【 CASE REPORT 】

IgG4-related Lung Pseudotumor and Pleural Inflammation with Autoimmune Hepatitis

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Abstract:
A 63-year-old man was admitted to our department following a secondary medical examination. Blood tests showed high levels of liver enzymes, IgG, IgG4, and antinuclear antibody. Computed tomography showed tumors in the bilateral lower lobes of the lungs and pleural thickening. After pleural and liver biopsy procedures, he was conclusively diagnosed with IgG4-related lung pseudotumor and pleural inflammation with autoimmune hepatitis. We started treatment with prednisolone 40 mg/day, and chest radiograph and blood tests showed signs of improvement. This was a rare case that suggested an association between IgG4-related disease and autoimmune hepatitis.

Key words: IgG4, lung pseudotumor, autoimmune hepatitis

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Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a relatively new concept reported by Hamano et al. in their 2001 study on autoimmune pancreatitis (AIP) patients (1). This systemic autoimmune disease is characterized by high serum IgG4 concentrations and extensive infiltration of IgG4-positive plasma cells and lymphocytes with fibrosis. IgG4-RD can involve one or multiple organs, and patients often present with a subacute enlarging mass in the affected organ, such as an orbital pseudotumor, a renal mass resembling renal cell carcinoma, or nodular lesions in the lung. IgG4-related respiratory disease results from IgG4-positive plasma cell infiltration and fibrillization; it presents as pseudotumors, which need to be distinguished from malignant lung tumors (2). Although most patients with IgG4-related respiratory disease respond to glucocorticoids, these pseudotumors are sometimes difficult to diagnose preoperatively and are distinguished from primary lung cancer after surgical resection (3, 4).

IgG4-RD also affects the liver, as confirmed by Umemura et al. in their investigation of IgG4 hepatopathy (5) and IgG4-associated autoimmune hepatitis (AIH) (6). They suggested an immunological association between IgG4-RD and AIH, but little evidence supports this hypothesis, so the actual situation remains unclear.

We herein report the case of a patient with IgG4-related lung pseudotumors with pleural inflammation and AIH. We diagnosed the lung pseudotumors by a pleural biopsy and successfully performed treatment with glucocorticoids without any surgical procedures.

Case Report

An asymptomatic 63-year-old man was referred to our hospital following a secondary medical examination. He had previously undergone thyroid surgery for Grave's disease, for which he took no medication. His family history was unremarkable. He had smoked 20 cigarettes a day for 40 years

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Table.   **Laboratory Finding.**

