



Immunoglobulin G4-Related Lung Disease Mimicking Lung Cancer: Two Case Reports

폐암으로 오인된 면역글로불린 G4 연관 폐 질환:
2예에 대한 증례 보고

Dae Yun Park, MD , Su Young Kim, MD* ,
Suk Hyun Bae, MD , Ji Young Lee, MD

Department of Radiology, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Korea

ORCID iDs

Dae Yun Park <https://orcid.org/0000-0003-3760-3131>
Su Young Kim <https://orcid.org/0000-0002-1824-0008>
Suk Hyun Bae <https://orcid.org/0000-0002-1888-2510>
Ji Young Lee <https://orcid.org/0000-0002-6099-601X>

Immunoglobulin G4 (IgG4)-related disease is a rare systemic fibroinflammatory condition characterized by elevated serum IgG4 levels and infiltration of IgG4-positive plasma cells in various organs. IgG4-related lung disease shows varied radiologic features on chest CT. Patients usually present with a solid nodule or mass mimicking lung cancer; therefore, distinguishing between IgG4-related disease and other conditions is often challenging. Additionally, co-existing radiologic findings of IgG4-related lung disease may mimic metastasis or lymphangitic carcinomatosis of the lung. We report two cases of histopathologically confirmed IgG4-related lung disease mimicking lung cancer. Chest CT revealed a solid nodule or mass with ancillary radiologic findings, which suggested lung cancer; therefore, IgG4-related lung disease was radiologically indistinguishable from lung cancer in both cases. Measurement of serum IgG4 levels and clinical evaluation to confirm involvement of various organs may be useful to establish the differential diagnosis. However, surgical biopsy evaluation is needed for confirmation.

Index terms Immunoglobulin G4-Related Disease; Lung; Computed Tomography, X-Ray; Positron-Emission Tomography

INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a rare fibroinflammatory disease characterized by a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis and, often but not always, elevated serum IgG4 levels (1). IgG4-RD most commonly

Received September 29, 2021
Revised January 17, 2022
Accepted March 2, 2022

*Corresponding author

Su Young Kim, MD
Department of Radiology,
Ilsan Paik Hospital, Inje University
College of Medicine,
170 Juhwa-ro, Ilsanseo-gu,
Goyang 10380, Korea.

Tel 82-31-910-7694

Fax 82-31-910-7366

E-mail swimminkim@naver.com

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

involves the pancreas, but it can involve other organs including the biliary tree, lymph node, salivary glands, lungs, retroperitoneum and kidneys. IgG4-related lung disease (IgG4-RLD) is relatively uncommon compared to IgG4-RD with other organ involvement (2). IgG4-RLD presents the following four types of radiologic features: solid nodular, round-shaped ground-glass opacity (GGO), alveolar interstitial and bronchovascular (3). These varied features can mimic many other diseases. We recently experienced two cases of pathologically proven IgG4-RLD in the form of a solid nodule or mass which was difficult to differentiate from lung cancer. Thus, we report these two cases of IgG4-RLD presenting as a solid nodule or mass with clinical and radiological findings.

CASE REPORTS

CASE 1

A 74-year-old male visited our hospital's outpatient department with a 10-day history of cough and sputum. He was an ex-smoker who quit smoking 20 years ago and had a history of myocardial infarction, congestive heart failure, and diabetes. His body temperature was 36.9°C. All laboratory findings were within normal limits. A chest radiograph showed unremarkable findings except a small amount of bilateral pleural effusion (Fig. 1A). Chest CT revealed a 1.6-cm-sized irregular subpleural nodule with pleural tails in the right lower lobe and scattered small nodules in both the lungs and pleurae. Several enlarged right lower lobar, segmental, and subsegmental lymph nodes were also noted (Fig. 1B). An ¹⁸F-fluorodeoxyglucose (FDG) PET/CT scan showed a maximum standard uptake value (SUV) of 2.6 within the nodule in the right lower lobe (Fig. 1C). The initial clinical and radiological diagnosis was lung cancer with disseminated metastasis. A video-assisted thoracoscopic wedge resection of the right lower lobe was performed and the pathologic specimen revealed lymphoplasmacytic infiltration suggesting IgG4-RLD. The IgG4-positive cell counts per high-power field (HPF) was up to 116 cells. There were no malignant cells in the specimen (Fig. 1D, E). The serum IgG4 level was elevated slightly (93.4 mg/dL). There was no clinical or radiologic evidence of pancreas involvement in the IgG4-RD.

