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A Case Report of Idiopathic Hypertrophic Pachymeningitis

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Summary. Idiopathic hypertrophic pachymeningitis (IHP) is a condition characterised by diffuse or local thickening and fibrosis of dura matter caused by inflammation of unknown origin. It is a diagnosis of exclusion. Autoimmune disorders (notably ANCA-associated vasculitis (AAV) and IgG4-related disease) pose one of the greatest diagnostic challenges in the differential diagnosis of hypertrophic pachymeningitis (HP). When these conditions are concerned, differential diagnosis without biopsy could not be certain, as there are no specific clinical or radiological features of local (only CNS affecting) AAV, IgG4-related disease, and idiopathic HP. We present a case of a 63-year-old female who attended our department due to severe headache and diplopia. After extensive testing, IHP was diagnosed. However, the patient was reluctant to dural biopsy, leaving the possibility of AAV or IgG4-related disease. Since patients with IHP and secondary HP often exhibit similar clinical and radiological signs, dural biopsy is crucial for the diagnosis. The presented clinical case focuses on the importance of dural biopsy for the exclusion of secondary causes of HP and establishing a definite diagnosis.

Keywords: idiopathic hypertrophic pachymeningitis, secondary hypertrophic pachymeningitis, IgG4-related disease, ANCA-associated vasculitis.

INTRODUCTION

Idiopathic hypertrophic pachymeningitis (IHP) is a disorder marked by widespread or localized thickening and fibrosis of the dura mater produced by an unknown source of inflammation [1]. IHP is the most frequently diagnosed type of hypertrophic pachymeningitis (HP) [2]. However, secondary causes, such as infectious, neoplastic, and autoimmune disorders, can also induce the thickening of dura matter [1]. Thus, IHP is usually the diagnosis of exclusion. Although diagnosing an infectious cause and malignancy has its own difficulties, extensive radiological imaging, serology, sputum, bronchoalveolar lavage (BAL), and cerebrospinal fluid (CSF) analysis are usually sufficient to ascertain the correct diagnosis. In contrast, some autoimmune causes, particularly ANCA-associated vasculitis (AAV) and IgG4-related disease, can only be excluded if dural biopsy with histopathological examination is performed [1, 3, 4]. Yet, only in a small proportion of HP cases, dural biopsy is taken [2]. Obtaining dural biopsy to ascertain the cause of HP could be challenging considering patients' reluctance for intervention. On the other hand, when distinguishing between AAV, IgG4-related disease, and IHP, the need for such intervention can be questioned, as all of these disorders are often treated with glucocorticoids or immunosuppressants, followed by rituximab in treatment-resistant cases [1, 5]. Nevertheless, the diagnosis without biopsy cannot be certain, as there are no specific clinical or radiological features of local (only CNS effecting) AAV, IgG4-related disease, and idiopathic HP, and laboratory findings usually intertwine [2]. AAV is diagnosed using classification criteria rather than diagnostic criteria, which do not necessarily result in a correct diagnosis [3]. This is especially true, when AAV presents with unusual symptoms and clinical findings. Although rare, HP is one of the atypical AAV presentations mentioned in the literature [6]. Similarly, IgG4-related disease rarely affects the pachymeninges, and when it occurs, it is often associ-

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ated with the involvement of other organs [7]. Yet, in a small proportion of IgG4-related HP cases (precisely 30%), HP was found to be the only presentation of the disease [7]. In addition, the clinical, histopathological, radiological, and demographic similarities of IgG4-related disease and IHP have led some authors to believe that some cases of HP previously classified as idiopathic should be reclassified as caused by IgG4-related disease [1]. These observations, together with the fact that only a minority of HP cases are pathologically proven, suggest that IHP may be overreported.

We present the case of a 63-year-old female who was diagnosed with IHP after secondary causes were ruled out. However, the diagnosis of AAV or IgG4-related disease remained possible, emphasizing the importance of dural biopsy in the differential diagnosis of HP.

CASE PRESENTATION

A 63-year-old female presented to our department due to severe headache recurring during night sleep over a 2-month period. It was usually relieved by non-steroidal anti-inflammatory drugs. In addition, 4 days before admission, the patient developed diplopia that was evoked by right-sided gaze. The patient had a history of arterial hypertension which was well controlled with antihypertensives; no other chronic or oncological diseases were previously diagnosed.

