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CASE REPORT

Immunoglobulin G4-related lymph node disease with an orbital mass mimicking Castleman disease: A case report

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Abstract

BACKGROUND

Immunoglobulin (Ig) G4-associated diseases are a group of systemic diseases involving multiple organs and are also known as IgG4-associated sclerosing diseases. IgG4-associated lymphadenopathy occurring in the lymph nodes is characterized by a lack of specificity due to its clinicopathological characteristics and must be differentiated from a variety of lesions, such as Castleman disease, lymphatic follicular reactive hyperplasia, and lymphoma.

CASE SUMMARY

A 65-year-old male patient, with Guillain-Barre syndrome for 5 years, presented to our hospital complaining of bilateral orbital mass for 2 years. After hospitalization, the results of the patient's laboratory tests showed that immunoglobulin subgroup IgG4 was 33.90 g/L and IgG was 30.30 g/L, but serum interleukin-6 was normal. The pathological morphology of orbital mass and cervical lymph node were consistent, which showed that a large number of plasma cells and eosinophils were observed in the lymphatic follicles, and the interstitial fibrous tissue was proliferative. Immunohistochemistry showed that CD20 (B cells) (+), CD3 (T cells) (+), CD38 (+), IgG (+), IgG4 positive cells > 100/high powered field, and IgG4/IgG > 40%. Combined with clinical and immunohistochemical results, lymphadenopathy was consistent with Castleman disease-like IgG4-associated sclerosing disease. Prednisone acetate treatment was given at 40 mg/d. After 2 wk, the superficial lymph nodes and orbital masses shrank, and the IgG4 level decreased. As prednisone acetate was regularly used at a reduced dosage, no recurrence of the disease has been observed.

Country/Territory of origin: China

Specialty type: Medicine, research and experimental

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Grade B (Very good): B
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CONCLUSION
This case suggested that it is necessary to proceed cautiously in clinical practice with such patients, and immunoglobulin, complement, interleukin-6, C-reactive protein, and other examinations should be performed to confirm the diagnosis.

Key Words: IgG4-associated disease; Castleman disease; Lymphadenopathy; Orbital neoplasm; Pathological morphology; Case report

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Core Tip: Immunoglobulin (Ig) G4-related disease is a group of systemic immune diseases. There is no unified standard for the differentiation of IgG4-related disease from plasma cell Castleman disease. These diseases are sometimes difficult to distinguish from one another. We reported a case of IgG4-related lymph node disease with an orbital mass mimicking Castleman disease. The pathological morphology was similar to Castleman disease, which may lead to misdiagnosis. This case suggested that it is necessary to proceed cautiously in clinical practice with such patients, and immunoglobulin, complement, interleukin-6, C-reactive protein, and other examinations should be performed to confirm the diagnosis.

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INTRODUCTION

Immunoglobulin (Ig) G4-related disease (IgG4-RD) is a group of systemic immune diseases characterized by elevated serum IgG4, a large amount of IgG4+ plasma cell infiltration in tissues, occasional eosinophilic granulocytes, interstitial fibroplasia, and small phlebitis obliterans[1-3]. Castleman disease is a clinically rare lymphoproliferative disorder. Castleman disease and IgG4-RD may present some common clinical manifestations, such as enlarged lymph nodes and elevated serum IgG4 levels, which make the clinical diagnosis and differential diagnosis more difficult and challenging [4]. Here, we report a case of IgG4-related lymph node disease with an orbital mass mimicking Castleman disease and review the relevant literature.

CASE PRESENTATION

Chief complaints

A 65-year-old male patient was admitted to the hospital on January 21, 2020 due to a "bilateral orbital mass for 2 years."

History of present illness

Two years prior, the patient developed binocular swelling, exophthalmos, and decreased vision accompanied by hand tremor without any other accompanying symptoms, and the above symptoms became progressively worse.

History of past illness

He suffered from Guillain-Barre syndrome 5 years ago and left hand tremor after recovery.

Personal and family history

The patient denied alcohol consumption and allergies to food or medicines.

Physical examination

Right orbital mass and bilateral cervical lymph node enlargement was observed. The large one was about 1.6 cm × 0.9 cm. No other obvious positive signs were found.

