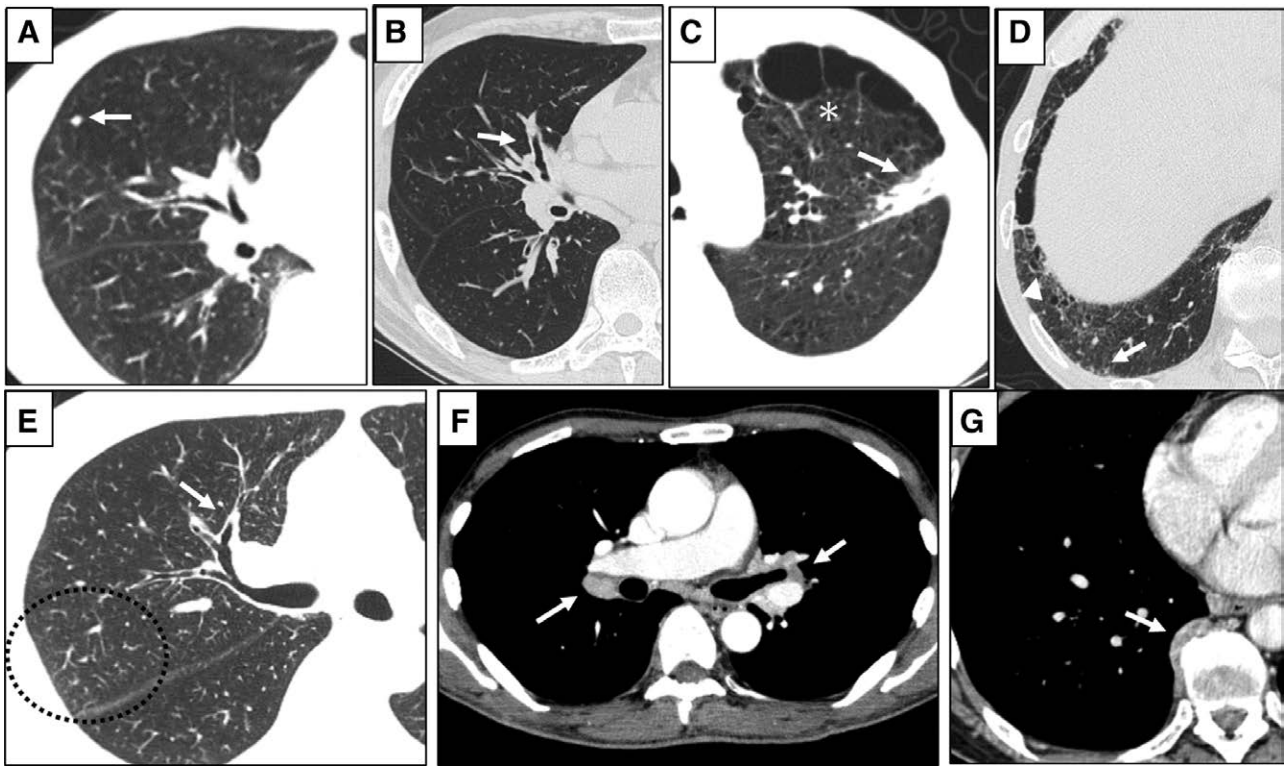

Figure 1. Typical chest high-resolution computed tomography images of a patient with autoimmune pancreatitis. (A) Solid nodule (arrow), (B) bronchovascular bundle thickening (arrow), (C) consolidation (arrow), emphysema (*), (D) reticular opacities (arrow), traction bronchiectasis (arrowhead), (E) centrilobular nodules (circle), and thickening of the bronchial wall (arrow), (F) hilar lymph node swelling, and (G) paravertebral band-like lesion.

Table 3

Multivariate logistic regression analysis for centrilobular nodules.

	Univariate analysis			Multivariate analysis		
Variable	**Odds ratio**	**95% CI**	***P* value**	**Odds ratio**	**95% CI**	***P* value**
Consolidation	4.385	0.564–34.075	.15			
Reticular opacities	3.212	0.775–13.317	.10			
Ground glass opacities	0.28	0.033–2.344	.24			
Bronchovascular bundle thickening	1.359	0.245–7.524	.72			
Interlobular septal thickening	10.364	1.686–63.701	**.01**	8.223	0.861–78.512	.06
Bronchial wall thickening	14.154	3.467–57.799	**<.01**	15.529	2.814–55.784	**<.01**
Solid nodules	0.733	0.182–2.957	.66			
Mass	2.036	0.172–24.082	.57			
Emphysema	0.671	0.132–3.414	.63			
Hilar and/or mediastinal lymph node swelling	2.857	0.336–24.278	.33			
Paravertebral band-like lesion	7.125	1.071–47.371	**.04**	6.389	0.553–73.829	.13

Bold font: *P* value < .05.
CI = confidence interval.

