

# An 84-Year-Old Man With Progressive Dyspnea and an Abnormal Chest CT Scan



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**CASE PRESENTATION:** An 84-year-old man without a history of smoking presented with progressive dyspnea of 6 months' duration accompanied by fatigue and unintentional weight loss. He denied fever, chills, chest pain, hemoptysis, rash, joint pains, or muscle aches. He had multiple hospitalizations for similar presentations that were diagnosed as pneumonia. History was significant for diastolic heart failure, hypertension, and type 2 diabetes mellitus.

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## Physical Examination Findings

The patient was afebrile with a heart rate of 60 beats per minute, a BP of 140/60, a respiratory rate of 18 breaths per minute, and oxygen saturation of 94% on room air. On examination, he had bibasilar crackles. The rest of the examination was within normal limits.

## Diagnostic Studies

Chest CT imaging demonstrated diffuse bilateral pulmonary nodules, some of which were pleural based, and extensive mediastinal adenopathy (Fig 1). Endobronchial ultrasonographic transbronchial needle aspiration and transbronchial biopsy were performed

and showed an atypical lymphoid infiltrate, with morphologic and immunohistochemical findings suspicious for B-cell Non-Hodgkin lymphoma, whereas the biopsy results revealed foci of prominent bronchial-associated lymphoid tissue, which was negative for malignancy. A PET scan showed hypermetabolic mediastinal adenopathy and pulmonary nodules. Given that the available data were not sufficient to diagnose and treat him for lymphoma, a CT-guided core needle biopsy of a lung nodule was performed. It showed lung tissue that was completely effaced by a plasmacytic infiltrate and fibrosis with storiform features (Fig 2).

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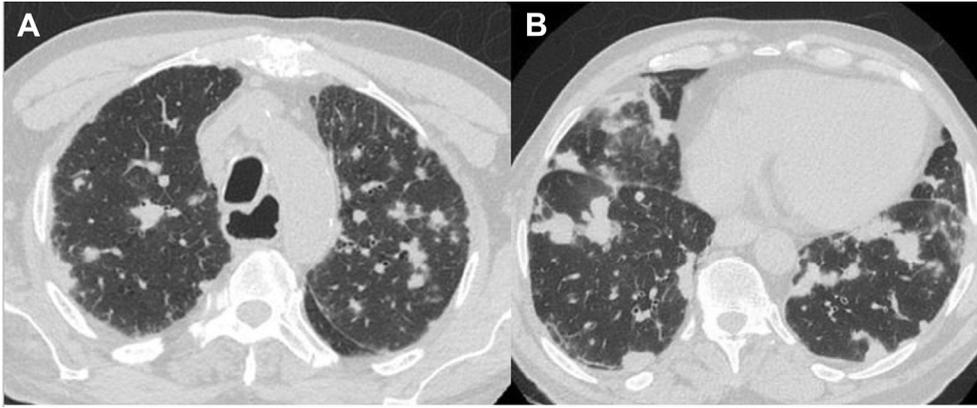


Figure 1 – Chest CT scan with representative images at presentation. Diffuse bilateral pulmonary nodules. Mediastinal windows showed extensive mediastinal adenopathy. A, Bilateral upper lobes. B, Bilateral lower lobes.

