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**Clivus-involved Immunoglobulin G4 related hypertrophic pachymeningitis  
mimicking meningioma: A case report and literature review**

A case of IgG4-RHP and review

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## **Abstract**

### **BACKGROUND**

Immunoglobulin G4 related disease (IgG4-RD) is recognized as the fibroinflammatory disease involving multiple organs with the obviously upward serum level of IgG4 and proliferation of fibrous tissue accompanied by numerous plasma cells. IgG4 related hypertrophic pachymeningitis (IgG4 RHP) is relatively rare and indistinguishable before the operation. The risk of long-term immunosuppression needs to be balanced with disease activity.

### **CASE SUMMARY**

This case was a 40-year-old male who presented with headache and bilateral abducent paralysis currently. Also, he was diagnosed with pulmonary tuberculosis ten years ago and treated regularly. Before operation and steroid therapy, the patient was suspected of tubercular meningitis in local. It was found clivus lesion through brain MRI this time. Then he was preliminarily diagnosed with meningioma and underwent Gamma Knife Surgery. For the deterioration of nerve function, transnasal endoscopic resection was performed. And the postoperative pathologic examination revealed that IgG4-RD should be considered. Moreover, the serum IgG4 was upward with 1.90 g/L (reference range was 0.035 - 1.500 g/L). After steroid therapy for two months, the lesion diminished on MRI, and the function of bilateral abducent nerves recovered.

### **CONCLUSION**

The IgG4 RHP was relatively rare and indistinguishable before the operation. Serum IgG4 and imaging examination could facilitate us to recognize IgG4 RHP. Operation is necessary when lesions progress and patients appear cranial nerve function deficit.

**Key Words:** Immunoglobulin G4 related disease (IgG4-RD); Hypertrophic pachymeningitis; Immunoglobulin G4 related hypertrophic pachymeningitis; clivus; case report

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**Core Tip:** Immunoglobulin G4 related disease (IgG4-RD) is recognized as the fibroinflammatory disease referred to multiple organs with obviously upward serum level of IgG4 and proliferation of fibrous tissue accompanied by numerous plasma cells. IgG4 related hypertrophic pachymeningitis (IgG4 RHP) is relatively rare and indistinguishable before the operation. Herein, we present a rare case of IgG4 RHP with the intact change of magnetic resonance imaging (MRI) and pathologic image. The case highlighted the differential diagnosis with other phymatoid lesions (such as meningioma, fungal infection, tuberculosis) and the importance of comprehensive multidisciplinary treatment. Operation is necessary when lesions progress and patients appear cranial nerve function deficit.

## **1** **INTRODUCTION**

Immunoglobulin G4 related disease (IgG4-RD) was initially noticed in patients with autoimmune pancreatitis in 2001 and formally named in 2010, classified as sarcoidosis with different manifestations in several organs and the same pathological characteristics<sup>[1, 2]</sup>. The main characteristic of IgG4-RD is the elevation of serum IgG4. Moreover, the lesions are often tumescent with abundant IgG4-positive plasma cells and fibrosis. Such inflammatory lesions could be seen in the pancreas, kidney, lungs, salivary glands, and other organs. Specifically, the conditions of IgG4-RD in the central nervous system are meningitis and hypophysitis<sup>[3]</sup>. As for the IgG4-related hypertrophic pachymeningitis (IgG4-RHP), the clinical and imaging manifestation is similar to meningioma, posing a challenge for preoperative diagnosis<sup>[4, 5]</sup>. Additionally, time and scope of operation should be considered carefully. Finally, this disease is related to some bacterial infections, such as tuberculosis. And we need to balance some conflicts

between these infections and corticosteroid therapy for IgG4-RD. Herein, <sup>1</sup>we reported a rare case with IgG4-RHP at the clivus area mimicking meningioma and went over relevant studies.

