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CASE REPORT

Immunoglobulin G4 (IgG4) Positive Associated Liver Disease

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SUMMARY

Background: **The goal was to explore the cognition of diagnosis and treatment level of IgG4-related diseases mainly involving lymph nodes.**
Methods: **The clinical manifestations, laboratory indicators, histopathology, and therapeutic effects of a patient with IgG4-RD suspected of lymphoma were analyzed and the relevant literature was reviewed.**
Results: **Lymph node biopsy showed reactive hyperplasia of lymph node tissue. The liver biochemical indexes were abnormal and the bone marrow smear showed atypical lymphocytes. Lymph node section: IgG4+ cells > 100/HPF (IgG4/IgG > 40%). The serum IgG4 level was 17,200 mg/L, and the diagnosis was IgG4-RD. Oral glucocorticoids took effect after 2 weeks, and no significant enlargement of lymph nodes was observed.**
Conclusions: **For the diagnosis of IgG4-RD, at present, histopathology is still the gold standard, but a single result cannot diagnose the disease. Comprehensive judgment should be made by combining clinical symptoms, serum IgG4 level and imaging results to prevent misdiagnosis and missed diagnosis, and to avoid over-diagnosis. Short-term hormonal diagnostic therapy may be used in highly suspected patients who cannot be diagnosed. Once diagnosed, standardized medication, adhere to follow-up, regular review, to prevent recurrence and adverse drug reactions.**
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KEYWORDS

IgG4-related disease, immunoglobulin, glucocorticoid

INTRODUCTION

IgG4-associated diseases (IgG4-RD) are a class of systemic immune fibroinflammatory diseases that have been gradually recognized in recent years. The pathological tissues are infiltrated with lymphoplasma cells, mainly IgG4-positive plasma cells. The histopathology often shows inflammation with fibrosis, obliterative phlebitis and other characteristic changes. The clinical manifestations were single-organ or multi-organ lesions, often accompanied by elevated serum IgG4 levels. Clinically, middle-aged and elderly people are more common, and the age of onset is more common between 60 and 70. Classic autoimmune diseases tend to occur in women, while IgG4-related diseases tend to occur in middle-aged and elderly men, which is the difference between the two. At present, there are no literature sta-

tistics on the incidence and mortality of the disease, and its pathogenesis is unknown. In view of the diversity, overlap and tumor-like phenomena of the clinical manifestations of the disease, misdiagnosis and missed diagnosis often occur. Autoimmune hepatitis (AIH) is a chronic progressive inflammatory disease of the liver mediated by the immune response of the body. It is usually manifested by elevated aminotransferase, jaundice, hyperglobulinemia and positive autoantibodies. At present, the relationship between IgG4 and immune liver injury is unclear, and whether IgG4-AIH is a hepatic manifestation of IgG4-RD or a subtype of AIH is unclear. The clinical case data of a patient with IgG4-associated liver disease characterized by lymph node enlargement is reported here.

CASE REPORT

The patient, male, 49 years old, was admitted to the hematology department of our hospital mainly due to progressive enlargement of lymph nodes for more than 2 years. The patient reported that he was in good health in the past, and there was no obvious cause for progressive enlargement of lymph nodes in multiple parts of the whole body at the early stage of the disease, and no pain was felt when touched. The local B-ultrasound indicated lymph node enlargement 6 months ago, and no special treatment was given, and outpatient follow-up observation was made. Two months ago, he felt abdominal distension, appetite and weight loss, and there were no other obvious abnormalities. The initial diagnosis was lymph node enlargement to be investigated. Lymph node biopsy considered reactive hyperplasia of lymph nodes. Alanine aminotransferase 184 U/L, aspartate aminotransferase 88 U/L, globulin 45.9 U/L, alkaline phosphatase 953 U/L, glutamyl transpeptidase 767 U/L, glucose 7.27 mmol/L, Anti-nuclear antibody (1:160), anti-SSA antibody (++), anti-Ro-52 antibody (++). Plasma cells accounted for 1% and atypical lymphocytes accounted for 1.5% in both bone marrow and peripheral blood. Lymph node section: IgG4+ cells > 100/HPF (IgG4/IgG > 40%) (Figure A - F). The serum IgG4 level was 17,200 mg/L, and the diagnosis was IgG4-RD. The imaging examination showed diffuse or local enlargement and soft tissue shadow, but the imaging examination of this disease is nonspecificity. Patients were instructed to follow a low-glycemic diet with glucocorticoids. After 2 weeks of treatment, the patient's appetite and sleep improved, no other obvious symptoms of discomfort, the neck and groin reached soybean sized lymph nodes, mobile, no tenderness, no tenderness in the sternum, clear breathing sound in both lungs, soft abdomen, liver, spleen, and lower ribs, no edema in both lower limbs, and no increase in blood sugar. There was no jaundice and low bilirubin throughout the course of the disease. The diagnosis was IgG4-related liver disease.