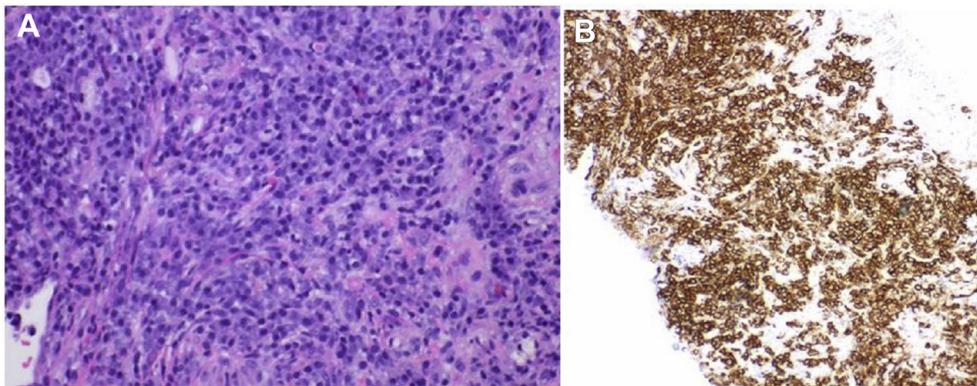


Figure 2 – A, H&E staining shows dense plasma cell infiltrate in the CT-guided biopsy of the lung nodule. B, Immunohistochemical staining with CD 138 marker showing that > 90% of the infiltrate consisted of plasma cells.

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*What is the diagnosis? How can the diagnosis be confirmed?*

**Diagnosis:** IgG4-related lung disease, confirmed by immunostaining lung biopsy with IgG4 immunostaining (Fig 3)

### Discussion

IgG4-related lung disease (IgG4-RD) is a male-predominant disorder (70%-80%), with a median age at presentation of 60 to 65 years (range, 17-80 years). From the pathologist's perspective, the root of the diagnostic conundrum for IgG4-RD is the heterogeneity of the histologic changes. Most of the lesions in the differential diagnosis have heavy plasmacytic infiltrates; thus, the mere combination of plasma cells and fibrosis cannot be used to secure a diagnosis. In these situations, reliable diagnostic criteria are crucial, with IgG4 immunostaining playing an important role. Perhaps the best example of a well-recognized diagnostic criterion is in the pancreas (autoimmune pancreatitis) in which a cut-off value of 50 IgG4-positive cells per high-power field has a sensitivity of 84% and a specificity of 100% for autoimmune pancreatitis.

The prevalence of pulmonary involvement in patients with IgG4-RD has only been described in observational studies. About 14% to 54% of patients with IgG-RD may have parenchymal or pleural lesions. Hilar and mediastinal adenopathy is the most frequent form of thoracic involvement and is present in up to 80% of patients with IgG4-RD. Another rare thoracic manifestation of IgG4-RD is fibrosing mediastinitis, with only a few case reports noted.

Although the pathophysiology of IgG4-RD is still not well recognized, studies have proposed a causal role for type 2 helper T cells, regulatory T cells, interleukin

(IL)-10, and transforming growth factor- $\beta$ . Allergic immune responses can be generated by specific type 2 helper T-cell cytokines, such as IL-4, IL-5, and IL-13, which boost peripheral blood eosinophilia and the secretion of IgG4 and IgE.

Symptoms including cough, dyspnea (particularly on exertion), and chest pain have been described in almost 50% of patients with IgG4-RD, whereas the rest exhibited abnormal findings on imaging without symptoms. Few patients have reported symptoms such as weight loss and night sweats. Although serum IgG4 levels are increased in the majority of patients with IgG4-RD, their absence does not exclude the diagnosis.

On imaging, IgG4-RD may present with lung nodules of distinctive sizes, lung masses, consolidation, sporadic ground-glass opacities, reticular opacities, and other manifestations of interstitial lung disease. Imaging can also demonstrate thickened bronchovascular bundles, bronchiectasis, central airway stenosis, and obstruction. Pleural involvement with thickening, pleura-based nodules, and effusions can be present but are less common.