CASE 2

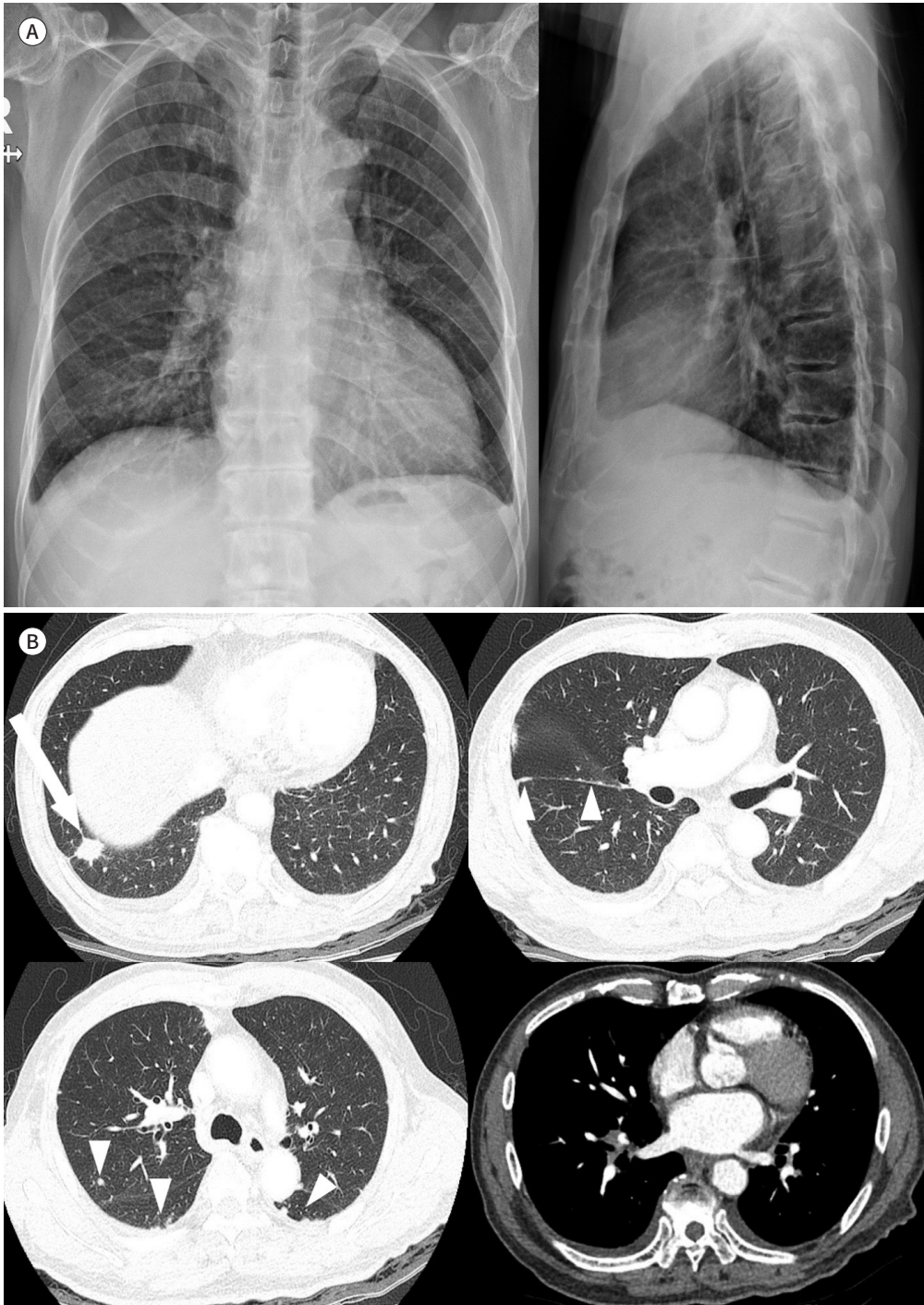
A 64-year-old male visited our hospital's outpatient department with chest discomfort. He was a current smoker with 40 pack-years and had an unremarkable prior medical history. His vital signs were as follows: blood pressure, 97/60 mm Hg; pulse, 60 beats/minute; respiration rate, 18 breaths/minute; and body temperature, 36.4°C. Initial laboratory tests showed a mildly elevated C-reactive protein level (2.1 mg/dL), and other laboratory findings were within normal limits. A chest radiograph showed a large mass like consolidation with perilesional linear opacities in the upper zone of the left lobe (Fig. 2A). Subsequent chest CT revealed an irregular large subpleural mass in the left upper lobe. Perilesional interlobular septa and bronchial wall thickening were also noted (Fig. 2B). Only a few small sized lymph nodes were observed in the mediastinum. An FDG PET/CT scan showed a maximum SUV of 8.7 within the mass (Fig. 2C). The initial clinical and radiological diagnosis was lung cancer with localized lymphangitic carcinomatosis. A left upper lobe lobectomy was performed and the

