Adenopathy and Pulmonary Infiltrates in a Japanese Emigrant in Brazil

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**Case Presentation**

A 77-year-old Japanese man living in Brazil for 70 years presented with a 6-month history of progressive dyspnea, weight loss (30 lb), low-grade fever, dry cough, and dry mouth. His medical history revealed hypertension and type 2 diabetes. He was a 40-pack-year ex-smoker and had worked in agriculture. Physical examination revealed bibasilar inspiratory crackles and enlarged (1 cm in diameter), mobile, and nontender cervical, supraclavicular, axillary, and inguinal lymph nodes (LNs).

Laboratory test results revealed mild anemia, with a hemoglobin level of 10.6 g/dL (normal, 13-18 g/dL) and normal leukocyte counts. The erythrocyte sedimentation rate was markedly elevated at 93 mm/h (normal, 5.3-20.2 mm/h); serum C-reactive protein level was 10.2 mg/L (normal, <3 mg/L). Other test results showed the following levels: creatinine, 1.48 mg/dL (normal, 0.7-1.2 mg/dL); urea, 60 mg/dL (normal, 10-50 mg/dL); amylase, 199 U/L (normal, 28-100 U/L); lipase, 268 U/L (normal, 13-60 U/L); total bilirubin, 0.31 mg/dL (normal, 0.2-1.0 mg/dL); total serum protein count, 11.6 g/dL (normal, 6.6-8.7 g/dL); serum albumin, 2.6 g/dL (normal, 3.4-4.8 g/dL); free thyroxine, 1.04 ng/dL (normal, 0.7-1.5 ng/dL); and thyroid-stimulating hormone, 6.51 µU/mL (normal, 0.4-4.5 µU/mL). The patient's serum globulin level was 9.0 g/dL (normal, 3.2-3.9 g/dL) with polyclonal hypergammaglobulinemia (6.8 g/dL); total IgG was 5,899 mg/dL (normal, 952-1,538 mg/dL). Urinary samples revealed no abnormalities.

Autoimmunity tests showed positivity for antinuclear antibodies (1:320), antidouble-strain DNA, antitymeloxygenase,
antineutrophil cytoplasmic antibodies, antithyroglobulin, and antithyroid peroxidase antibodies. Serologic tests for HIV, hepatitis B, and hepatitis C were negative.

Pulmonary function tests were normal. A chest radiograph showed linear opacities predominantly in the lower-lung fields and mediastinal and hilar enlargement (Fig 1A). High-resolution CT (HRCT) scanning of the chest revealed patchy ground-glass attenuation (GGA), reticulation, mild honeycombing, traction bronchiectasis, and bronchiolectasis, with architectural distortion of lung parenchyma and small pulmonary nodules (Fig 1C). There were several enlarged hilar, mediastinal, supraclavicular, internal thoracic, and axillary LNs (Fig 1D). Abdominal CT scanning revealed enlargement of periaortic, peripancreatic, and iliac LNs. No abnormalities were observed in liver, spleen, pancreas, or retroperitoneum.

Figure 1  A, Chest radiograph showing mediastinal and bilateral hilar enlargement and diffuse linear and nodular opacities in both lung parenchyma. B, PET scan shows increased uptake of 18F-fluorodeoxyglucose in the left shoulder and in the cervical, mediastinal, abdominal, and inguinal lymph nodes. C, Chest high-resolution CT scan reveals honeycombing (black arrowheads), nodules (white arrowheads), patchy ground-glass attenuation (white *), and traction bronchiolectasis (arrow). D, Diffuse and symmetric adenopathy (black *).

In order to evaluate whether lesions were metabolically active, a PET scan was performed. The PET scan showed increased uptake of 18F-fluorodeoxyglucose in cervical, mediastinal, abdominal, and inguinal regions corresponding to the enlarged LNs, right-lower-lung field, left shoulder, and proximal region of the right humerus (Fig 1B).