As is apparent from the discussion so far, clinical and radiologic manifestations are rather nonspecific, and instituting the diagnosis of IgG4-RD requires a high index of suspicion. Reports of IgG4-RD with an initial manifestation mimicking lymphoma have been reported. In the majority of the cases, tissue biopsy with histopathologic examination helps distinguish IgG4-RD from processes such as sarcoidosis, lung cancer, and lymphoma. The biopsy method will be influenced by the location, nature, and distribution of the lesions plus the clinical background. Histopathologic diagnosis of IgG4-RD needs the presence of typical

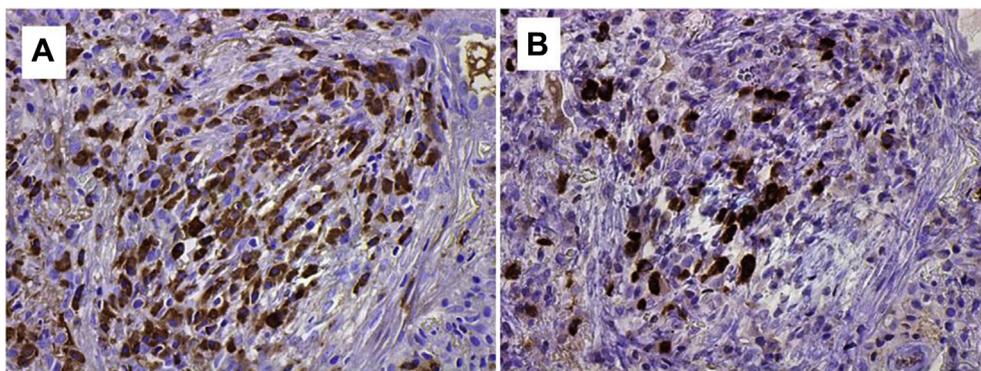


Figure 3 – Immunohistochemical staining of the CT-guided lung biopsy sample showing (A) dense IgG-positive plasma cells (IgG,  $\times 40$ ) and (B) up to 30 IgG4-positive plasma cells per high-power field (IgG4,  $\times 40$ ).

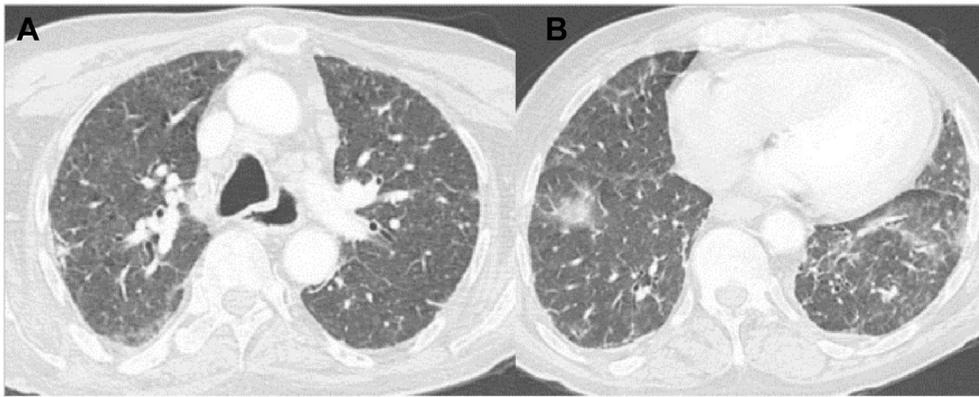


Figure 4 – Repeated chest CT imaging after treatment shows substantial improvement in the bilateral pulmonary nodules. Mediastinal windows also show interval reduction in adenopathy. A, Bilateral upper lobes. B, Bilateral lower lobes.

lymphoplasmacytic infiltrates with associated storiform fibrosis (which may be minor or absent in the lung), obliterative phlebitis, and IgG4-positive cells (> 40% of plasma cells IgG4 positive and > 20-50 IgG4-positive cells per high-power field for lung).