Laboratory examinations

After hospitalization, the results of the patient's laboratory tests showed that the erythrocyte sedimentation rate was 47.0 mm/h, D-dimer was 1450.00 ng/mL, immunoglobulin subgroup IgG4 was 33.90 g/L, IgG was 30.30 g/L, total protein was 64.7 g/L, and albumin was 26.1 g/L. Antinuclear antibody was weakly positive (titer 1:100), complement C3 was 0.79 g/L, complement C4 was 0.10 g/L, and complement C1q was 102.20 mg/L. Urinary protein was 4+, but serum interleukin (IL)-6 was normal. Thyroid function, thyroid stimulating hormone receptor antibody, routine blood tests, C-reactive protein (CRP), brain natriuretic peptide (BNP)/pro-brain natriuretic peptide (PBNP), and rheumatoid factors were not significantly abnormal, and extractable nuclear antigen antibody spectrum, anti-cyclic citrate peptide antibody, anti-neutrophilic cytoplasmic antibody, and anti-phospholipid antibody were negative.

Imaging examinations

On January 9, 2021, orbital computed tomography (CT) performed in the outpatient department showed bilateral external eye muscle and periocular changes, exophthalmos, swelling of the right eyelid, and multiple bone resorption changes in the medial orbital wall on both sides.

On January 21, 2021, ultrasound examination showed nodular goiter (thyroid imaging reporting and data system 3 type) and right cervical lymph node enlargement.

On February 2, 2021, ultrasonography showed bilateral lymph node enlargement. The large one on the right was 1.6 cm × 0.9 cm, and the large one on the left was 1.9 cm × 1.1 cm.

On January 29, 2021, positron emission tomography/CT results showed that the bilateral ophthalmic muscles, lacrimal glands, intraorbital soft tissue, subcutaneous soft tissue nodules in the back, bilateral mediastinal pleura, and several superficial and deep lymph nodes all showed increased metabolism, accompanied by retroperitoneal fibrosis (Figure 1).

Pathological morphology and immunohistochemistry

On January 25, 2021, right orbital mass resection was performed, and postoperative pathological diagnosis showed that a large number of plasma cells and eosinophils were observed in the lymphatic follicles. The interstitial fibrous tissue was proliferative (Figure 2A and B). Immunohistochemistry showed CD20 (B cells) (+), CD3, CD4, and CD8 (T cells) (+), CD38 and CD138 (plasma cells) (+), S100 was scattered (+), CD1α was scattered (+), Langerin (-), Epstein-Barr encoding region (-), Ki-67 (+, approximately 40%), IgG (+), IgG4 positive cells > 100/high powered field, and IgG4/IgG > 40% (Figure 2C-F). Combined with clinical and immunohistochemical results, these results were consistent with IgG4-associated sclerosing disease.

On February 4, 2021, the pathological results of the left neck lymph node biopsy showed that the lymph node structure was still present, mainly exhibiting follicular hyperplasia, small blood vessels in the follicle were extended, and a large number of plasma cells were observed in the interfollicular area (Figure 3A and B). Immunohistochemical results showed that CD20 (B cells) (+), CD3 (T cells) (+), CD38 plasma cells (+), IgG (+), IgG4 (+), CD21 (follicular dendritic cell network) (+), Ki-67 (+); (approximately 90% in follicles and approximately 20% in the interfollicular area), and IgG4/IgG > 40% (Figure 3C-F). Combined with clinical and immunohistochemical results, lymphadenopathy was consistent with Castleman disease-like IgG4-associated sclerosing disease.

FINAL DIAGNOSIS

The final diagnosis of the presented case was Castleman disease-like IgG4-associated sclerosing disease.

