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IgG4-Related Interstitial Lung Disease and Lymphadenopathy: Report of a Case

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Abstract

IgG4-related disease is an immune-related condition that can affect multiple organ systems. Since it was first described in 2003, this heterogeneous disease had gained much attention, but the general acknowledgement of this disease remained relatively low, so misdiagnoses are common during clinical practice. Here we report a case of a 41-year-old female patient with recurrent lymphadenopathy, rash on her limbs and aggravating dyspnea, who suffered from these symptoms for 5 years before she was finally diagnosed with IgG4-related interstitial lung disease and lymphadenopathy.

Case Presentation

A 41-year-old female was admitted for recurrent lymphadenopathy and rash with aggravating dyspnea. The patient complained that she began to notice multiple painless enlarged lymph nodes on both sides of her neck 5 years ago, this symptom was fluctuating and accompanied by a rash on the limbs (Figure 1), and she began to have exertional dyspnea ever after. The first time she went to hospital, a thoracic CT suggested diffuse interstitial lung diseases (Figure 2). The patient received a lymph-node biopsy, multinucleated giant cells and epithelioid cells were found within the lymph node, so she was diagnosed with Tuberculosis and started Chemotherapy. Yet the therapy was discontinued for "lack of effectiveness", the patient then received irregular traditional Chinese herbal medicine ever since, with fluctuating lymph node enlargement and rash, and aggravating short of breath after activity. One month prior to admission, the patient began to feel abdominal distention and her abdominal circumference increased gradually. A thorough physical examination revealed multiple cervical and supraclavicular lymph node enlargement, multiform rash on the face and limbs, bilateral rales and rhonchi, and a remarkable extended abdomen and shifting dullness. Blood tests revealed moderate anemia, hypoalbuminemia, hyperglobulinemia, and hypoxemia. Ultrasonography revealed enlarged liver and spleen, multiple serous cavity effusion, and an estimated pulmonary hypertension. Thoracic CT revealed diffuse interstitial lesions of lung (Figure 3A). Bone marrow smear revealed clustered plasma cells on the end of the smear, and immunoglobulin analysis revealed prominent elevated IgG level. A supraclavicular lymph node biopsy was performed, multinucleated giant cells and epithelioid cells were found, yet anti-fast staining was negative, there were massive plasma cell infiltration in the sinuses, and immunohistochemistry staining revealed a 40% positive of IgG4 among IgG positive cells (Figure 4). Furthermore, the serum IgG4 level was greater than 4.52 g/L (normal reference 0.03 to 2.01). IgG4-related disease was diagnosed and the patient received glucocorticoid therapy.

Literature Review

IgG4 related diseases

IgG4-related disease is an immune-mediated condition that can affect multiple organ systems and mimics many malignant, infectious and inflammatory disorders. It was first described in 2003 [1] and have gain much attention ever since, a wide range of diseases which were once regarded as individual disorders are now recognized as part of IgG4-related disease, including autoimmune pancreatitis, Mikulicz's disease, inflammatory pseudotumor, etc., [2]. The epidemiology of IgG4-related disease remains poorly understood due to its recent recognition; in fact, it is still a relative new concept for clinicians [3]. The diagnosis of IgG4-related disease should be made based on clinical manifestations, laboratory and imaging findings, and typical histopathology [4-6]. The manifestations of IgG4 related disease varies greatly according to the organs involved, and there are no disease-specific symptoms or signs, hence delayed diagnoses are common [7]. Elevated serum IgG4 levels (>1.35 g/L) may help diagnosis, but high serum IgG4 concentrations are neither sufficiently sensitive nor specific for diagnosis, since there are 30% to 50% of patients have normal

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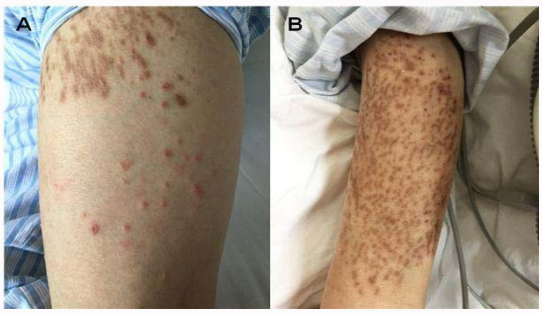

Figure 1: Rash on the limbs. (A) Scattered papules (lower part) with pruritus on the left thigh of the patient, accompanied by hyperpigmentation (upper part) which were the sequelae of prior episodes of rash. (B) Extensive hyperpigmentation on the left forearm of the patient resulted from prior lesions.

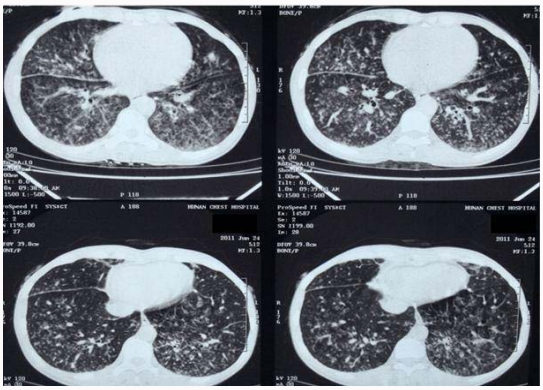

Figure 2: Lung imaging at the onset of disease. Diffuse bilateral interstitial changes (including thickening lobular septa and plura, proliferative nodules, ground glass opacities, and fibrosis) can be seen on these images.