Blood Index	Result	(Normal range)	Blood Index	Result	(Normal range)
WBC	4,660 /μL	(3,300-9,000)	Cre	0.67 mg/dL	(0.60-1.00)
Ly.	31.1 %	(18.0-49.0)	Na	137 mEq/L	(137-147)
Neu.	53.5 %	(40.0-75.0)	K	4.3 mEq/L	(3.5-5.0)
Mo.	8.4 %	(2.0-10.0)	IgG	3,306 mg/dL	(870-1,700)
Eo.	6.4 %	(0.0-8.0)	IgG4	415 mg/dL	(4.8-105.0)
Baso.	0.6 %	(0.0-2.0)	IgA	526 mg/dL	(110-410)
Hb	14.0 g/dL	(13.5-17.5)	IgM	67 mg/dL	(33-190)
Plt	10.7×10^4 /μL	$(14.0-34.0 \times 10^4)$	fT3	3.08 pg/mL	(2.300-4.0)
TP	8.2 g/dL	(6.7-8.3)	fT4	1.43 ng/dL	(0.900-1.7)
Alb	3.1 g/dL	(3.8-5.2)	TSH	<0.005 μIU/L	(0.500-5.0)
TTT	16.1 U	(0.0-4.0)	ACE	36.3 IU/L	(7.7-29.4)
ZTT	36.9 U	(2.0-12.0)	IL2-R	2,580 U/mL	(124-466)
T-Bil	0.6 mg/dL	(0.2-1.2)	HA-IgM	(-)	(-)
AST	238 IU/L	(12-30)	HBs-Ag	(-)	(-)
ALT	280 IU/L	(10-42)	HCV-Ab	(-)	(-)
LDH	241 IU/L	(124-226)	HEV-IgA	(-)	(-)
ALP	352 IU/L	(122-330)	CMV-IgM	(-)	(-)
ChE	143 IU/L	(234-470)	CMV-IgG	(+)	(-)
g-GTP	36 IU/L	(12-65)	EB-EBNA	(+)	(-)
AMY	97 IU/L	(45-140)	ANA	640 tighter	(<40)
CPK	16 IU/L	(61-257)	AMA	(-)	(-)
BUN	14.4 mg/dL	(8.0-23.0)			
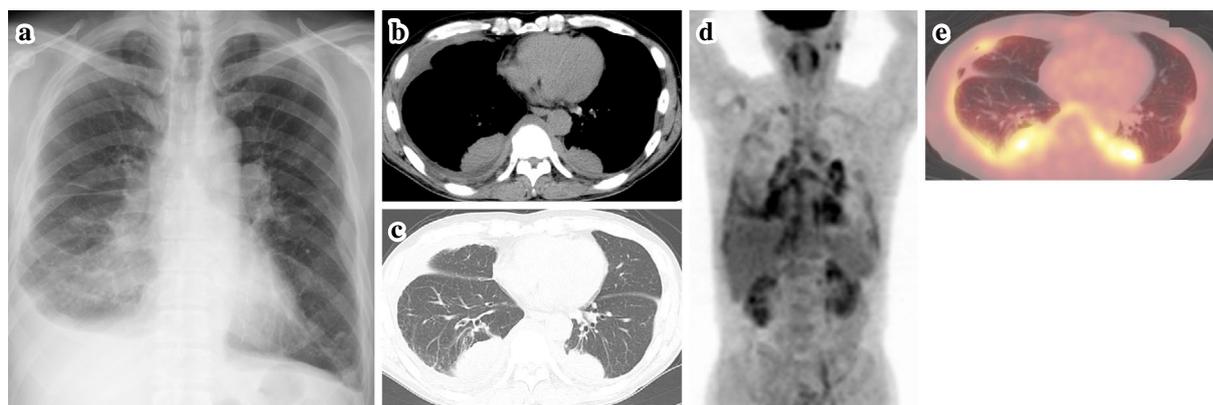
Figure 1.   **Imaging findings before treatment. (a) Chest radiograph reveals consolidation in the right lower lung field and blunted right costophrenic sulcus. (b) (c) CT reveals 35-mm tumors at S10 of both lungs, bilateral thickening of the pleura, and right-sided pleural effusion (b: mediastinal window; c: lung window). (d), (e) PET-CT reveals increased the FDG uptake in the lung tumor and pleura (SUVmax: 5.87).**

(Brinkman index: 800) and consumed around 500 mL of beer a day (ethanol 20 g/day). A physical examination was likewise unremarkable.

Blood tests revealed high levels of liver enzymes, IgG, IgG4, and antinuclear antibody (Table). Chest radiograph showed blunting of the right costophrenic sulcus and consolidation in the right lower lung field (Fig. 1a). Computed tomography (CT) showed 35-mm contrast-enhancing tumors at S10 of both lungs, bilateral thickening of the pleura, right-sided pleural effusion, and abnormalities of abdominal organs (Fig. 1b and c). Positron emission tomography (PET)-CT revealed an increased FDG uptake in the lung tu-

mors and pleura (SUVmax: 5.87) (Fig. 1d and e).