pathologic specimen revealed lymphoplasmacytic infiltration, arteritis and fibrosis suggesting IgG4-RLD. The IgG4-positive cell count per HPF were up to 60 cells. There were no malignant cells in the specimen (Fig. 2D, E). There was no clinical or radiologic evidence of pan-

Fig. 1. A 74-year-old male with IgG4-related lung disease.

A. Chest radiographs (PA and right lateral) show no remarkable findings in either lung.

B. Chest CT scan (axial images) show an irregular subpleural nodule with a pleural tail in the right lower lobe (arrow) and multiple small nodules scattered across both lungs and pleurae (arrowheads). Several enlarged right lower lobar, segmental, and subsegmental lymph nodes are also observed.



creas involvement in the IgG4-RD.

This study has got an ethical review exemption from the Institutional Review Board of author's institution, we achieved the requirement for written informed consent from the partic-

Fig. 1. A 74-year-old male with IgG4-related lung disease.

C. FDG PET/CT scan shows mild FDG uptake (standardized uptake value maximum = 2.6) within a nodule (arrow) in the right lower lobe.

D. Histopathological examination shows a benign spindle cell proliferative lesion with lymphoplasmacytic infiltrates (hematoxylin & eosin stain, $\times 200$).

E. Immunohistochemical analysis of IgG4 shows up to 116 IgG4-positive plasma cells per high-power field ($\times 400$).

FDG = fluorodeoxyglucose, Ig = immunoglobulin

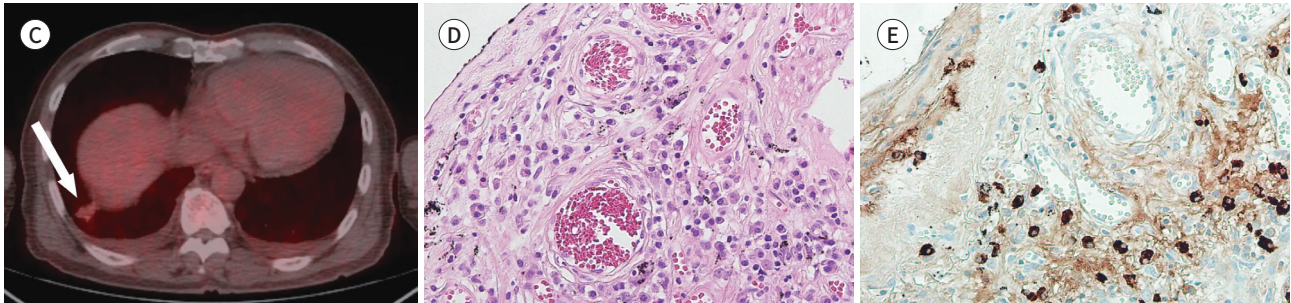


Fig. 2. A 64-year-old male with IgG4-related lung disease.

A. Chest PA shows a bulging opacity (arrow) around the aortic arch in the left upper lobe with perilesional linear lines (arrowheads).

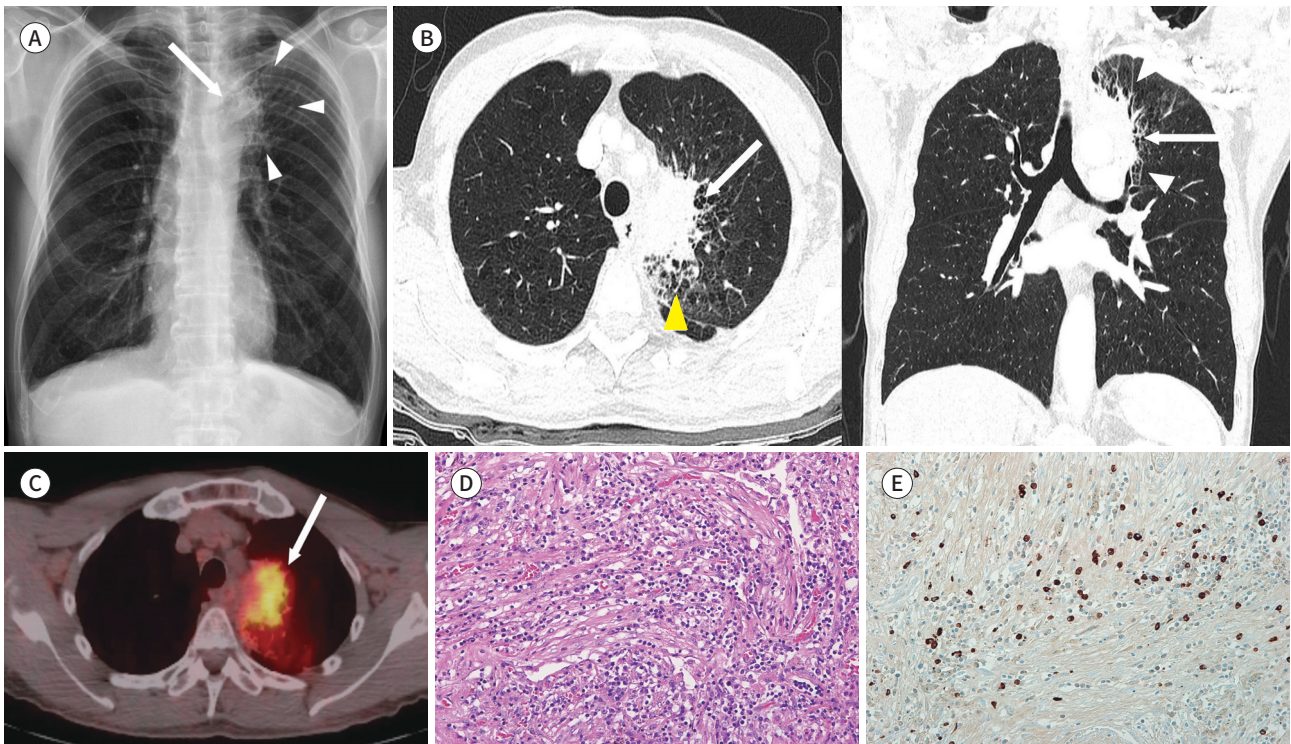
B. Chest CT scans (axial and coronal reformatted) show a large irregular subpleural mass (arrows) with an interlobular septum and bronchial wall thickening (arrowheads).