IgG4-RD is a corticosteroid-responsive illness, but spontaneous reversion of both pulmonary and extrapulmonary lesions has been well recognized. The best regimen of corticosteroid therapy has not been outlined for IgG4-RD, and treatment recommendations have been deduced from our comprehension of autoimmune pancreatitis. Most patients respond to a prednisone dose of 0.6 mg/kg/d. A promising response is commonly seen in 2 to 4 weeks of treatment. After the initial 2 to 4 weeks of therapy, the prednisone dose is progressively reduced over the ensuing few months, with continuous monitoring for full resolution or relapse. Maintenance treatment with smaller doses of prednisone (5-10 mg daily) has been shown to decrease the relapse rate in patients with pancreatic IgG4-RD. There have been a limited number of reports concerning treatment with other immunosuppressive agents in patients with recurrent or refractory IgG4-RD. Azathioprine, mycophenolate mofetil, and rituximab have been used; nonetheless, the data regarding their efficacy are restricted to retrospective case series and case reports.

Although the response to steroid treatment is favorable in the majority of patients with IgG4-RD, long-term follow-up data are currently unavailable. These patients may experience nonpulmonary manifestations of IgG4-RD in the future. Correlation with malignancy has been defined in patients with IgG4-RD. The malignancies include pancreatic cancer and lymphoma in addition to lung cancer, although the cause for this increased incidence is not clear at this time.

### Clinical Course

Immunostaining with an IgG4 immunostain showed about 30 IgG4-positive plasma cells per high-power field. Serum immunoglobulin subtype analysis results revealed an IgG4 level > 300 mg/dL (normal range, 4-86 mg/dL). The patient was prescribed pulsed-dose steroids at 1 mg/kg followed by a prolonged slow taper over 4 months, which resulted in clinical and radiological improvement (Fig 4). A repeat serum IgG4 level one month later was reduced at 120 mg/dL.

### Clinical Pearls

1. Elevated serum levels of IgG4 can support but are not required to clinch the diagnosis of IgG4-RD, since serum IgG4 levels can be normal in some patients, and IgG 4 levels can be elevated in 5% of the population without any disease.
2. On imaging, the most common thoracic manifestation of IgG4-RD is mediastinal or hilar adenopathy, appreciated in up to 80% of cases. In the lung parenchyma, nodular lesions and bronchovascular involvement are the most common lesions. Various combinations of pulmonary abnormalities can be found in the same patient.
3. Diagnosis can be reached by the clinical and radiological presentation and findings of dense lymphoplasmacytic infiltrates and abundant IgG4-positive plasma cells and storiform fibrosis on histopathologic analysis. Reaching the diagnosis requires a high index of clinical suspicion, thus necessitating an increased awareness of IgG4-RD and its many manifestations.
4. The mainstay of treatment is corticosteroids, with most patients demonstrating a good initial response. The relapse rate is high and can involve the lung or a new organ system, thus requiring close follow-up.

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## Suggested Reading

Inoue D, Zen Y, Abo H, et al. Immunoglobulin G4-related lung disease: CT findings with pathologic correlations 1. *Radiology*. 2009;251(1):260-270.

Zen Y, Inoue D, Kitao A, et al. IgG4-related lung and pleural disease: a clinicopathologic study of 21 cases. *Am J Surg Pathol*. 2009;33(12):1886-1893.

Zen Y, Nakanuma Y. IgG4-related disease: a cross-sectional study of 114 cases. *Am J Surg Pathol*. 2010;34(12):1812-1819.

Khosroshahi A, Stone JH. A clinical overview of IgG4-related systemic disease. *Curr Opin Rheumatol*. 2011;23(1):57-66.

Ryu JH, Sekiguchi H, Yi ES. Pulmonary manifestations of immunoglobulin G4-related sclerosing disease. *Eur Respir J*. 2012;39(1):180-186.

Guma M, Firestein GS. IgG4-related diseases. *Best Pract Res Clin Rheumatol*. 2012;26(4):425-438.

Deshpande V, Zen Y, Chan JKC, et al. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol*. 2012;25(9):1181-1192.

Raj R. IgG4-related lung disease. *Am J Respir Crit Care Med*. 2013;188(5):527-529.

Theofilos D, Triantafillidou C, Zetos A, et al. A 44-year-old man with chronic cough, weakness, and a mediastinum mass. *Chest*. 2015;148(3):e86-e90.