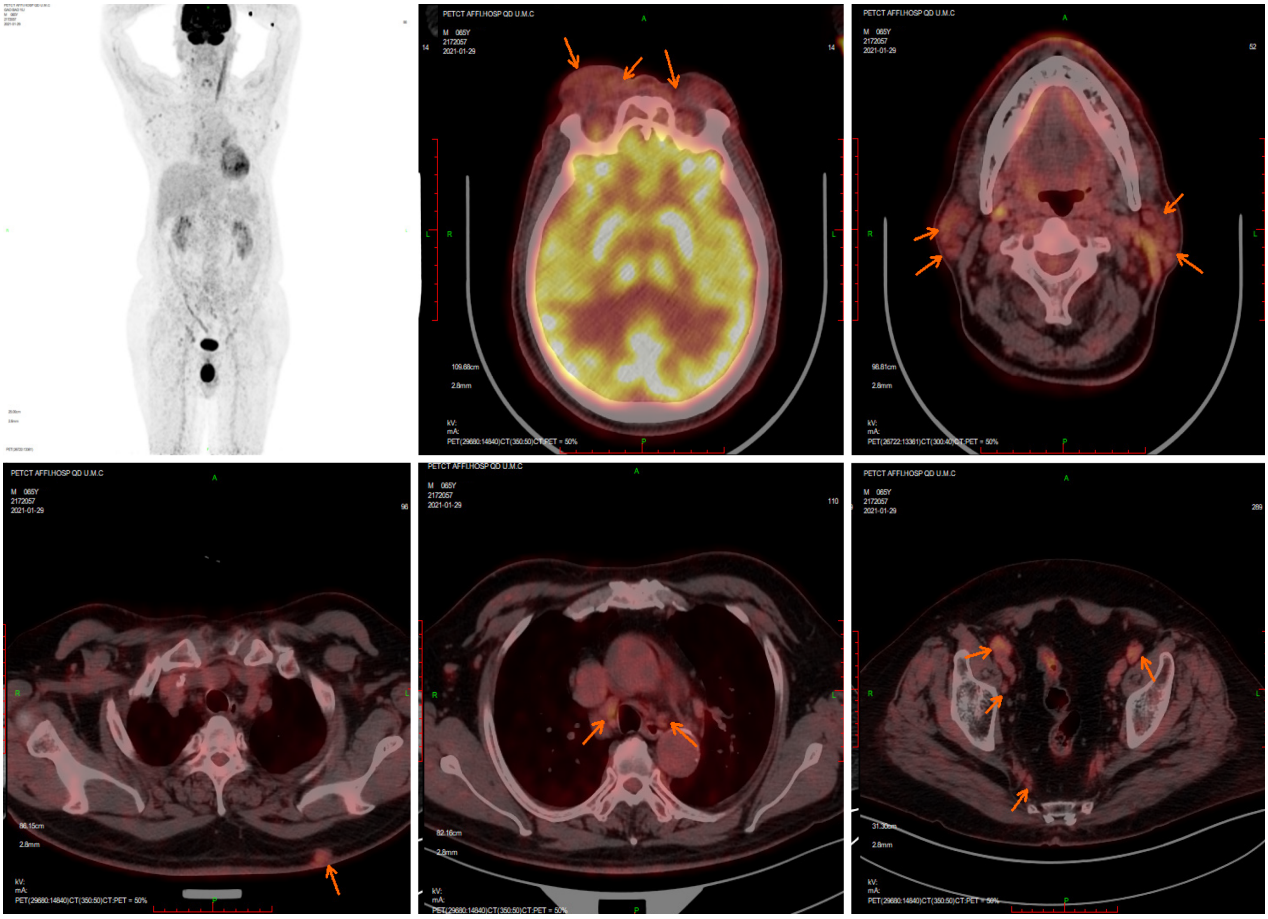

Figure 1 Positron emission tomography computed tomography on January 29, 2020. Positron emission tomography computed tomography revealed that bilateral ophthalmic muscles, lacrimal glands, intraorbital soft tissue, subcutaneous soft tissue nodules in the back, bilateral mediastinal pleura, and several superficial and deep lymph nodes all showed increased metabolism, accompanied by retroperitoneal fibrosis.

TREATMENT

Prednisone acetate treatment was given at 40 mg/d. After 2 wk, the superficial lymph nodes and orbital masses shrank, and the IgG4 level decreased upon re-examination.

OUTCOME AND FOLLOW-UP

At present, prednisone acetate was regularly used at a reduced dosage, and no recurrence of the disease has been observed.

DISCUSSION

IgG4-associated diseases are a group of systemic diseases involving multiple organs and are also known as IgG4-associated sclerosing diseases. Clinically involved organs include the pancreas, bile duct, retroperitoneum, lung interstitium, breast, kidney, salivary gland, liver, lymph node, and other tissues and organs, and the affected organs are different at different ages[5]. The typical histological features of IgG4-RD include dense lymphoplasmacytic infiltrates, storiform-type fibrosis, and obliterative phlebitis[6]. The diagnosis of at least two of the above three criteria is needed, usually diffuse lymphoplasmic cell infiltration and storiform-type fibrosis[7,8]. However, lymph nodes, the lung, and other organs and tissues often do not have the characteristic manifestations of storiform-type fibrosis and phlebitis obliterans. IgG4-correlated disease in the lymph nodes is easily misdiagnosed due to the lack of specificity of its clinical pathological features, which have been identified in a variety of pathological conditions, such as Castleman disease, inflammatory pseudotumor,

