MPO-ANCA-Positive Hypertrophic Pachymeningitis With Elevated Serum IgG4: A Case Report and Literature Review.

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Case report

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Abstract

Background: We report a case of serum myeloperoxidase (MPO)-anti-neutrophil cytoplasmic antibody (ANCA)-positive hypertrophic pachymeningitis with elevated serum immunoglobulin G (IgG)4.

Case presentation: He was a 67-year-old man who appeared headache and hearing loss 7 years ago. He was treated with methylprednisolone and mycophenolate when he was diagnosed with hypertrophic pachymeningitis 2 years ago. He went to the hospital this time because of fatigue and appetite, the results of his blood tests indicated a progressive increase in creatinine and an increase in MPO and IgG4. His kidney biopsy revealed very few infiltrating IgG4-positive cells. Instead, fibrinoid necrosis of arterioles was observed. Considering the clinical process and these findings, the disease was considered more likely to be ANCA-associated hypertrophic pachymeningitis with elevated serum IgG4 level.

Conclusions: Our case highlights the importance of the pathological examination and the medical history. Pathological examination and previous medical history play an essential role in the diagnosis of the disease. Only when the disease is correctly diagnosed can it be further treated effectively and get a better prognosis.

Data Sources: Data were collected from the patient's electronic medical records and the hospital laboratory medicine database.

Background

Hypertrophic pachymeningitis (HP) is a rare disease in the department of neurology. It is a group of diseases characterized by localized or diffuse thickening and fibrosis of the cranial or spinal dura, or even both, with chronic headache, cerebral nerve damage, cerebellar ataxia, epilepsy and intracranial venous sinus thrombosis as the main clinical manifestations^[1, 2]. In epidemiological surveys in Japan, the incidence of hypertrophic pachymeningitis was 0.949/100,000^[3]. According to the etiology it can be divided into idiopathic and secondary HP. HP secondarily developing in association with a variety of conditions, such as infection (common pathogens are staphylococcus aureus, mycobacterium tuberculosis, fungi, pseudomonas aeruginosa, treponema pallidum), autoimmune disease, trauma and tumors^[4-8]. HP is labelled idiopathic in the absence of an identifiable cause [1]. Recently, Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and IgG4 related diseases have been shown to lead to hypertrophic pachymeningitis (HP), representing as many as 34.0% and 8.8% of all HP cases in Japan^[3]. In the article we report an interesting case of MPO-ANCA-positive hypertrophic pachymeningitis with elevated serum IgG4 level.

Case Presentation

A 67 years old Chinese male, complained headache accompanied by hearing loss, with obvious hearing loss in the right ear and obvious headache in the right temporal, and was admitted to the local hospital 7

years ago. Craniocerebral magnetic resonance (MRI) indicated thickening of the right dura which could be intensified. The patient was diagnosed as inflammatory pseudotumor and given treatment. Six years ago, the patient was treated with traditional Chinese medicine (the specific ingredient is not known), and the patient's hearing recovered slightly, and the headache symptoms were still worse. Three years ago, the patient had an epileptic seizure, and the enhanced computed tomography (CT) and MRI showed obvious uneven thickening and strengthening of the dura mater, and the right side was obvious. The patient is thought to have hypertrophic pachymeningitis and treated with glucocorticoids. Two years ago, the patient was admitted to a superior hospital and was finally diagnosed with hypertrophic pachymeningitis and treated with glucocorticoids and immunosuppressants. The patient was treated with levetiracetam for epilepsy control. Glucocorticoids and immunosuppressants were discontinued as prescribed by the doctor, and occasionally seizures occurred.