Neurological examination showed significant horizontal diplopia when looking to the right, which disappeared with both eyes closed. No obvious ophthalmoplegia or nystagmus was observed. The initial brain CT showed no signs of acute intracranial pathology. On admission, blood tests (complete blood count (CBC) with differential, concentration of glucose, electrolytes, urea, and creatinine) were normal, except for slight elevation of C-reactive protein (11.6 mg/L). Further testing revealed cerebrospinal fluid (CSF) pleocytosis of 13 cells/ L with mononuclear predominance (89.4%) and increased protein (0.74 g/L). CSF flow cytometry was negative for haematological malignancy. Serum protein electrophoresis was normal, serum IgM and IgG antibodies for Lyme disease were negative. Brain MRI (Fig.) was performed. It showed mild bilateral cortical diffusion restriction of the frontal lobes, T2 hyperintensity of bilateral frontal cortex, contrast enhancement, and bilateral thickening of the dura mater. Additional findings included mucosal thickening of maxillary sinuses, ethmoidal cells, and the left frontal sinus.

It was found that the patient experienced Raynaud's phenomenon, recurrent upper chest rash related to UV exposition, and frequent episodes of epistaxis, which were successfully treated with thermocoagulation 4 years ago. Moreover, the patient suffered from chronic serous otitis media. Further testing was carried out to ascertain the cause of pachymeningitis and to rule out infection, cancer, and autoimmune diseases. Chest radiography, abdominal ultrasound, nasal endoscopy, capillaroscopy, urinalysis, CBC, erythrocyte sedimentation rate, complement (C3 and C4) and other rheumatology screening tests (anti-dsDNA, anti-beta-2 glycoprotein-1, anti-cardiolipin, anti-nuclear and extractable nuclear antigen antibodies) were unremarkable. The patient refused dura mater biopsy to be performed. However, anti-neutrophil cytoplasmic antibodies with perinuclear staining (p-ANCA or MPO-ANCA) were positive (titer 1:40). In addition, serum IgG4 level was elevated (2.465 g/L). Hence, rheumatologic disorder was suspected as a possible cause of hypertrophic pachymeningitis.

Nevertheless, with the assistance of rheumatologists, who concluded that the findings were insufficient to classify the disease as p-ANCA-related systemic vasculitis (due to the lack of classification criteria) and as IgG4-related disease (due to the lack of diagnostic criteria), the diagnosis of idiopathic hypertrophic pachymeningitis was made. After the exclusion of infectious and oncological processes, treatment with intravenous dexamethasone (4 mg b.i.d.) was initiated. The patient reported a decline in diplopia and a complete absence of headache the following week. Upon discharge, dexamethasone was replaced with oral prednisolone (25 mg b.i.d.).

Follow-up MRI without contrast (the patient refused to use it due to a previous adverse reaction to the contrast material) after nearly two months showed a marked decrease

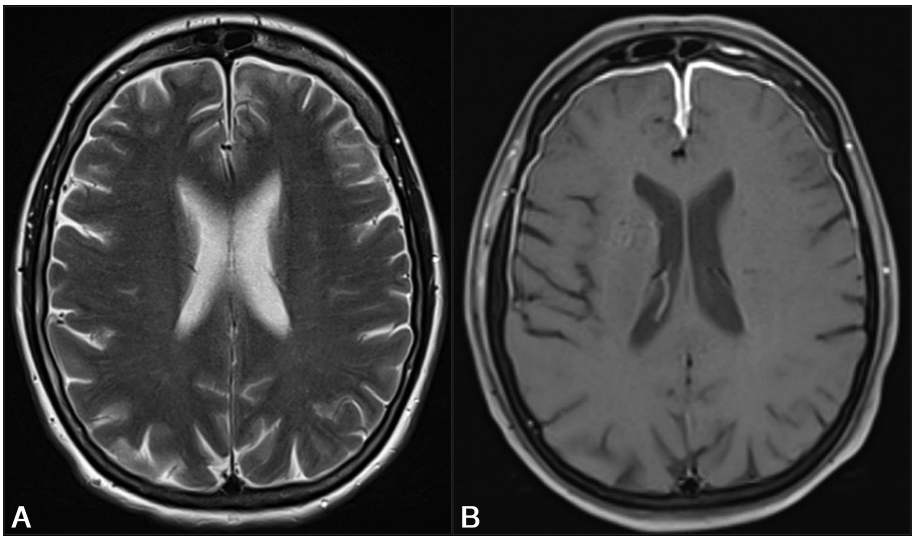

Fig. **Axial T2-weighted (A) and T1-weighted image (B) of brain MRI demonstrating mild T2 hyperintensity of bilateral frontal cortex and contrast enhancement of the dura mater**

in diffusion restriction in the frontal lobes. Clinically, headache and diplopia resolved completely with glucocorticoid treatment. The patient had no complaints, routine neurological examination was normal.