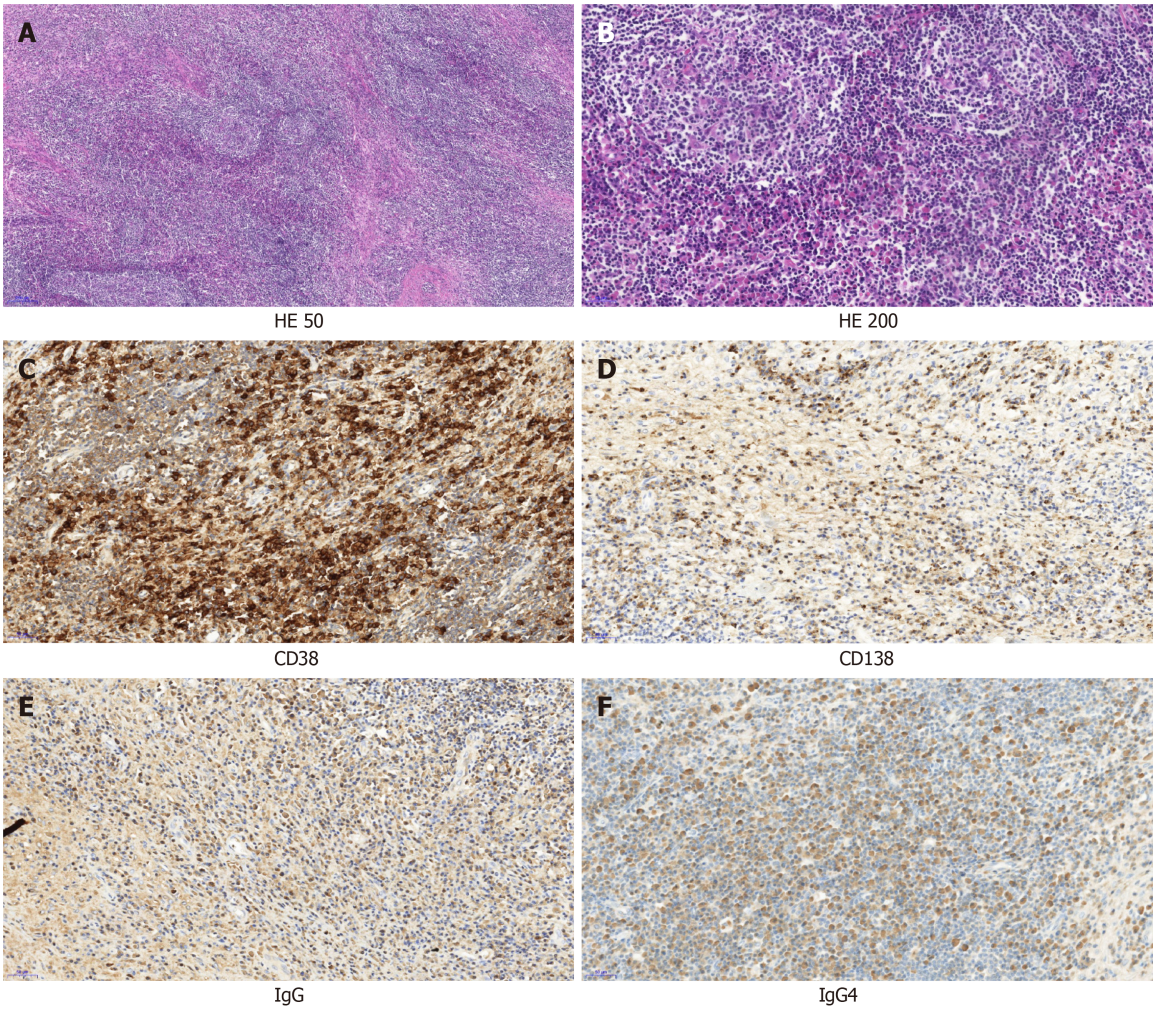

Figure 2 Pathological morphology and immunohistochemistry of orbital mass. A: At low magnification, the histological morphology showed lymphoproliferative tissue, scattered lymphoproliferative follicles, and interstitial fibrous tissue proliferation (× 50); B: Histological morphology at high magnification showed hyperplasia of small vessels in the follicles, and a large number of plasma cells infiltrated between the follicles (× 200); C: CD38 immunohistochemical staining showed a large number of positive plasma cells in the interfollicular space; D: Immunohistochemical staining of CD138 showed a large number of positive plasma cells in the interfollicle; E: Immunoglobulin (Ig) G positive plasma cells could be seen by immunohistochemical staining; F: IgG4-positive plasma cells could be seen by immunohistochemical staining; The IgG4/IgG ratio was greater than 40%. HE: Hematoxylin and eosin stain; Ig: Immunoglobulin.

and lymphoid follicle hyperplasia of reactivity (such as lymphoma), and final diagnosis should combine medical history, physical examination, serological examination, imaging, pathology, and immunohistochemistry[9-11].