C. FDG PET/CT scan showing increased FDG uptake (standardized uptake value max = 8.7) within a mass (arrow) in the left upper lobe.

D. Histopathological examination shows a benign spindle cell proliferative lesion with lymphoplasmacytic infiltrates, arteritis, and fibrosis (hematoxylin & eosin stain, $\times 200$).

E. Immunohistochemical analysis of IgG4 shows up to 60 IgG4-positive plasma cells per high-power field ($\times 400$).

FDG = fluorodeoxyglucose, Ig = immunoglobulin



ipant (IRB No. 2022-03-021).

DISCUSSION

IgG4-RD is a rare systemic fibroinflammatory disease with a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells (1). In 2001, Hamano et al. (4) first reported elevated serum IgG4 levels in patients with sclerosing pancreatitis. In 2003, Kamisawa et al. (5) proposed a new disease entity of IgG4-RD involving not only the pancreas but also multiple organs, including the bile duct retroperitoneum, and salivary glands. The incidence and prevalence of IgG4-RD are not clearly known, and in general, it is predominantly seen in adults, mostly older males (5). IgG4-RD was first reported in 2004 (6). It is relatively uncommon and has been reported in 9.5% to 51.2% of autoimmune pancreatitis cases (7). IgG4-RD presents the following four types of radiologic features: solid nodular, round-shaped GGO, alveolar interstitial, and bronchovascular (3). Each radiologic features can mimic other diseases such as primary lung malignancy, nonspecific interstitial pneumonia, lymphoproliferative disorders such as sarcoidosis and multicentric Castleman disease and lymphangitic carcinomatosis. These radiologic features of IgG4-RD can exist alone or can co-exist with each other (3).

In Case 1, chest CT showed an irregular nodule with randomly distributed multiple small nodules in both the lungs and pleurae, and several enlarged right lower lobar, segmental, and subsegmental lymph nodes, suggesting lung cancer with metastasis. Although IgG4-RD can present as solid nodules and commonly involve thoracic lymph nodes, a pleural manifestation of IgG4-RD presenting scattered small pleural nodules is very rare. To our best knowledge, there are few cases of IgG4-RD presenting tiny scattered pleural nodules that mimic metastasis like in our case (8). Thus, it was difficult to differentiate IgG4-RD from lung cancer with disseminated metastases. Furthermore, diagnosis was more difficult as there was no evidence of pancreas involvement.

In Case 2, chest CT demonstrated a large irregular mass with perilesional interlobular septa and bronchial wall thickening. Moreover, an FDG PET/CT scan showed strong FDG uptake within the mass. These features strongly suggested lung cancer with lymphangitic spread. As mentioned above, radiologic findings of each type of IgG4-RD can co-exist, so the findings were a combination of the solid nodular and bronchovascular types of IgG4-RD.

In our first case, the serum IgG4 level was slightly elevated (93.4 mg/dL), but not pathognomonic for IgG4-RD. Many patients with IgG4-RD presented increased serum IgG4 levels (> 140 mg/dL), but this abnormality had a low sensitivity (63%) (5). From 3% to 30% of patients were reported to have normal serum IgG4 levels (9).

Our two cases did not show pancreas involvement in IgG4-RD. IgG4-RD without pancreas involvement is very rare. A previous survey showed that 8% of IgG4-RD patients had IgG4-RD without autoimmune pancreatitis (10). Thus, in our two cases, it was very challenging to make a clinical and radiologic diagnoses of IgG4-RD, and a surgical biopsy was needed.