An axillary LN biopsy was performed, and the specimen showed marked sinusoidal plasmacytosis (Fig 2). Plasma cells were not atypical, and there was no follicular hyperplasia or hyaline sclerosis of germinal centers. Atypical lymphocytes were absent, and no necrosis or vasculitis was observed. In situ hybridization of Epstein-Barr virus was negative.
Subsequently, open-lung biopsies of the right-middle and -lower lobes were performed. Lung histology showed intense areas of interstitial plasmacytic infiltration associated with alveolar septal thickening and architectural distortion of parenchyma. Furthermore, a lung nodule composed of intense sclerosis and plasma cells was observed. A component of phlebitis was present but was not exuberant. Immunostaining in both lung and LNs revealed numerous IgG-positive plasma cells expressing both κ and λ light chains. Approximately 50% of IgG-positive plasma cells were IgG4 positive (Fig 2). The nonplasmacytic infiltrate was composed of typical B and T cells as well as of macrophages. IgG4 serum levels were subsequently measured and were >1,000 mg/dL (normal, <140 mg/dL). As part of laboratorial investigation for the differential diagnoses, immunohistochemistry for human herpesvirus 8 was negative, and IL 6 levels were elevated at 8.3 pg/mL (normal, <5.9 pg/mL).

**What is the diagnosis?**

*Diagnosis: IgG4-related systemic sclerosing disease with interstitial lung disease and lymphadenopathy*

**Discussion**

*Clinical Discussion*

IgG4-related systemic sclerosing disease (IRSSD) is a recently described entity characterized by plasmacytic infiltration and sclerosis in a wide variety of exocrine glands and other organs, more commonly the pancreas, bile duct, salivary glands, lachrymal glands, liver, retroperitoneum, kidney, lung, LNs, and aorta. [1]  [2] Hashimoto thyroiditis and pleural involvement also have been reported. [3]

IgG4 is the rarest of the IgG subclasses, accounting for 3% to 6% of total IgGs. [1]  [2] In suspected cases, the diagnosis is confirmed by the presence of elevated serum IgG4 associated with histologic infiltration of IgG4-positive plasma cells. [4] Different names have been used to describe this entity, such as IgG4-positive multiorgan lymphoproliferative syndrome, [4] hyper-IgG4 disease, [5] and IgG4-related lymphoplasmacytic vasculitis and interstitial fibrosis. [1] We believe that the term IRSSD should be used to name this entity because it encompasses the most important hallmarks of the disease, that is, the
IgG4-positive plasma cell infiltration and sclerosis present in affected tissues.

An association between retroperitoneal fibrosis (RPF) and systemic fibrosing diseases (eg, inflammatory pseudotumor, fibrous pseudotumor, myofibroblastoma, plasma cell granuloma, idiopathic systemic fibrosis, generalized form of Ormond disease) with IRSSD has been noted. Because these diseases are very rare, there might be different manifestations of the same process, so we could speculate that they might share some etiopathogenic factors. In 70% of cases, RPF is idiopathic. In the remaining 30% of cases, it may be secondary to malignancy, radiation, medications, asbestosis, autoimmune diseases, and aortitis.

Differential diagnosis might be extensive and include various systemic diseases, as the patient presented with fever, weight loss, lymphadenopathy, and lung disease. Most important are chronic infections such as HIV, TB, histoplasmosis, and paracoccidioidomycosis; collagen vascular diseases such as systemic lupus erythematosus, rheumatoid arthritis, and Sjögren syndrome; vasculitis such as Wegener granulomatosis; and other lymphoproliferative disorders such as lymphoma, lymphomatoid granulomatosis, and multicentric Castleman disease (MCD).

The prevalence of lung involvement in IRSSD is unknown. In an autoimmune pancreatitis (AIP) series, four of 30 patients with AIP developed IgG4-related interstitial lung disease. In contrast, among 21 patients with lung involvement, 43% had other organs involved. The most commonly affected patients are men in the sixth decade of life who usually present with dry cough, dyspnea, or even no symptoms. Pulmonary function tests typically show normal lung volumes and moderate to severe reduction in diffusion capacity. Various pleuropulmonary abnormalities were described and include bronchiolitis obliterans with organizing pneumonia, inflammatory pseudotumor, bronchiectasis, honeycombing, nodules, pleural thickening (sometimes with calcification), and pleural pseudotumor.

We report on a 77-year-old Japanese man with IRSSD involving lung, LNs, and probably the pancreas. Diabetes or its progression has been described as a manifestation of IgG4-related AIP, but in this patient, diabetes was diagnosed many years before the onset of the respiratory symptoms. Subclinical chronic renal failure as diagnosed based on laboratory tests, could be associated with IgG4 kidney infiltration or RPF, but the patient also had diabetes and hypertension, and there were no signs of kidney-specific disease or RPF on CT scan. Increased bone 18 F-fluorodeoxyglucose uptake was interpreted as degenerative.