Saeki et al[24] reported that patients with IgG4-related kidney disease with hypocomplementemia were more likely to have lung involvement than those without hypocomplementemia. Another study reported an association between lung and kidney lesions.[25] Niwamoto et al[26] classified IgG4-RD into 5 subgroups according to the pattern of affected organs, as follows: Group 1, lung dominant group; Group 2, retroperitoneal fibrosis and/or aortitis dominant group; Group 3, salivary glands limited group; Group 4, Mikulicz's disease dominant group; and Group 5, autoimmune pancreatitis with systemic involvement group. The cases registered in the present study were classified as Group 5 according to Niwamoto's classification. In Group 5, Niwamoto et al reported lung and kidney lesions in 61% and 27% of the patients, respectively, consistent with the present study results.

Furthermore, centrilobular nodules are frequently identified on HRCT images in patients with AIP. Previously, Inoue et al and Kang et al reported 5 radiologic subtypes of abnormalities: bronchovascular, solid nodular, round GGO, alveolar interstitial, and alveolar consolidative abnormalities,[12,18] although the frequencies of these abnormalities differ between studies. However, there are only a few reports on the involvement of centrilobular nodules.[27] The present study identified an association between centrilobular nodules and bronchial wall thickening. Additionally, a transbronchial biopsy sample demonstrated infiltration of IgG4-positive lymphoplasmacytic infiltration in the bronchus. We have previously reported airway involvement in patients with AIP.[7] We consider HRCT findings of bronchial wall thickening and centrilobular nodules to indicate

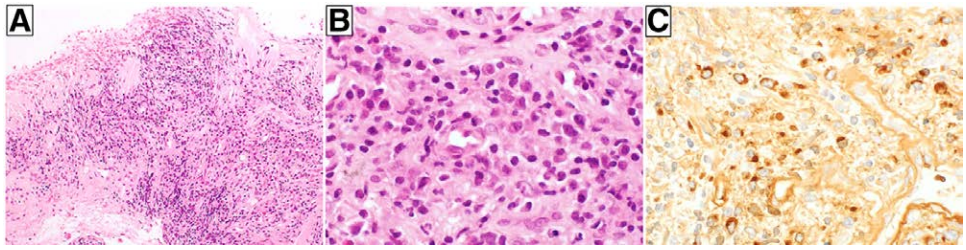

Figure 2. Histopathological findings of transbronchial lung biopsy from patients with autoimmune pancreatitis with centrilobular nodules and bronchial wall thickening on chest high-resolution computed tomography. (A and B) Infiltration of inflammatory cells (lymphocytes and plasma cells) is observed in the submucosal area of the bronchus (hematoxylin and eosin staining; magnification: 10× and 40×, respectively). (C) Immunohistochemical staining revealed that most infiltrating inflammatory cells were positive for IgG4; magnification: 40×. IgG4 = immunoglobulin G4.

Table 4

Clinical characteristics of autoimmune pancreatitis with or without respiratory lesions.

Characteristic	AIP with respiratory lesions n = 51	AIP without respiratory lesions n = 23	*P* value
Median age at diagnosis, yr	67.0 (48.0–92.0)	66.0 (46.0–76.0)	.71
Male/female, n (%)	38 (74.5)/13 (25.5)	19 (82.6)/4 (17.4)	.44
Respiratory symptoms	14 (27.5)	5 (21.7)	.60
Smoking history, n (%)	32 (62.7)	17 (73.9)	.34
Allergy, n (%)	18 (35.3)	9 (39.1)	.75
Laboratory findings			
IgG, mg/dL	2533 (1244–6913)	1926 (1228–2544)	**<.01**
IgG4, mg/dL	777 (3–2970)	399 (146–1440)	**<.01**
C3, mg/dL	86 (28–199)	114 (50–218)	**<.01**
C4, mg/dL	17.1 (0.70–47.3)	21.4 (2.4–49.3)	**.02**
CH50, U/mL	7.70 (2.0–317)	5.9 (2.8–127)	.53
sIL-2R, U/mL	953 (356–4695)	779 (390–2788)	.09
Affected organs			
Number of affected organs	5 (2–10)	4 (1–6)	**<.01**
Salivary gland	23 (45.1)	7 (30.4)	.23
Lymph node	49 (96.1)	16 (69.6)	**<.01**
Lacrimal gland	19 (37.3)	7 (30.4)	.57
Kidney	22 (43.1)	3 (13.0)	**.01**
Liver	2 (3.9)	1 (4.33)	1.00
Nasal sinus	8 (15.7)	1 (4.3)	.25
Bile duct	35 (68.6)	16 (69.6)	.93
Retroperitoneum	8 (15.7)	4 (17.4)	1.00
Pituitary	2 (3.9)	0 (0.0)	1.00
Thyroid gland	0 (0.0)	1 (4.3)	.65
Pericardium	1 (2.0)	0 (0.0)	1.00
Blood vessel	5 (9.8)	1 (4.3)	.65
Prostate (in men [n = 57])	9 (17.6)	3 (13.0)	.74

Data are presented as medians (ranges) or numbers (%).
Bold font: *P* value < .05.
AIP = autoimmune pancreatitis.