Studies have shown that FDG positron emission tomography/CT has a sensitivity of 85.7% and a specificity of 66.1% in the diagnosis of IgG4-RD and may have a potential differential ability for patients with clinically suspected IgG4-RD[12]. We presented a case of IgG4-RD with Castleman disease-like alterations that included positron emission tomography/CT. IgG4 immunostaining was necessary for the diagnosis of IgG4-RD, and a proportion of IgG4+/IgG+ plasma cells greater than 40% and the IgG4+ cell count are important parameters[13,14]. This case met the criteria. Effective initial treatment with glucocorticoids is one of the characteristics of IgG4-RD, and rituximab therapy should be considered for patients for whom glucocorticoids are ineffective or who are dependent on glucocorticoids[15].

Castleman disease, first reported in 1956, is a clinically rare lymphoproliferative disorder. According to the different scope of involvement, it was divided into unicentric Castleman disease and multicentric Castleman disease (MCD). Histologically, the disease was divided into a clear vascular type, plasma cell type, and mixed type. MCD usually manifests as multiple lymph node enlargement, hepatosplenomegaly, kidney injury, pulmonary symptoms and signs, and ascites and can be accompanied by high fever, night sweats, and other systemic symptoms[16]. Because the disease is relatively rare in clinical practice, there is no unified first-line treatment plan at present, but simple glucocorticoids have poor efficacy. Combined chemotherapy, rituximab, or anti-IL-6 treatment are often necessary, and the prognosis