The patient was admitted to our hospital due to "fatigue with poor appetite for 20 days" this time. The patient showed fatigue, poor appetite, nausea, dizziness, and discomfort without obvious inducement 20 days ago, accompanied by lower limb pain after activity. He had no chest tightness, no suffocation, no palpitation, no discomfort in the centerless anterior area, no back pain, no facial edema and lower limb edema, and no significant decrease in urine volume, and he was admitted to our department for further examination and treatment. Since the onset of the disease, the patient has clear mind, general spirit, poor diet, poor sleep, basically normal urine and feces, weight loss. He has a history of stomach ulcers for more than 30 years. He suffered from coronary heart disease for 4 years and underwent coronary stent implantation due to acute myocardial infarction 4 years ago. He found his blood pressure elevated 20 days ago. He had no history of diabetes. He denied the history of infectious diseases such as hepatitis and tuberculosis. He had no history of trauma, blood transfusions, drug, or food allergies. He had no familial genetic disease and history of infectious diseases.

Physical examination at admission revealed that he had a temperature of 36.3°C, heart rate of 92 bpm, respiratory rate of 18 breaths per minute, blood pressure of 178/106 mmHg and oxygen saturation of 98% in room air. His physical examination showed no abnormality in cardiopulmonary abdominal examination and no edema in lower limbs.

Laboratory data revealed urine analysis: occult blood: 1+; urinary red blood cell: 24.70/ul, urine protein negative; Urinary renal tubule function display: urine α 1 microglobulin: 39.20mg/L; Blood routine: white blood cell count (WBC) : $12.74 \times 10^9/L$; neutrophil cell count (NEU): $9.38 \times 10^9/L$; red blood cell count (RBC): $2.85 \times 10^{12}/L$; hemoglobin (HB) : 80.00g/L; C-reactive protein (CRP): 113.21mg/L; Blood biochemistry: total protein (TP) 59.6g/L; albumin (ALB) : 21.6 g/L; urea nitrogen (BUN): 17.80 mmol/L; Creatinine (Cr): 365 μ mol/L; kalium (K): 3.39 mmol/L; sodium (Na): 129 mmol/L; chlorine (Cl): 91mmol/L; calcium (Ca): 1.92 mmol/L; Anti-neutrophil cytoplasmic antibody (ANCA): myeloperoxidase (MPO) 5.6 U/ml. Two days later, we reviewed the relevant blood test indicators, the results showed, ALB: 24.3g/L; BUN: 28.2mmol/L; Cr: 524 μ mol/L; Na: 130mmol/L; Cl: 93mmol/L; Ca: 1.98mmol/L; WBC: $31.42 \times 10^9/L$; NEU: $28.14 \times 10^9 /L$; RBC: $2.78 \times 10^{12} /L$; HB: 79.00g /L; ESR: 124. 00 mm/h; CRP: 103.59mg/L; complement 3(C3): 0.82g/L; rheumatism complete set was negative. MPO 7.4 U/ml; immunoglobulin G

(IgG)4: 4.9g/L; Abdominal ultrasound: no obvious abnormality was found in the liver, bile, pancreas and spleen, no obvious abnormality was found in the portal vein system and hepatic vein system. Parotid ultrasonography: no obvious abnormality was found in bilateral parotid glands. Submandibular gland ultrasound: no obvious abnormality was found in bilateral submandibular glands, and no obvious abnormality was found in bilateral neck. Lower limb vascular ultrasound showed: arteriosclerosis and plaque formation in both lower limbs, no obvious abnormality in deep veins of both lower limbs, and no obvious abnormality in superficial veins of both lower limbs. Echocardiography showed the abnormal segmental motion of the left ventricular wall and abnormal left ventricular filling. CT showed double emphysema, double pulmonary fiber foci, thickening of the stomach wall, slight inflammatory changes around both kidneys. CT showed no evidence of retroperitoneal fibrosis. Urological ultrasonography showed the normal volume of both kidneys, slightly stronger echo of the parenchyma of both kidneys, poor perfusion of color doppler imaging of blood flow of both kidneys, abnormal spectrum. Brain MRI revealed thickening of the dura mater (Fig. 1). The patient initially diagnosed acute renal failure. Combined with positive IgG4 and ANCA, we considered acute renal failure according two aspects: ANCA-associated vasculitis renal damage, and IgG4-related diseases. To confirm the pathological type, the patient underwent an ultrasound-guided renal biopsy. Pathological results indicated that the glomerulus presented diffuse ischemic changes, accompanied by diffuse renal tubulointerstitial damage, and a fibrinoid necrotic structure suggested that small vasculitis could not be excluded. The specific description is as follows: Immunofluorescence examination: one glomerular was detected, but no obvious fluorescence distribution was observed. IgA-, IgG-, C3-, F-, IgM-, C1q-, Kappa-, Lambda-. HE and special staining showed a total of 11 glomeruli, 2 of which were completely fibrotic, the capillary walls of the glomerulus were significantly shrunk, the segments were slightly thickened, the mesangial region was slightly proliferated, mesangial cells were 3–5/mesangial regions, mesangial matrix was slightly enlarged, endothelial cells were swollen, and one glomerulus was found to have focal segmentalized sclerosis with balloon adhesion. Masson staining showed no significant myoglobin deposition. About 60% of renal tubules were slightly atrophic, a few tubules were dilated and granulocyte degeneration was observed, a small amount of protein tubules were observed, and about 30% of renal interstitial fibrosis was observed, accompanied by more lymphocytes, plasma cells and scattered granulocyte infiltration. Immunohistochemistry: IgG4 were scattered (+), Congo red stain was negative (-) (Fig. 2). The fibrinoid necrosis of arteriole with inflammation was found in the interstitium (Fig. 3). A final diagnosis of acute renal failure, ANCA-associated microvasculitis was made. Subsequently, we treated the patient with methylprednisolone and mycophenolate, and the patient underwent regular outpatient review, with blood creatinine maintained at about 140umol/l.