A cytology analysis of the pleural effusion showed no evidence of malignancy. A transbronchial lung biopsy (TBLB) was considered for a definitive histological diagnosis, but because of the peripheral location of the tumors, a video-assisted thoracoscopic pleural biopsy was performed instead. A pathological examination revealed fibrosis and inflammatory cell infiltrates, comprising mostly lymphocytes and plasma cells. Immunostaining of the pleural biopsy samples showed an IgG4/IgG-positive plasma cell ratio of over 40% and ≥10 IgG4-positive plasma cells per high-power field (HPF) (Fig. 2a-c). A liver biopsy showed periportal in-
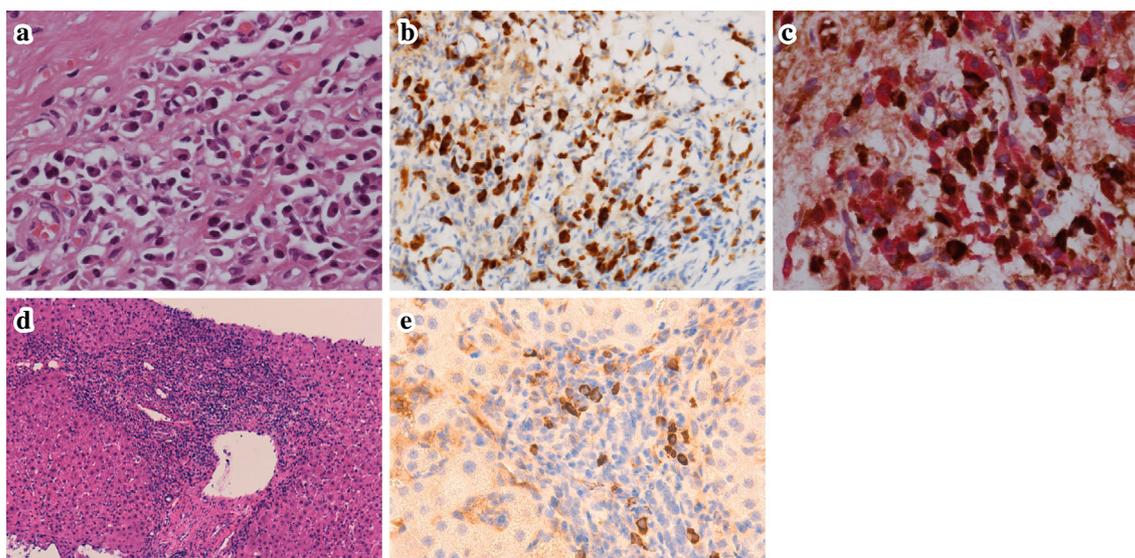
Figure 2. Pathologic findings of the right pleura and liver (a-c: pleura; d, e: liver). (a) The right visceral pleura has lymphoplasmacytic infiltration and marked fibrosis comprising mostly lymphocytes and plasma cells [Hematoxylin and Eosin (H&E) staining, ×100]. (b) (c) IgG4 immunostaining shows an IgG4/IgG-positive plasma cell ratio of ≥40% and ≥10 IgG4-positive plasma cells per HPF, which is more clearly shown by double immunostaining with IgG4 and IgG [b: IgG4 immunostaining, ×400; c: Double immunostaining with IgG4 (brown) and IgG (red), ×400]. (d) A liver biopsy reveals periportal inflammatory cell infiltrate and interface hepatitis comprising mostly plasma cells. No rosette formation, fat deposition, fibrosis, or inflammation is observed around the bile duct (H&E staining, ×100). (e) IgG4 immunostaining reveals ≤9 per HPF IgG4-positive plasma cells (IgG4 immunostaining, ×400).
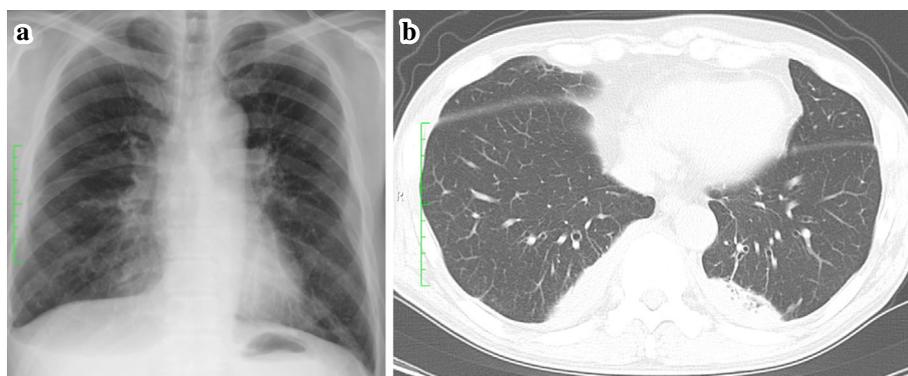
Figure 3. Imaging findings at one month after treatment. (a) Chest radiograph reveals the resolution of the consolidation in the right lower lung field and the blunted right costophrenic sulcus. (b) CT imaging reveals tumor shrinkage and reduced bilateral thickening of the pleura and pleural effusion.