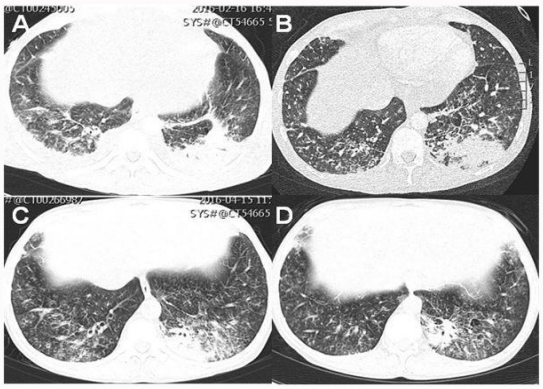

Figure 3: Sequential CT scan of the patient. (A) CT acquired upon admission (February 16, 2016), on the basis of the lesions described in Figure 2, there was segmental solidation in the lower left lung field and bilateral plural effusions. (B to D) CT acquired after therapy with prednisone was initiated (March 09, 2016, April 15, 2016, May 19, 2016, respectively). The solidation lesion in the lower left lobe alongside with the bilateral interstitial lesions gradually dissipated.

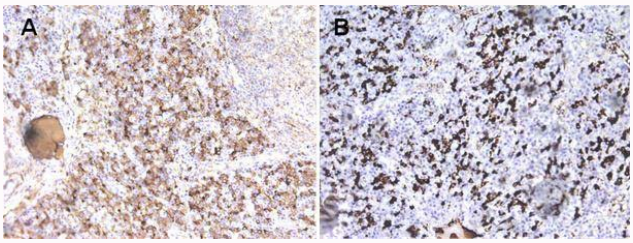

Figure 4: Pathological findings of the lymph node biopsy. (A) Immunohistochemistry stain against IgG, (B) Immunohistochemistry stain against IgG4. The ratio of IgG4/IgG was greater than 40%.

serum IgG4 concentrations. Other noteworthy findings include hyperglobulinemia, eosinophilia and elevated serum IgE. Imaging tests may help not only to timely diagnosis, but also to establish the extent and prognosis of disease. Organ enlargement with associated inflammatory and fibrotic tissue is commonly identified; imaging findings in organ systems unrelated to chief complaint often suggest multiple organ involvement; and findings of profound fibrosis usually indicate poorer outcome. Tissue biopsy is the gold standard for diagnosis in most settings. The main histological features of IgG4 related disease including dense lymphoplasmacytic infiltrates, storiform-type fibrosis, and obliterative phlebitis; high percentage of IgG4-positive plasma cells (IgG4: IgG at least 40%) is a hallmark of the disease. It is now widely agreed that a diagnosis requires both the typical histological features and the elevated IgG4 positive plasma cells. Generally, IgG4 related disease responds well to glucocorticoid therapy, but recurrent or refractory cases are common, especially for late-stage patients [8]. There is an urgent need for awareness of IgG4 related disease to achieve earlier diagnoses and better prognosis.

What we can Learn from this Case

The diagnosis of this patient is delayed for 5 years since onset of symptoms, by the time therapy is started; she is at a very late stage of disease and have severe interstitial lung disease, cor pulmonale, and congestive heart failure, indicating a poor outcome for this patient. Greater awareness of IgG4 related disease is needed to ensure early diagnosis and better outcome for this disease. There were several leads suggesting diagnosis of IgG4 disease in this case: 1) Subacute/chronic course of disease and fluctuating symptoms, which were very important to differentiate form malignancies; 2) Multiple organ systems involvement (skin, lymph node, lung, bone marrow, etc.,); 3) Profound hyperglobulinemia which indicated an immune-mediated pathophysiology; 4) severe interstitial lung disease with no explainable etiology.

The diagnosis of this case is based on the integration of clinical manifestations (lymphadenopathy, rash, dyspnea), laboratory tests (hyperglobulinemia and high serum IgG4 concentration), imaging findings (mainly interstitial lung lesions) and pathological data (increased plasma cell count in bone marrow smear, massive plasma cell infiltrates and high numbers of IgG4 positive plasma cells within lymph nodes). We did not risk performing lung biopsy given the clinical status of the patient, this to some extent compromised the confidence of diagnosis since there were no storiform fibrosis and obliterative phlebitis, and diagnosis of IgG4 related disease through lymph-node biopsy is difficult because lymph nodes are unlikely to show the degree of fibrosis seen in other organs.

Multinucleated giant cells and epithelioid cells were seen in the lymph node biopsy of this patient, these findings and a high T.B. spot count made tuberculosis a probable differential diagnosis or co-morbidity in this case. Since glucocorticoid therapies are contradicted among active tuberculosis patients, it's a hard decision to make whether or not to start glucocorticoid therapy. In this particular case the patient received therapy after multi-discipline consultation, but we believe more pathological and cohort studies are needed to clarify

the significance of multinucleated giant cells and/or epithelioid cells in lesions of IgG4 related disease, and the significance of high T.B. spot count among these patients, so as to make better clinical decisions.

Patient Outcome

The patient received glucocorticoid therapy, her manifestations and lung imaging improved greatly after 2 months of treatment (Figure 3B-D), and the patient's symptoms remained well-controlled after 2 years of follow-up.

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