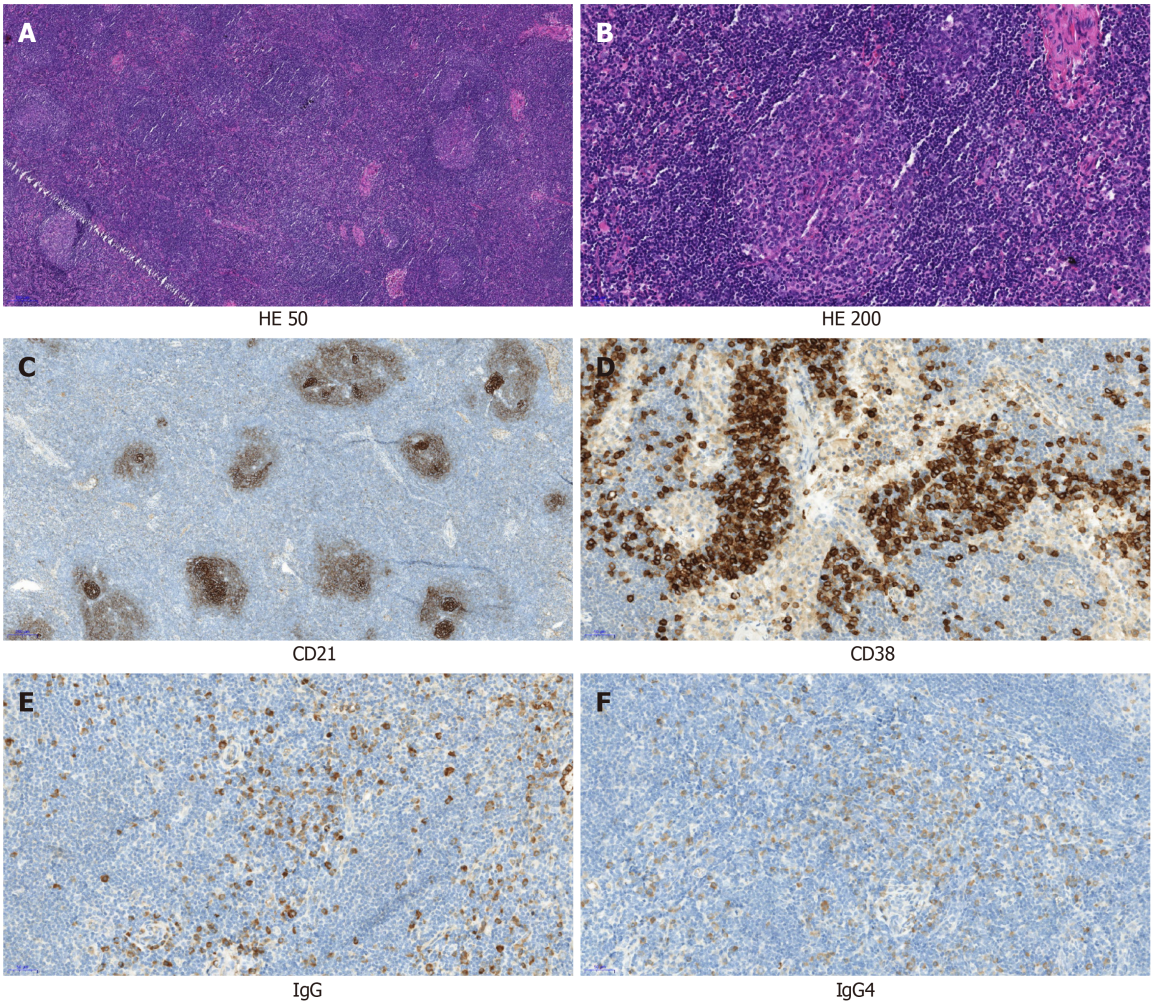

Figure 3 Pathological morphology and immunohistochemistry of cervical lymph nodes. A: At low power histological morphology, most of the lymphoid sinuses of the lymph nodes disappeared, and proliferative lymphatic follicles were evenly distributed throughout the lymph nodes. Lymphocytes in the mantle region were widened, and small blood vessels between the follicles were increased, with partial hyalinization, similar to Castleman disease morphological changes (× 50); B: At high magnification, small blood vessels in the follicles were observed to grow and proliferate, a large amount of lymphatic tissue proliferated between the follicles, and plasma cells were infiltrated (× 200); C: Immunohistochemical staining of CD21 showed a network of follicular dendritic cells scattered throughout the lymphatic follicles of the lymph node; D: CD38 immunohistochemical staining showed a large number of positive plasma cells in the interfollicular space; E: Immunoglobulin (Ig) G positive plasma cells could be seen by immunohistochemical staining; F: IgG4-positive plasma cells could be seen by immunohistochemical staining; the IgG4/IgG ratio was greater than 40%. HE: Hematoxylin and eosin stain; Ig: Immunoglobulin.

is poor[17-20].

It has been reported that IgG4-associated lymphadenopathy may have Castleman disease-like characteristics, and some scholars believe that a subset of plasma cell Castleman disease is actually IgG4-associated lymphadenopathy[21,22]. IgG4-RD share similarities with Castleman disease, but there are also differences. MCD and IgG4-RD can be distinguished based on the following aspects: (1) Clinical manifestations: lymph node enlargement in MCD is more prominent and is often accompanied by fever, anemia, severe hypoproteinemia, and other systemic symptoms, while lymph node lesions of IgG4-RD are usually less than 2 cm in diameter and often involve the lacrimal glands, salivary glands, pancreas, and retroperitoneum; (2) Inflammation indicators: CRP, IL-6, and vascular endothelial growth factor are usually significantly increased in MCD patients; (3) In terms of immunoglobulin and complement, increased IgG in MCD patients may be accompanied by increased IgA and IgM, with normal complement levels, while the course of IgG4-RD may involve the activation process of complement, leading to decreased complement levels; (4) Pathological features: IgG4+ plasma cells may appear in MCD patients, but IgG4+/IgG+ plasma cells usually account for less than 40%; and (5) Therapeutic response of glucocorticoids: IgG4-RD patients respond well to initial treatment with glucocorticoids, while MCD patients generally respond poorly[4,23-25].

The patient in this case had lacrimal gland, lymph node, retroperitoneal, and other lesions, decreased complement C3, normal IL-6 levels, IgG4+/IgG+ plasma cells greater than 40%, and a good response to glucocorticoid treatment. All of these features were in line with IgG4-associated lymphadenopathy. However, the pathological morphology of this patient was very similar to that of Castleman disease, which may lead to misdiagnosis. Therefore, it is necessary to proceed cautiously in clinical practice with such patients, and Ig, complement, IL-6, CRP and other examinations should be performed to confirm the diagnosis.

CONCLUSION

There is no unified standard for the differentiation of IgG4-RD from plasma cell Castleman disease, and these diseases are sometimes difficult to distinguish from one another. It is necessary to proceed cautiously in clinical practice with such patients Histopathological characteristics, laboratory testing, and clinical treatment should be considered comprehensively to provide a basis for clinical treatment and prognosis evaluation.

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