flammatory cell infiltrates that comprised mostly plasma cells and interface hepatitis; there was no fat deposition, fibrosis, or inflammation around the bile duct. Immunohistopathologic findings of the liver specimens showed IgG4-positive plasma cells at <9 per HPF (Fig. 2d and e). A diagnosis of AIH was made based on an International Autoimmune Hepatitis Group score of 22.

We ultimately diagnosed the lung tumor and liver lesion as IgG4-related pseudotumors with pleural inflammation and AIH. We started the patient on 40 mg/day prednisolone. A week later, his liver function returned to the baseline average. A month after starting the medication, chest radiograph

and CT showed a reduction in the size of the pseudotumor and resolving pleural thickening and effusion (Fig. 3). Blood tests at this time showed IgG and IgG4 levels of 1,460 mg/dL and 190 mg/dL, respectively. The patient was maintained on a regimen of 5 mg/day prednisolone and has thus far remained relapse-free (Fig. 4).

Discussion

IgG4-RD is a relatively new disease concept, and 14.0% of cases are IgG4-related respiratory disease (7). Matsui et al. retrospectively evaluated 48 patients with IgG4-related
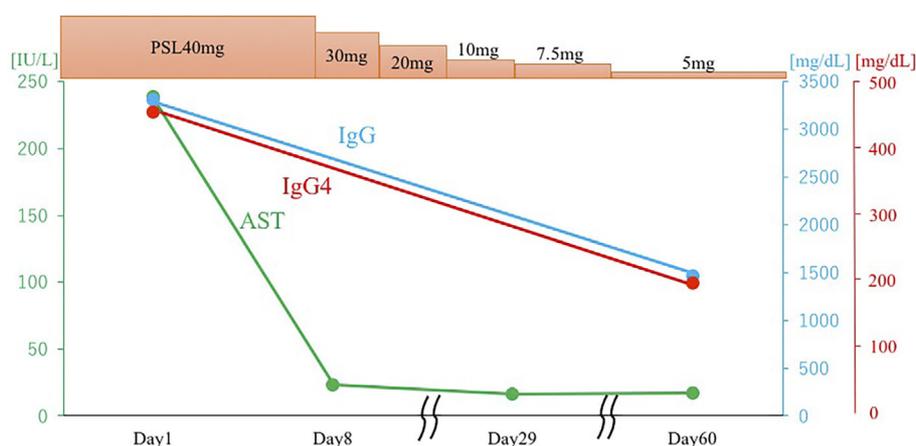
Figure 4.   Time course of treatment.

respiratory disease and revealed that most of the patients were men (78%); that middle-aged to elderly men were more likely to be affected; that patients had high serum concentrations of IgG and IgG4, but normal white blood cell count and serum C-reactive protein concentration; and that they had a good response to corticosteroids. The CT findings of IgG4-related respiratory disease were reported to include hilar and mediastinal lymphadenopathy, thickening of the bronchial wall or bronchovascular bundles, thickening of the interlobular septa, nodules, subpleural consolidation, and peribronchovascular consolidation (2). Inoue et al. reported that 5 of 13 patients (38.5%) had nodular lesions (8). In the present case, the CT findings were nodular lesions and mediastinal lymphadenopathy, which were similar to those of primary lung cancer. Therefore, IgG4-related respiratory disease could not be distinguished from lung cancer based on CT findings alone.