**Radiologic Discussion**

Different radiologic abnormalities have been described, consisting of lung mass, large or small nodules, GGA, thickening of bronchovascular bundles, bronchiectasis, honeycombing, cysts, and LN enlargement. An HRCT scan classification was proposed by Inoue et al, consisting of four major subtypes: solid nodular, round-shaped GGA, alveolar interstitial, and bronchovascular. Although there were lung nodules in the patient's HRCT scan, the major abnormality was honeycombing, reticulation, and GGA consistent with the alveolar interstitial type.

In the present case, differential diagnoses based on radiologic findings are extensive and could be divided into parenchymal and mediastinal abnormalities. Parenchymal abnormalities raise suspicion to disorders that could present with fibrosis and inflammation, such as idiopathic pulmonary fibrosis, chronic hypersensitivity pneumonitis, and fibrotic nonspecific interstitial pneumonia. The most important differential diagnoses regarding mediastinal LN enlargement with parenchymal abnormalities include sarcoidosis, neoplastic lymphoproliferative disorders, and MCD.

Lymphadenopathy is present in up to 80% of patients with IRSSD. Inoue et al reported on six patients with enlarged LNs out of 13 with IRSSD lung involvement, showing that lymphadenopathy is commonly observed with lung disease.

Few descriptions of PET scans in IRSSD have been reported. In a case series of lung inflammatory pseudotumor with marked IgG4-positive plasma cell infiltration, a PET scan revealed a marked uptake in pulmonary nodules and hilar LNs. Another case description with an IgG4-related lung nodule and enlarged hilar and mediastinal LN showed PET positivity on the nodule, but no information was given about LN uptake.

**Pathologic Discussion**

IRSSD is characterized by lymphoplasmacytic infiltration and varying degrees of sclerosis in the affected organs, with more IgG4-positive plasma cells in tissues. There is no definition about the quantity of IgG4-positive plasma cells in tissue to diagnose IRSSD, and reports use cutoff values varying from >10 to >50 cells per high-power field. Another consistent pathologic finding is infiltration by IgG4-positive plasma cells in venules (obliterative phlebitis).

In the present case, lung pathology revealed typical IgG4-rich, polytypic plasma cell infiltration associated with sclerosis, forming two types of lesions: irregular parenchymal nodules and interstitial expansion. These lesions corresponded to HRCT scan findings. The component of obliterator phlebitis was mild. LN presented marked interfollicular expansion of
polytypic, IgG4-positive plasma cells, one of the three types of histologic involvement described by Cheuk et al[6] in a case series of 12 patients with IgG4-related lymphadenopathy.

In the present case, the dense plasmacytic infiltrate and the absence of granulomas in lung biopsy specimens excluded the initial diagnoses of idiopathic pulmonary fibrosis, chronic hypersensitivity pneumonitis, fibrotic nonspecific interstitial pneumonia, and sarcoidosis. Two main histologic differential diagnoses arose from the conjunct histologic analyses of the lungs and LNs: a malignant lymphoproliferative process (lymphomas or lymphomatoid granulomatosis) and plasma cell MCD. A malignant lymphoproliferative process was excluded by the polytypic pattern of plasma cells, without light chain restriction and mixed, nonatypical CD3 and CD20 intermixed lymphocytic infiltrate. The absence of necrosis, lymphocyte atypia, and Epstein-Barr virus made diagnosis of lymphomatoid granulomatosis unlikely. Plasma cell MCD is an important histologic differential diagnosis in this setting because both diseases share similarities in clinical presentation and histology and therefore may represent different phenotypes of plasma cell disorders. [13] Recently, cases of IRSSD presenting with lymphadenopathy and increased serum IL-6 levels have been described,[13] as in our case. However, Cheuk et al[6] compared the quantity of IgG4-positive plasma cells in the LNs of both entities. In plasma cell MCD cases, the ratio of IgG4-positive to IgG-positive plasma cells did not reach values of 30%, which is different from the case presented here. Such differentiation is important because both entities differ in response to steroids. [9]

Conclusion

IRSSD prognosis is good, and treatment is with corticosteroids, but a case successfully treated with cyclosporine also has been described. [1] . [2] In the present case, the patient became asymptomatic and gained weight after lung biopsy. This description is the second of spontaneous lung disease remission. [2] Amylase and lipase levels normalized, and a new chest HRCT scan showed partial improvement of lung lesions. No corticosteroid treatment was administered. After 20 months follow-up, no recurrence was observed.


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