Discussion

Hypertrophic pachymeningitis (HP) is a rare inflammatory disorder characterized by local or diffuse thickening of the intracranial or spinal dura mater [3, 9]. According to the etiology it can be divided into idiopathic and secondary HP. Secondary HP can be associated with ANCA-associated disease, IgG4-related disease, syphilis, tuberculosis, rheumatoid arthritis, and cancer [10]. Clinically, enhanced brain MRI

is the most useful examination for the diagnosis of HP, and it also can exclude other differential diseases as required ^[10]. The patient went to see a doctor due to recurrent headache, hearing loss and epileptic seizure. Examinations such as brain MRI and lumbar puncture were performed and the patient was diagnosed as hypertrophic pachymeningitis. No evidence of infection was found at that time. The symptoms were relieved after the administration of methylprednisolone shock treatment, and then long-term oral methylprednisolone and mycophenolate as the maintenance treatment.

The patient went to the hospital this time because of fatigue and poor appetite. Laboratory tests showed positive IgG4 and positive MPO, considering that IgG4-related diseases and ANCA-associated vasculitis could not be excluded.

IgG4-related disease (IgG4- RD) is chronic and progressive autoimmune disease of unknown cause that can lead to fibroinflammatory lesions in almost all organs ^[11, 12]. The serum IgG4 cell level of the patient with IgG4- RD was significantly increased, and the affected tissues and organs were enlarged or nodular/proliferative lesions due to the abundant infiltration of lymphocytes and IgG4-positive plasma cells and the tissue fibrosis. The central nervous system mainly involves the pituitary gland, dura mater and skull ^[13]. The disease can cause multiple organs to be affected simultaneously or successively, or it can involve only one organ. The prominent serological characteristic of IgG4-RD was the elevation of IgG4 level.

Serum IgG4 concentration increases are neither sensitive nor specific for the diagnosis of IgG4-RD, but it is still considered as one of the important indicators for the diagnosis of IgG4-RD ^[14]. Serum IgG4 concentration can be normal in 3%-30% patients with IgG4-RD ^[15]. Moreover, elevated serum IgG4 concentrations can also be seen in other conditions, such as patients with interstitial lung disease, ANCA associated vasculitis, malignant tumors, and allergic diseases ^[12, 16, 17]. The diagnosis of IgG4-RD depends on histopathology, clinical imaging, serological and related immunological examination. Current diagnostic criteria include the following three, one is the enlarged or hypertrophic affected organs, the second is the elevated serum level of IgG4 (≥ 135 mg/dl), and the third is the pathological findings (ratio of IgG4+/ IgG + cells $> 40\%$ and ≥ 10 IgG4 + plasmacytes/high power field ^[18, 19]. The patient had only elevated serum IgG4 and did not meet the diagnostic criteria for IgG4-RD diseases.