We performed fluorodeoxyglucose (FDG)-PET to evaluate the lung tumors. This technique is useful for identifying an adequate and viable biopsy site, detecting other organ lesions, and distinguishing a given condition from other autoimmune diseases and lymphoproliferative disorders (9). According to previous reports, FDG accumulates with an SUVmax of 1.1-8.3 for IgG4-RD (10, 11) and 3.0-8.4 for IgG4-related respiratory disease (11, 12). This extent of FDG accumulation was similar to that in lung cancer (SUVmax 0.4-48.1) (13); therefore, distinguishing between IgG4-related respiratory disease and lung cancer was usually difficult by PET-CT. Although Zhang et al. suggested that the early and rapid resolution of an increased FDG uptake after steroid-based treatment can be useful for verifying IgG 4-RD and excluding malignancies (10), FDG-PET might not be useful for the initial diagnosis before treatment. In our case, the pulmonary tumors and the pleura showed an increased FDG uptake; indeed, the SUV of the lung mass was similar to that in past reports. However, there was no other information useful for distinguishing benign tumors from malignant tumors.

Matsui et al. proposed the diagnostic criteria for IgG4-related respiratory disease in 2015 (14). Assessing these criteria involves performing comprehensive diagnostic work-ups, including evaluations of the clinical features, blood tests results, radiologic images, and a pathologic examination. However, the differential diagnosis of IgG4-related respiratory disease is difficult based only on the clinical features, blood tests, and radiologic findings. Instead, a pathologic examination and biopsy are important for distinguishing benignity from malignancy.

For the histopathologic diagnosis of lung cancer and mesothelioma, a TBLB and video-assisted thoracoscopic pleural biopsy have been reported to have sensitivity rates of 78-88% and 80-99%, respectively (15). A pleural biopsy is preferred for lesions that have accompanying pleural effusion and thickening and are located in the peripheral part of the lung (15). Pleural biopsies have been reported useful for IgG4-related respiratory disease (16, 17). In the present case, a pleural biopsy of the peripherally located lung lesion also provided the correct diagnosis of IgG4-related respiratory disease. These findings suggested that a pleural biopsy was an efficient method for the preoperative diagnosis of IgG4-related respiratory disease.

The efficacy of glucocorticoids for patients with IgG4-RD has been reported, with response rates ranging from 82% to 98% (18-20). Patients with IgG4-related respiratory disease have also been reported to improve after several weeks of glucocorticoids without any surgical intervention (2).

However, in previous reports of IgG4-related respiratory disease, 81.0% of patients were diagnosed by surgery, and only 19.0% of patients were diagnosed by a transbronchial biopsy or needle aspiration (21). These reports suggested that the preoperative diagnosis of IgG4-related respiratory disease was still difficult and that unnecessary operations might be avoided by performing an aggressive biopsy, such as a pleural biopsy or TBLB.

The relationship between IgG4-RD and AIH has been reported, and the disease concepts of "IgG4-hepatopathy" (4) and "IgG4-associated AIH" (5) were even proposed. IgG4-hepatopathy comprises the histopathologic changes of IgG4+ plasma cell infiltration in patients with IgG4-related sclerosing cholangitis and type 1 AIP. It shows portal inflamma-

tion, interface hepatitis, large bile duct damage, portal sclerosis, and cholestasis; these histologic patterns coexist among cases. Nakanuma et al. further considered that some patterns of IgG4-hepatopathy might be other liver manifestations of IgG4-RD (22).

In contrast, IgG4-associated AIH presents with a high serum IgG4 level and abundant IgG4 plasma cell infiltration. The diagnostic criteria for AIH include high serum IgG values. Umemura et al. found that some AIH cases also had high serum IgG4 values or IgG4-positive plasma cell infiltration in the liver; they therefore proposed the new disease concept of IgG4-associated AIH. Because of the high serum IgG4 and IgE concentrations and lobular hepatitis with marked IgG4-bearing plasma cell infiltration, they also hypothesized an allergic reaction to hepatocytes or molecules in the liver parenchyma as a possible pathogenesis of IgG4-associated AIH. Two diagnostic criteria have been suggested by Umemura et al. for IgG4-associated AIH: serum IgG4 levels of ≥135 mg/dL and an IgG4-positive plasma cell count of ≥10 cells per HPF in biopsy samples of liver with AIH (23). An alternative to the latter criterion was suggested by Chung et al. and sets the IgG4-positive plasma cell count at ≥5 cells per HPF (24). Both Umemura et al. and Chung et al. suggested that IgG4-associated AIH patients responded better to steroid treatment and had a greater amount of inflammation than those with classic AIH (23, 24). In contrast, Umemura et al. reported that IgG4-associated AIH had relatively high serum IgE and IgG4 levels (23), whereas Chung et al. based his assessment on relatively high International Autoimmune Hepatitis Group scores (24). In the absence of serum IgG4 values and IgG4 immunostaining of liver biopsies, the association between IgG4 and AIH is difficult to predict based solely on sex, age, and the liver enzyme function.