In conclusion, IgG4-RD is a rare systemic disease with varied and overlapped radiologic features. It can mimic many other diseases. In particular, the solid nodular type of IgG4-RD is difficult to differentiate from lung cancer. Co-existing radiologic features, such as the bronchovascular type, can mimic lymphangitic carcinomatosis, and pleural involvement present-

ing a pleural nodule or effusion can mimic disseminated metastasis like in our cases. Elevation of serum IgG4 levels and involvement of other organs may be helpful for diagnosis, but may not always be present. Eventually a surgical biopsy may be required to diagnose IgG4-RD.

Author Contributions

Conceptualization, K.S.Y.; data curation, B.S.H.; investigation, L.J.Y.; methodology, B.S.H.; project administration, K.S.Y.; supervision, K.S.Y.; validation, K.S.Y.; visualization, P.D.Y.; writing—original draft, P.D.Y.; and writing—review & editing, K.S.Y.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Funding

None

REFERENCES

1. Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med* 2012;366:539-551
2. Park K, Choi YW, Kang BK, Lee JY, Park JS, Shin SJ, et al. Systemic manifestations of immunoglobulin G4-related disease: a pictorial essay. *J Korean Soc Radiol* 2021;82:575-588
3. Kim Y, Choi HY. Immunoglobulin G4-related disease in the thorax: imaging findings and differential diagnosis. *J Korean Soc Radiol* 2021;82:826-837
4. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001;344:732-738
5. Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, et al. A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003;38:982-984
6. Duvic C, Desrame J, Lévêque C, Nedelec G. Retroperitoneal fibrosis, sclerosing pancreatitis and bronchiolitis obliterans with organizing pneumonia. *Nephrol Dial Transplant* 2004;19:2397-2399
7. Morales AT, Cignarella AG, Jabeen IS, Barkin JS, Mirsaeidi M. An update on IgG4-related lung disease. *Eur J Intern Med* 2019;66:18-24
8. Ishikawa H, Uruga H, Fujii T, Kurosaki A, Morokawa N, Takaya H. IgG4-related disease in the differential diagnosis of lung nodules. *Respirol Case Rep* 2020;8:e00550
9. Khosroshahi A, Wallace ZS, Crowe JL, Akamizu T, Azumi A, Carruthers MN, et al. International consensus guidance statement on the management and treatment of IgG4-related disease. *Arthritis Rheumatol* 2015;67:1688-1699
10. Uchida K, Masamune A, Shimosegawa T, Okazaki K. Prevalence of IgG4-related disease in Japan based on nationwide survey in 2009. *Int J Rheumatol* 2012;2012:358371

폐암으로 오인된 면역글로불린 G4 연관 폐 질환: 2예에 대한 증례 보고

박대윤 · 김수영* · 배석현 · 이지영

면역글로불린 G4 (Immunoglobulin G4; 이하 IgG4) 연관 질환은 혈청 IgG4의 상승과 조직으로의 IgG4 양성 형질세포의 침윤을 특징으로 하는 드문 섬유 염증성 질환이다. 흉부 전산화단층촬영에서 IgG4 연관 폐 질환은 다양한 영상학적 소견을 보여 다른 질환과의 감별이 어렵고 특히 고형 결절 혹은 종괴의 형태로 나타나는 경우 폐암과의 감별이 필요하다. IgG4 연관 폐 질환에서 나타날 수 있는 다른 영상학적 소견 또한 폐암과 연관되어 나타나는 전이나 림프관성 암증처럼 보일 수 있다. 저자들은 수술을 통하여 병리학적으로 확진된 IgG4 연관 폐 질환 2예를 경험하였다. 두 증례는 CT에서 고형결절 혹은 종괴의 형태로 나타났으며 폐암과 연관되어 보일 수 있는 다른 영상학적 소견을 동반하고 있어 폐암과의 감별이 매우 어려웠다. 혈청 IgG4 수치나 다른 장기의 침범 여부가 감별에 도움을 줄 수 있으나 정확한 확진을 위해서 조직검사가 필요하다.

인제대학교 의과대학 일산백병원 영상의학과