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IgG4-related lung disease as a differential diagnosis of a lymphoproliferative disease: atypical presentation of an atypical disease

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SUMMARY

IgG4-related disease (IgG4-RD) is an immunomodulated inflammatory disease that usually affects the pancreas and parotid glands. Although lung involvement is rare, it has been recently reported and could mimic various other diagnoses. We present a case of IgG4-RD whose symptoms and images raised the suspicion of a malignant lymphoproliferative lung neoplasm. It is imperative to differentiate both diseases, since their treatment and prognosis vary.

BACKGROUND

This case is relevant because it shows a rare manifestation of IgG4-related disease (IgG4-RD) in the lungs, which could be mistaken for malignant neoplasms.

When vital organs are affected in IgG4-RD, effective treatment is necessary, since it can cause serious organ damage.¹

CASE PRESENTATION

A 63-year-old man, with a remote history of gout and a heavy smoker, came to our clinic with a story of weight loss of 13 kg in 1 year, cough and dyspnoea. Physical examination demonstrated extensive inguinal and cervical enlarged lymph nodes.

INVESTIGATIONS

A CT study was performed, which showed: cervical, mediastinal, hilar, axillary, retroperitoneal and iliac lymphadenopathy (figure 1). Generalised, smooth and uniform thickening of the interlobular septa was also observed in the entire lung parenchyma



Figure 1 CT of the chest with contrast. Note the evident mediastinal, axillary, hilar and cervical enlarged lymph nodes.

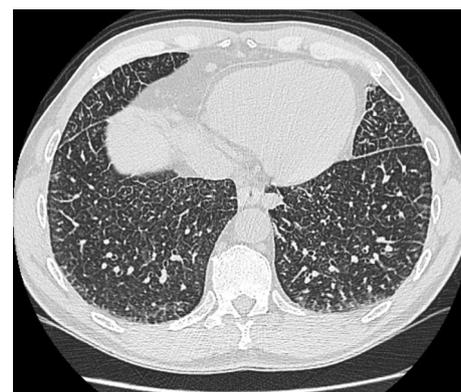


Figure 2 CT of the chest in lung window. Extensive and generalised smooth thickening of the interlobular septa.

(figure 2). There was also a spiculated mass-like image on the right apex, which had pleural retraction, air bronchogram and homogeneous density without significant enhancement (figure 3).

Blood work showed elevation of immunoglobulins in serum, particularly high IgG levels at 6161 mg/dL (normal value <1600 mg/dL), with IgG4 levels at 1600 (normal value <135 mg/dL).

Lung tissue and cervical lymph node biopsies were performed; histology was negative for malignancy and showed numerous positive IgG4 plasma cells (more than 40 positive cells per higher power field in both samples). The lung biopsy showed a mononuclear lymphoplasmacytic infiltrate with significant storiform fibrosis, and IgG ratio greater than 40%, which was highly suggestive of IgG4-RD (figure 4).

The adenopathy also showed lymphoplasmacytic infiltration with abundant IgG4-positive plasmatic cells.

DIFFERENTIAL DIAGNOSIS

Initially, a malignant lymphoproliferative process with lymphangitic carcinomatosis of the lung was considered as the most probable diagnosis. Given the extensive adenopathies, Castleman disease was also considered, although the lack of lymph node enhancement and the lung interstitial and mass-like involvement made it less likely.

A primary lung malignancy also seemed likely; in an older, heavy smoker patient with cough and weight loss, the suspicion of primary lung cancer should be high.

Lastly, although probably lower than lymphoproliferative diseases and lung cancer, sarcoidosis



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Figure 3 CT of the chest in lung window. Irregular and spiculated mass located at the right superior lobe, highly suspicious of malignancy.

should be considered. It can typically cause lymphadenopathy (hilar, mediastinal and less typically extrapulmonary), interstitial changes and less often mass-like opacities.²

TREATMENT

Therapy with corticosteroids has been shown to be effective in both pulmonary and extrapulmonary lesions,³ although there is no consensus on the regimen for steroid maintenance therapy. The guidelines of Japanese consensus for the treatment of autoimmune pancreatitis recommend ‘an initial prednisolone dosing of 0.6 mg/kg/day for 2–4 weeks, tapered every 1–2 weeks by 5 mg/day, based on biochemical markers, clinical improvement and imaging’.⁴ A maintenance dose of 2.5–5 mg is recommended, which should be discontinued after 3 years of treatment, depending on improvement after increase in dosage, considering readministration in case of relapse.⁴ Following that recommendation, treatment was initiated with oral prednisone 60 mg/day, with a slow tapering plan over the two following months.