To our knowledge, only a few reports have described the coexistence of IgG4-RD and AIH (22, 23, 25, 26). Venkatesh et al. concluded that their case was incidental (25), but Umemura et al. reported otherwise (23). Our case involved a middle-aged man with thoracic lesions and AIH; therefore, we evaluated his serum IgG4 level and IgG4 immunostaining on a liver biopsy. Our case did not have IgG4-related sclerosing cholangitis or type 1 AIP, so he did not have IgG4-hepatopathy. This met the latter criterion for IgG4-associated AIH but not the former. Nevertheless, the two diseases occurred at the same time, so we assessed the hepatic lesion as IgG4-associated AIH.

We diagnosed our patient with IgG4-related respiratory disease and IgG4-associated AIH. The incidence of another IgG4-RD in patients already afflicted with IgG4-related respiratory disease is high; the incidence of AIP in particular is 67% (2). In addition, the incidence of IgG4-hepatopathy in patients with AIP was reported to be 27% (5). The incidence rate of IgG4-associated AIH in patients with IgG4-RD may be similar because both IgG4-hepatopathy and IgG4-associated AIH similar types of diseases concepts based on previous studies of IgG4-RD (6). Therefore, it is possible

that some patients with IgG4-related respiratory disease exhibit IgG4-hepatopathy or IgG4-associated AIH. However, we do not often perform liver biopsies for patients with IgG4-respiratory disease and cannot identify liver lesions, as these lesions appear as micro-changes in contrast to thoracic lesions. Unfortunately, why the two lesions differ in size is unknown, and the association between IgG4-RD and AIH remains unclear; therefore, the accumulation of more reports on similar cases is needed.

In conclusion, we presented a case of IgG4-related lung pseudotumor and pleural inflammation with AIH that was successfully treated with glucocorticoids and no surgical procedures. This case underscored the necessity of distinguishing IgG4-related pseudotumors from malignant tumors and raised the possibility that some cases of AIH may include IgG4-RD.

The authors state that they have no Conflict of Interest (COI).

References

1. Hamano H, Kawa S, Ochi Y, et al. Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. Lancet **359**: 1403-1404, 2002.
2. Matsui S, Hebisawa A, Sakai F, et al. Immunoglobulin G4-related lung disease: clinicoradiological and pathological features. Respirology **18**: 480-487, 2013.
3. Odaka M, Mori S, Asano H, Yamashita M, Kamiya N, Morikawa T. Thoracoscopic resection for a pulmonary nodule with the infiltrate of IgG4-positive plasma cells. Asian J Endosc Surg **5**: 176-178, 2012.
4. Fujiu K, Sakuma H, Miyamoto H, Yamaguchi B. Immunoglobulin G4-related inflammatory pseudotumor of the lung. Gen Thorac Cardiovasc Surg **58**: 144-148, 2010.
5. Umemura T, Zen Y, Hamano H, Kawa S, Nakanuma Y, Kiyosawa K. Immunoglobin G4-hepatopathy: association of immunoglobin G4-bearing plasma cells in liver with autoimmune pancreatitis. Hepatology **46**: 463-471, 2007.
6. Umemura T, Zen Y, Hamano H, et al. IgG4 associated autoimmune hepatitis: a differential diagnosis for classical autoimmune hepatitis. Gut **56**: 1471-1472, 2007.
7. Zen Y, Nakanuma Y. IgG4-related disease: a cross-sectional study of 114 cases. Am J Surg Pathol **34**: 1812-1819, 2010.
8. Inoue D, Zen Y, Abo H, et al. Immunoglobulin G4-related lung disease: CT findings with pathologic correlations. Radiology **251**: 260-270, 2009.
9. Nakatani K, Nakamoto Y, Togashi K. Utility of FDG PET/CT in IgG4-related systemic disease. Clin Radiol **67**: 297-305, 2012.
10. Zhang J, Chen H, Ma Y, et al. Characterizing IgG4-related disease with 18F-FDG PET/CT: a prospective cohort study. Eur J Nucl Med Mol Imaging **41**: 1624-1634, 2014.
11. Tokue A, Higuchi T, Arisaka Y, Nakajima T, Tokue H, Tsushima Y. Role of F-18 FDG PET/CT in assessing IgG4-related disease with inflammation of head and neck glands. Ann Nucl Med **29**: 499-505, 2015.
12. Kitada M, Matuda Y, Hayashi S, et al. IgG4-related lung disease showing high standardized uptake values on FDG-PET: report of