## **CASE PRESENTATION**

### ***Chief complaints***

A 40 year-old male was admitted for headache, bilateral temporal visual field defect and limitation of abduction in both eyes.

### ***History of present illness***

Five years before admission, the patient noticed the symptom of a discontinuous and aggravating headache. For the symptomatic deterioration, the patient was admitted to the neurology department of a local hospital. As for the pulmonary tuberculosis past history, the patient was suspected of tuberculosis meningitis in a local hospital and treated with anti-tuberculosis drugs as diagnostic therapy. However, the symptom did not alleviate. Then the patient was diagnosed with meningioma in our hospital for a clival lesion found by MRI, which took up  $2.6 \times 1 \text{ cm}^2$  with isointensity signal in T1-weighted and T2-weighted magnetic resonance image (MRI). The lesion was homogenously enhanced through contrast MRI with a dural tail sign as shown in Figure 1. Without cranial nerve function defect, the patients chose Gamma Knife Surgery (GKS) with a dose of 11 Gy and 45% isodose curves, and regular follow-up was performed.

### ***History of past illness***

The patient had suffered from pulmonary tuberculosis 11 years ago and accepted standard anti-tuberculosis treatment for one year.

### ***Personal and family history***

No other particular personal and family history was reported.

### ***Physical examination***

This patient appeared right abducent paralysis, hoarse voice, bitemporal hemianopsia and slight swallowing difficulty. No other positive signs were found.

### ***Laboratory examinations***

The lumbar puncture was performed and we found that the number of karyocytes (mainly mononuclear cells) and protein levels in cerebrospinal fluid had risen (Table 1).

After pathological results showed IgG4-RD, further systemic evaluation was performed to find other lesions associated with IgG4 related disease. The serum IgG level was 17.20g/L (reference range was 8.00 -15.50 g/L), and the serum level of IgG4 was 1.90 g/L (reference range was 0.035 - 1.500 g/L). Tuberculosis associated gamma interferon release experiment displayed positive with TB-IGRA (T-N) of 414.21 pg/mL.

### ***Imaging examinations***

After admission, the routine laboratory test and preoperative preparation were performed. It was found that the lesion became larger as the size of  $3.8 \times 2.9 \times 2.9\text{cm}^3$  which adjacently compressed the brain stem (Figure 1). It showed that there were small pneumatoceles in the upper lobe of the right lung by CT thorax. Moreover, the examination of visual field confirmed binocular hemianopia (Figure 2). No other positive results were found.

### **FINAL DIAGNOSIS**

The postoperative pathology confirmed the proliferation of fibrous tissue accompanied by numerous lymphocytes and plasma cells, which is displayed in Figure 3. The result of immunohistochemistry staining displayed positive CD138 and IgG4. And the result of the gene rearrangement test displayed negative IgH. The IgG4 related disease was considered based on the results mentioned.

## **TREATMENT**

The patient underwent the transnasal endoscopic approach resection which aimed to partially remove the lesion, alleviate the headache caused by meningeal tension and get the pathology results. During the operation, we found that the lesion extended to sphenoid sinus and nasopharynx without a clear boundary. Notably, local mucosa got edema and tight. The clivus bone had been partially damaged, and the clivus epidural became thicker. The intraoperative frozen section examination revealed the proliferation of spindle cells accompanied by many lymphocytes and plasma cells.

For the pathological result of IgG4-RD, solu medrol was administrated at a dose of 80 mg per day, and methotrexate was administrated at 10 mg every week. Famotidine, calcium carbonate and Vitamin D3 tablets were prescribed against adverse reactions during the treatment. After discharge from the hospital, the solu medrol was tapered over four weeks to 50 mg per day. The patient declared those symptoms, such as headache and hoarse voice, gradually alleviated after one month. The follow-up was arranged three months after the operation, which showed that the movement of abduction could be achieved for binocular. And the MRI of the brain exhibited that the residual lesion obviously shrunk (Figure 1). Also, the change for bilateral visual fields was displayed in Figure 2.