ANCA-associated vasculitis (AAV) is the most common cause of HP ^[20]. An investigation in Japan found that HP caused by AAV accounted for 34%, significantly higher than HP caused by IgG4-RD, which accounted for 8.8% ^[3]. The patient was MPO positive for many times, and ANCA-associated vasculitis could not be excluded from the diagnosis.

AAV is a rare necrotizing vasculitis with few or no immune deposits, characterized by inflammation and fibrinoid necrosis of the small vessel wall as the main pathological manifestations ^[20]. AAV can affect any one of the system organs. Recently, AAV has been shown to lead to hypertrophic pachymeningitis (HP), which accounts for most AAV cases ^[20]. In the acute phase, patients with AASV usually have increased ESR, increased CRP, and increased white blood cell count. Some patients usually have normal

or mildly decreased complement C3. The patient was consistent with the above acute stage and MPO was positive for many times, and the pathology of renal biopsy was fibrinoid necrosis of small arteries. AAV was considered to be a definite diagnosis of this patient.

The patient was previously diagnosed with hypertrophic pachymeningitis and had been treated with methylprednisolone and mycophenolate. The laboratory test after admission this time revealed elevated levels of MPO and IgG4. Laboratory results and pathology suggested AAV. With the vasculitis under control, the patient had no further seizures. The patient had been positive for urinary protein at the time of diagnosis of hypertrophic dura meningitis. Using disease monism to explain, this patient's AAV may be the cause of hypertrophic pachymeningitis. It has been reported that AAV is the most common cause of HP ^[20] and the patients with ANCA-associated vasculitis could show elevated serum IgG4 levels even if they did not meet IgG4-related disease criteria ^[21]. Finally, we diagnosed the patient with MPO-ANCA-positive hypertrophic pachymeningitis with elevated serum IgG4.

Conclusions

We summarize the following points from this case. First, special attention should be paid to an elevated serum level of IgG4 as a marker of IgG4-RD or other associated disorders, especially when a patient is positive for ANCA. AAV can show elevated serum IgG4 levels. Second, in complex diseases, especially those that are difficult to differentiate and diagnose, it is very important to improve the pathological examination in time and pay attention to the patient's response to treatment. Third, don't ignore the history. Patients with rare diseases in the past must carefully analyze their medical history and treatment history, and look for the relationship between the history and the current disease in order to find the most effective treatment.

List Of Abbreviations

MPO: myeloperoxidase; ANCA: anti-neutrophil cytoplasmic antibody; HP: hypertrophic pachymeningitis; IgG4: immunoglobulin G (IgG)4; MRI: magnetic resonance; CT: computed tomography; IgG4- RD: IgG4-related disease; AAV: ANCA-associated vasculitis.

Declarations

Ethics approval and consent to participate

The patient gave his consent for the publication of this case report and any accompanying images.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editors-in-Chief of this journal.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

Yanxia Gao and Zhaoli Gao participated in its design and drafted the manuscript. Zhaoli Gao collected the clinical and imaging data. Zhao Hu helped to draft the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

Brain MRI revealed thickening of the dura mater. Red arrows indicate the thickened dura mater.

Figure 2

Histologic features of section of kidney biopsy($\times 400$). It indicated that the glomerulus presented diffuse ischemic changes, accompanied by diffuse renal tubulointerstitial damage, and a fibrinoid necrotic structure suggested that small vasculitis could not be excluded. HE: hematoxylin-eosin staining; Masson: Masson staining; PAS: Periodic acid Schiff; PASM: periodic acid-silver methenamine.

Figure 3

The fibrinoid necrosis of arteriole with inflammation was found in the interstitium($\times 400$). HE: hematoxylin-eosin staining; Masson: Masson staining; PAS: Periodic acid Schiff; PASM: periodic acid-silver methenamine.