two cases. J Cardiothorac Surg **8**: 160, 2013.

13. Davies A, Tan C, Paschalides C, et al. FDG-PET maximum standardised uptake value is associated with variation in survival: Analysis of 498 lung cancer patients. Lung Cancer **55**: 75-78, 2007.

14. Matsui S, Yamamoto H, Minamoto S, Waseda Y, Mishima M, Kubo K. Diagnostic criteria for IgG4-related respiratory disease. An Jpn Respir Soc **4**: 129-132, 2015 (in Japanese, Abstract in English).

15. Rivera MP, Mehta AC, Wahidi MM. Establishing the Diagnosis of Lung Cancer: Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest **143**: e142S-e165S, 2013.

16. Stamatopoulos A, Patrini D, Koletsis E, et al. IgG4 related lung disease extending to the thoracic vertebrae. Respir Med Case Rep **19**: 162-165, 2016.

17. Wibmer T, Kropf-Sanchen C, Rudiger S, et al. Isolated IgG4-related interstitial lung disease: unusual histological and radiological features of a pathologically proven case. Multidiscip Respir Med **8**: 22, 2013.

18. Kamisawa T, Shimosegawa T, Okazaki K, et al. Standard steroid treatment for autoimmune pancreatitis. Gut **58**: 1504-1507, 2009.

19. Sandanayake NS, Church NI, Chapman MH, et al. Presentation and management of post-treatment relapse in autoimmune pancreatitis/immunoglobulin G4-associated cholangitis. Clin Gastroenterol Hepatol **7**: 1089-1096, 2009.

20. Ebbo M, Daniel L, Pavic M, et al. IgG4-related systemic disease: features and treatment response in a French cohort: results of a multicenter registry. Medicine **91**: 49-56, 2012.

21. Zen Y, Inoue D, Kitao A, et al. IgG4-related lung and pleural disease: a clinicopathologic study of 21 cases. Am J Surg Pathol **33**: 1886-1893, 2009.

22. Nakanuma Y, Ishizu Y, Zen Y, Harada K, Umemura T. Histopathology of IgG4-related autoimmune hepatitis and IgG4-related hepatopathy in IgG4-related disease. Semin Liver Dis **36**: 229-241, 2016.

23. Umemura T, Zen Y, Hamano H, et al. Clinical significance of immunoglobulin G4-associated autoimmune hepatitis. J Gastroenterol **46**: 48-55, 2011.

24. Chung H, Watanabe T, Kudo M, et al. Identification and characterization of IgG4-associated autoimmune hepatitis. Liver Int **30**: 222-231, 2010.

25. Venkatesh PG, Navaneethan U. Azathioprine induced pancreatitis in a patient with co-existing autoimmune pancreatitis and hepatitis. J Pancreas **12**: 250-254, 2011.

26. Ishizu Y, Ishigami M, Kazuya T, et al. Immunoglobulin G4-associated autoimmune hepatitis later complicated by autoimmune pancreatitis: a case report. Hepatol Res **46**: 601-606, 2016.