Table 5

Chest high-resolution computed tomography findings in patients with autoimmune pancreatitis before and after glucocorticoid treatment.

Chest HRCT findings	Improved	Stable	Improvement rate, %
Consolidation	3	1	75.0
Reticular opacities	3	4	42.9
Linear opacities	6	0	100.0
Traction bronchiectasis	0	1	0.0
Ground glass opacities	9	1	90.0
Interlobular septal thickening	5	0	100.0
Bronchovascular thickening	7	0	100.0
Bronchial wall thickening	21	2	91.3
Solid nodules	12	3	80.0
Centrilobular nodules	14	0	100.0
Mass	3	0	100.0
Cyst	0	3	0.0
Emphysema	0	11	0.0
Hilar and/or mediastinal lymph node swelling	55	1	98.2
Paravertebral band-like lesion	5	0	100.0
Pleural abnormality	4	0	100.0

Data are presented as numbers.
HRCT = high-resolution computed tomography.

broncho-bronchiolar lesions and IgG4-positive plasma cell infiltration in the airway. However, studies with larger sample sizes are required to validate these findings.

Finally, reticular opacities and emphysema were frequently observed in patients with AIP, but responsiveness to GC treatment was poor. According to the 2019 American College of Rheumatology/European League Against Rheumatism, classification criteria[13,14] and the 2020 revised comprehensive diagnostic criteria for IgG4-RD,[15] the diagnosis should be reconsidered if lesions do not respond well to GC treatment. Based on this, we considered it inappropriate to classify reticular opacities, traction bronchiectasis, cysts, and emphysema as IgG4-RD lesions based on their poor responsiveness to GC treatment. Therefore, we reconsidered and excluded these from the analysis of pulmonary lesions of AIP. Excluding cases with only reticular opacities, traction bronchiectasis, emphysema, or cysts did not alter the results. In most cases, reticular opacities and GGO were found simultaneously; moreover, the latter improved with GC treatment, whereas the former did not.

We previously reported that the infiltration rate of IgG4-positive cells in idiopathic IPs independent of IgG4-RD was 13.6%.[28] This indicated that IgG4-positive cell infiltration in the lungs occurs independently of IgG4-RD. Furthermore, we reviewed 16 patients with "IgG4-positive IP" who showed abundant IgG4-positive cells in the lungs and elevated serum IgG4 levels without extrathoracic IgG4-RD lesions.[10] Fifteen of the 16 patients were treated with GC, and all 15 patients with GGO on chest CT showed improvement, whereas reticular opacities deteriorated after GC treatment in 6 of the 15 patients. Moreover, 3 patients died due to disease progression despite treatment, including GC and antifibrotic drug treatment. Therefore, we consider that IgG4-positive IP and IgG4-RD should be treated as distinct conditions.

This study also found a case of overlapping GGO and reticular opacities on chest HRCT. GGO improved with GC treatment, whereas reticular opacity did not. The clinical courses of these cases were consistent with the results obtained in the investigation of IgG4-positive IP. These should be regarded as

cases of IgG4-positive IP rather than of AIP with respiratory involvement.

Most patients with IgG4-RD are smokers and males, and there is considerable overlap with patients with IP or chronic obstructive pulmonary disease. Considering these facts, it may be appropriate to regard the reticular opacities and emphysema seen in AIP as comorbidities rather than as the involvement of IgG4-RD.

This study had some limitations. First, this was a retrospective, single-center study with a small sample size. Second, there was also variability in steroid doses for AIP treatment, and the prognosis was not evaluable. Therefore, a protocol-based prospective study with a larger sample size is warranted. Despite these limitations, we demonstrated respiratory lesions in patients with AIP and showed that emphysema and reticular opacities in patients with AIP are independently developed complications.

5. Conclusion

Chest HRCT findings in patients with AIP are vital because they may reflect disease activity in patients with fewer respiratory symptoms. Findings such as thickening of the bronchial wall, solid nodules, centrilobular nodules, GGO, BVB thickening, and hilar and/or mediastinal lymph node swelling were frequently observed and improved with GC treatment. However, it appears appropriate to regard emphysema and reticular opacities as independently developed complications.

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