## **OUTCOME AND FOLLOW-UP**

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## **DISCUSSION**

IgG4-RD is a multiple organ-affected disease, whose clinical manifestations often vary from different organs. It was reported that several kinds of bacterial infection

could be a factor for this disease related to stimulation with toll-like receptor ligands<sup>[6, 7]</sup>. Several studies noticed the comorbidity of tuberculosis and IgG4-RD, in which this case was accordance<sup>[8-11]</sup>.

IgG4-RD of the CNS is mainly related to IgG4-related hypertrophic pachymeningitis and hypophysitis. Among them, IgG4 RHP is relatively rare, with the primary clinical manifestation of headache and other nerve function disabilities. Also, it was apparent that the cranial nerve function could partially recover when the disease remitted. At the first onset of the disease, the phenomenon of multi-organ affected is not widespread (57%)<sup>[6]</sup>. Therefore, it is required for regular follow-up and systemic evaluation.

Through this case, we summarized the differential diagnosis of IgG4 RHP, such as meningioma, tuberculosis meningitis, fungal meningitis and metastatic tumor. Also, the complete MRI images showed the lesion alteration during treatment. However, there were limited studies for this rare disease. And higher evidence-based studies are demanded to promote diagnosis and treatment of IgG4 RHP.

As for the diagnosis, it referred to the serum concentration of IgG4, radiology, and pathology examination. It was hard to distinguish IgG4-RHP and meningioma before the operation and pathologic examination. The serum level of IgG4 was able to facilitate diagnosis while it was not always increasing. As reported by Carruthers *et al*, sensitivity and specificity were separately 90% and 60%. Moreover, the negative predictive value and the positive predictive value of the serum IgG4 assay were respectively 96% and 34%, which could be helpful and convenient to exclude the diagnosis of IgG4-RD related to CNS<sup>[12]</sup>. And it is helpful to distinguish tuberculosis and IgG4-RD for the fact that serum IgG4 does not significantly increase in tuberculosis<sup>[13]</sup>. Further, imaging results could be a crucial clue for preoperative diagnosis. The lumbar puncture enabled to supply of the necessary information for differentiation from CNS infections and malignant tumors. IgG4 in cerebrospinal fluid was upward<sup>[14]</sup>. However, the concentration of IgG4 in cerebrospinal fluid was not supposed to identify this disease from other inflammatory pachymeningitis<sup>[6]</sup>.



Additionally, the radiology examination played an essential role in diagnosis. The lesion could be observed as a linear dural thickening or a bulging mass. Explicitly, the linear dural thickening lesion was able to appear both in the brain and spine. And the tumoral lesion was frequently located in the clivus area. The heterogeneity was observed on MRI because of active inflammation. Commonly, T1-weighted MRI would exhibit the hyperintense or isointense signal. And hypertrophic pachymeningitis was usually thickened and hypointense on T2 weighted MRI, while it would become relative hyperintensity when inflammation aggravated [3, 4, 6, 7, 15]. And the lesion would be homogenously enhanced through enhanced MRI. In this case, the lesion showed an isointensity signal in T1-weighted and T2-weighted images and homogenously got enhanced through contrast MRI with a dural tail sign. CT was able to recognize bone involvement, and the lesion would commonly be hyperdense and contrast when enhanced CT was performed. When it comes to meningioma, CT frequently displayed that the occupancy was isodensity or slightly higher density with the round, leafy, or flat shape<sup>[3, 6]</sup>. Calcification could be visible in some tumors<sup>[6]</sup>. Compared with IgG4 RHP, the meningioma had a similar characteristic. T1 weighted image was often presented on isointensity or mildly hypointensity signal, and T2 weighted image was usually presented on isointensity or mildly hyperintensity signal. Besides, the meningioma could be markedly characterized by the tail of the meninges.