DISCUSSION

IgG4-related diseases are a class of immune-mediated inflammatory lesions of fibrous tissue. They are rare diseases and systemic diseases, which can involve multiple tissues and organs. The clinical manifestations are very complex. IgG4-related diseases have hidden clinical onset, most lack specific manifestations, and can be accompanied with other diseases at the same time. Some scholars believe that the possible reason is that inflammatory changes in fiber tissue stimulate pathogenic factors and promote the development of diseases. It has also been suggested that the direct infiltration of IgG4-positive plasma cells into tissues and organs and the by-products produced by certain immune hyperactivity may cause damage to major organs, and most of the affected organs show common pathological features and prominent clinical and serological similarities [1,2]. IgG4-RD generally does not show systemic symptoms, such as fever, fatigue, etc., and some cases even have no obvious clinical symptoms. This patient has poor appetite and weight loss, and it is not clear whether it is related to other diseases (such as lymphoma). IgG4-RD usually involves pancreas, liver and gallbladder, kidneys, and submandibular glands, lacrimal glands and lymph nodes on the body surface. In this case, lymph nodes and liver are mainly involved. Patients with liver disease have different degrees of immune imbalance, which can lead to the activation of B cells in the body and their transformation into plasma cells. The liver itself cannot synthesize immunoglobulin, but it can regulate the metabolism of immunoglobulin through its influence on intestinal absorption. Foreign antigens cannot be promptly and effectively cleared by the diseased and necrotic liver cells. At the same time, the combination of auto-antibodies leads to the increase of immunoglobulin [3,4]. It is not clear whether IgG4-AIH is the liver manifestation of IgG4-RD or a subtype of AIH. Most patients with AIH have obvious elevation of bilirubin and jaundice. In this case, jaundice was not found and bilirubin was not high. In addition, when rituximab was used to clear B lymphocytes in some patients with refractory IgG4-RD, it was found that the number of myofibroblasts and cytoplasmic contents in the pathological tissues were significantly reduced [5,6], suggesting that B lymphocytes play a key role in IgG4-RD. The onset of IgG4-RD is chronic occulted or subacute, and the systemic symptoms are not obvious. Most patients are complicated with allergic diseases, such as eczema, asthma, peripheral blood eosinophilia, etc. In this case, the routine blood values of the patient were normal, and the eosinophilia did not increase. According to the 2015 International Consensus Guidelines for the Management and Treatment of IgG4-RD: 1. Diffuse or localized enlargement of one or more organs. 2. Serum IgG4 level increased (135 mg/L). 3. Histopathological findings: IgG4+ plasma cell infiltration (IgG4/IgG40% or 10 IGG4-positive plasma cells 100/HPF). A diagnosis with 1 + 2 + 3 can be confirmed, 1 + 3 is likely, and 1 + 2

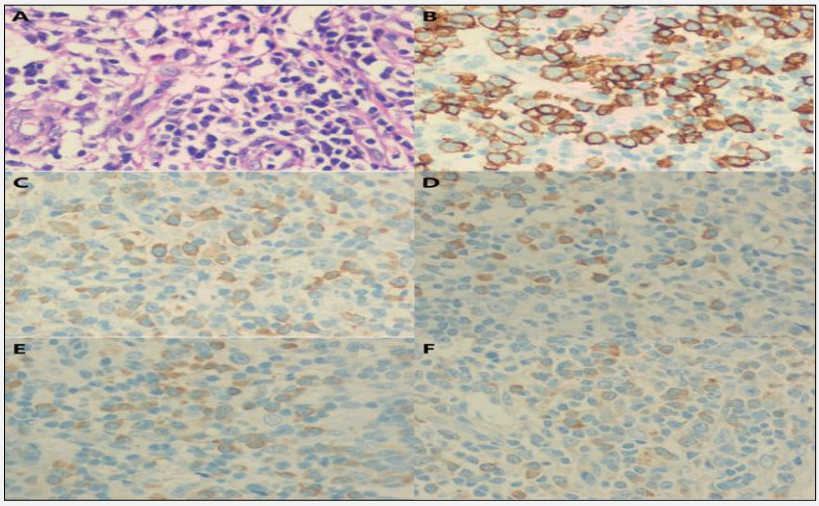

Figure A. H - E staining of pathological sections of lymph nodes (10 x 40). Figure B. CD138 staining of pathological lymph node sections (10 x 40). Figure C. kappa staining in pathological sections of lymph nodes (10 x 40). Figure D. lambda staining of pathological lymph node sections (10 x 40). Figure E. IgG staining of pathological lymph node sections (10 x 40). Figure F. IgG4 staining of pathological lymph node sections (10 x 40).

may diagnose IgG4-RD. Therefore, the diagnosis of IgG4-RD requires many aspects, including clinical manifestations, laboratory examination, imaging examination and histopathological examination. Single test index cannot diagnose the disease. At present, IgG4-related diseases are still difficult diseases in China at this stage, which are easy to miss or misdiagnose. Most of them are already late when diagnosed, resulting in irreversible functional damage. Therefore, the early diagnosis of IgG4-RD is particularly important, and it is of great significance to carry out active and effective clinical treatment and improve the quality of life of patients. In this case, the patient had multiple lymph node enlargement, lymph node biopsy indicated reactive lymphocyte hyperplasia, and no obvious discomfort was observed, resulting in a long time for diagnosis. IgG4-RD itself belongs to the category of rheumatology and immunology diseases, but due to the diversity and overlap of clinical manifestations of IgG4-RD, most patients were initially treated in other departments. This puts forward higher requirements for clinicians. Clinical history should be considered in many aspects, especially in patients with a history of allergy, parasitic infection, and other autoimmune diseases or tumors, to prevent misdiagnosis or missed diagnosis.

Declaration of Interest:

All authors declaration: 1. No funding was received for this study. All views and data in this paper are supported by references and data. The manuscript has not been published before and is not being considered for publication elsewhere. 2. All authors have contributed to the creation of this manuscript for important intellectual content and read and approved the final manuscript. We declare there is no conflict of interest. 3. This paper is published with the consent of patients, in line with ethical requirements.

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