OUTCOME AND FOLLOW-UP

Prednisone therapy relieved our patient’s dyspnoea and pulmonary lesions. Currently, the patient is still under corticosteroid therapy. A CT was performed 2 months after treatment, which showed remission of the right lobe mass with significantly less interstitial involvement. It is accepted that IgG4-RD must be followed up with serum levels of IgG4 in order to evaluate relapsing (up to 50% of patients show high levels of it before relapsing).⁵

For patients who are steroid refractory, immunosuppressants can be considered, including rituximab.⁴

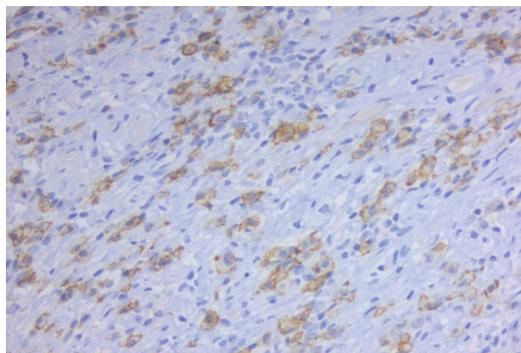


Figure 4 Lung biopsy tissue. H&E staining, original magnification $\times 40$. The immunohistochemistry shows IgG4/IgG-positive plasma cell ratio of $>40\%$.

DISCUSSION

IgG4-RD is a systemic disease, consisting of tumefactive lesions with lymphoplasmacytic infiltrates with abundant IgG4-positive plasma cells, elevated IgG4 serum concentrations and storiform fibrosis. Lesions can compromise various organs, including pancreas, salivary glands, mediastinum, liver, etc.⁴ There have been recent reports of IgG4-related interstitial lung disease (ILD), some cases involving other organs.⁶

The radiological characteristics of ILD are varied and can mimic lung malignancy, usual interstitial pneumonia, organising pneumonia, non-specific interstitial pneumonia and sarcoidosis.⁷ Inoue *et al* collected 13 cases of ILD and reported that it could be classified into four subtypes: a solid-nodular type, round ground-glass opacity type, alveolar interstitial type and bronchovascular type,⁸ being the case presented a mixture between the solid-nodular type and the bronchovascular type, given the mass-like lesion and the extensive and smooth thickening of the interlobular septa.

Elevated IgG4 serum concentration is useful for screening but does not offer a definitive diagnosis⁷; IgG4 serum levels >135 – 144 mg/dL have shown a sensitivity of 87% and a specificity of 83% according to a meta-analysis conducted by Hao *et al*.⁹

It is important to consider that in other diseases, such as bronchiectasis, asthma, emphysema, hypersensitivity pneumonitis and in approximately 5% of the general population, high levels of IgG4 in serum could be found.⁴

Considering this, three elements have been established as comprehensive diagnostic criteria for IgG4-RD, detailed in Umehara *et al*’s work: (1) the presence of organ enlargement, mass or nodular lesions; (2) a serum IgG4 concentration >135 mg/dL and (3) histopathological findings of >10 IgG4 cells/high power field and an IgG4+/IgG + cell ratio $>40\%$.¹⁰

The presence of multiple adenopathies is frequent in IgG4-RD, being the first manifestation in some cases.¹¹

When lymphadenopathy is generalised, the differential diagnosis becomes more complex. In our patient, the initial diagnosis considered lymphoma, but other diseases such as Castleman disease and disseminated malignancy were also considered as differentials.¹²

Our case fulfilled the diagnostic criteria for IgG4-RD, with an extensive involvement outside the lung, therefore, the diagnosis was made.

Learning points

- ▶ Diagnosing IgG4-related lung disease (RLD) can be a challenge, since initial imaging changes tend to be nonspecific, leading to confounding interpretations, such as malignancy, infectious process or other pulmonary disorders
- ▶ The patient’s clinical history, culture results (if available), pathology and laboratory results (high serum levels of IgG4) can be helpful diagnostic tools
- ▶ The spectrum of differential diagnosis of IgG4-related disease (RD) is wide, and it includes, among others, malignant primary or lymphoproliferative processes. Considering this, surgical biopsy is essential for a conclusive diagnosis
- ▶ Glucocorticoids are the first line treatment for patients with IgG4-RD, and a positive response supports the potential diagnosis of IgG4-RLD. However, biopsy gives the definite diagnosis.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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