It is advisable to focus on some characteristics when we face difficulty in identifying the meningioma and IgG4-RHP. We could notice that the symptom of IgG4 RHP was severe and diverse, while cases of meningioma would not exhibit these various symptoms. All these symptoms appeared with the inflammatory irritation and compression to adjacent nerves and dura mater<sup>[16]</sup>. Another characteristic of IgG4 RHP was that the tail signal was broader than meningioma on MRI for the diffuse inflammation along with the dura mater. The lesion of meningioma seems relatively confined and phymatoid compared with IgG4-RHP. Plus, the lesion of IgG4 RHP frequently implicated extracranial parts.

Moreover, other diseases like metastatic tumors and fungal infections should be considered. It was observed that metastatic tumors could spread and proliferate along meninges, causing various severe symptoms. In this situation, the history of malignant tumor provided clues to the diagnosis. Likewise, the central nervous system fungal infection can show similar features, which could be identified by the examination of cerebrospinal fluid.

Also, central nervous system tuberculosis is another antidiastole. Patients with tuberculous meningitis often have a fever, headache, and focal neurological symptoms. And tuberculous meningitis is often secondary to pulmonary or intestinal tuberculosis. As for radiology examination, CT often exhibits nodular or punctate calcifications and hydrocephalus, and enhanced scans are often accompanied by meningeal strengthening. MRI frequently shows a hypointense T1WI signal and hyperintense T2WI signal lesion. The enhancement scan could display irregular bar or nodular strengthening lesions of the meninges. Cerebrospinal fluid is essential for the diagnosis of tuberculous meningitis. Moreover, TB-IGRA could facilitate this diagnosis.

The purpose of the operation was not only to perform a biopsy but also to alleviate symptoms. We know that the lesion would distract meninges and then cause the symptom of headache. Similarly, the lesion oppresses cranial nerves to cause relevant symptoms. The resection could reduce meninges tension, release oppression and finally alleviate headache and nerve deficits. Further, it is suitable to use the transnasal endoscopic approach for a clival lesion of IgG4 RHP. When the lesion is too broad to remove altogether, it is rational to leave some parts and keep the integrity of the dura mater, which could prevent severe complications such as cerebrospinal fluid leakage and intracranial infection.

Accounting for the non-surgical treatment of IgG4 RHP, glucocorticoid, and immunosuppressor was considered to utilize. A consensus statement from Japan advised to initially treat patients with prednisolone (0.6 mg/kg/d) for four weeks. And the dose of steroid was gradually decreased through three to six months and finally maintained the dose of 2.5 to 5.0 mg/d for three years<sup>[17]</sup>. Other immunosuppressors

could be considered for attendant usages, such as methotrexate, cyclophosphamide, mycophenolate mofetil, and azathioprine<sup>[6, 7]</sup>. Also, some consensus recommended utilizing calcium carbonate and Vitamin D3 tablets to prevent Glucocorticoid-induced osteoporosis<sup>[18, 19]</sup>. Additionally, it is essential to exclude some latent infections before using glucocorticoids and immunosuppressors. In this case, the patient had a history of tuberculosis and we performed the chest CT and TB-IGRA test and so on to ensure being without present infection. Finally, it was a struggle and tortuous way for our patients to conquer the disease. When we meet a similar imaging alteration, serum IgG4 might be helpful for diagnosis.

## **CONCLUSION**

IgG4-RHP is a relatively rare disease that seems complicated to diagnose preoperatively. The purpose of surgery is to obtain the specimens required for pathological examination and then make the follow-up treatment. It is essential to perform a rigorous follow-up and systematic assessment of the whole body.

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SIMILARITY INDEX

PRIMARY SOURCES

1

Hailiang Tang, Guanfu Ding, Ji Xiong, Hongda Zhu, Lingyang Hua, Qing Xie, Ye Gong. "Clivus lesion revealed inflammatory pseudotumor associated with IgG4-related disease: a case report", World Neurosurgery, 2018

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