DISCUSSION

In the case presented, initial symptoms of the patient were headache and diplopia – the most commonly reported manifestation of HP [2]. To ascertain the diagnosis, lumbar puncture and brain MRI were performed. Since the findings suggested the diagnosis of HP, additional testing was carried out to determine possible secondary causes. After exclusion of infectious diseases and malignancy, a possible autoimmune etiology was suspected. However, it should be noted that serological tests for syphilis and CSF, sputum and BAL fluid polymerase chain reaction for tuberculosis were not performed. We agree that these tests are important in establishing the diagnosis of HP, although these causes of HP are extremely rare [2], especially considering the patient's refusal to perform dural biopsy. This is one of the limitations of this case report. More extensive testing on other possible causes (sarcoidosis, CNS fungal infections, some viral infections, notably Epstein-Barr virus, etc.) may also have been helpful in establishing the diagnosis.

Raynaud's phenomenon, recurring upper chest rash caused by UV exposure, and chronic serous otitis media all contributed to the suspicion of autoimmune etiology. AAV and IgG4-related disease are the two most common groups of autoimmune disorders associated with HP [2]. Granulomatosis with polyangiitis (GPA) is the most prevalent type of AAV that can cause HP [8]. Involvement of the upper and lower respiratory tract, together with urine changes due to kidney damage and granulomatous inflammation, are characteristic features of GPA included in the classification criteria for GPA [9]. Nevertheless, GPA, like other AAVs, has no proposed diagnostic criteria, only the classification mentioned above. This is partly due to the great heterogeneity of AAV presentations [10]. Classification criteria are used in the diagnosis of AAV; however, they do not allow identification of every case of AAV with 100% accuracy [10]. Thus, some cases might be misclassified. The issue of classification criteria becomes more important when atypical presentations of AAV occur. For example, Katikineni et al. described 8 atypical cases of AAV in a cohort of 171 patients, arguing that atypical presentations can significantly delay diagnosis and treatment [6]. One of the described atypical presentations of AAV is HP caused by GPA [6]. Indeed, the diagnosis of AAV can often be challenging, given the ability of AAV to cause both systemic and local (affecting only CNS) disease [2, 8, 11]. MRI findings in our case included mucosal thickening of the maxillary sinuses, ethmoidal cells, and the left frontal sinus. In addition, the patient suffered from chronic serous otitis media, had episodes of epistaxis, and was p-ANCA positive. These findings were indicative of AAV, as they are more common in patients with HP secondary to AAV [2, 6, 8]. However, we excluded AAV as the cause of HP because the patient did not meet the criteria for AAV classification. Nevertheless, due to the patient's refusal to undergo dural biopsy, we could not rule out HP secondary to AAV indefinitely.

IgG4-related disease is another possible autoimmune cause of HP, characterised by IgG4 positive cell tissue infiltration and fibrosis [7]. The pancreas, salivary glands, biliary ducts, and retroperitoneum are the most frequently affected organs in IgG4-related disease, but pachymeningeal damage is also possible [12]. In HP secondary to IgG4-related disease, organ systems other than the CNS are commonly affected; however, isolated cases of HP may occur [7]. IgG4-related disease is diagnosed according to diagnostic criteria that include characteristic radiological and clinical signs of IgG4-related disease affecting at least one organ, elevated blood IgG4 level, and typical biopsy findings [4]. We considered the possibility of IgG4-related disease in our clinical case, thus serum IgG4 concentration was measured. Serum IgG4 concentration was elevated, therefore according to diagnostic criteria, IgG4-related disease was possible [4]. Unfortunately, we were unable to confirm the diagnosis of Ig4-related disease despite elevated IgG4 level due to the lack of dural biopsy, as a definite diagnosis requires histopathological analysis [4].

In the case presented, an overlap of features suggestive of AAV (mucosal thickening of maxillary sinuses, ethmoidal cells, and the left frontal sinus, chronic serous otitis media, elevated p-ANCA) and IgG4-related disease (elevated serum IgG4 level) was present. This overlap between AAV and IgG4-related disease is reported in approximately 4% of HP cases [2]. The phenomenon is primarily seen in patients with GPA, suggesting a pathogenetic link between GPA and IgG4-related disease [13]. However, as no dural biopsy was obtained, it is unclear whether this is a true overlap syndrome or just a coincidental finding.

CONCLUSSIONS

HP can be caused by various reasons, and its differential diagnosis is often a challenge. We presented the case of a 63-year-old female patient whose initial HP symptoms were headache and diplopia. However, after extensive testing the cause of HP was not established because dural biopsy, which is one of the key elements in HP diagnosis, could not be obtained. Although a diagnosis of possible IgG4-related disease can be made for this patient, it cannot be definite without histopathological analysis. Thus, without dural biopsy, the diagnosis of IHP cannot be made with certainty, as clinical and radiological signs and laboratory screenings in patients with IHP and autoimmune diseases often overlap.

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KLINIKINIO HIPERTROFINIO PACHIMENINGITO ATVEJO APRAŠYMAS

Santrauka

Idiopatinis hipertrofinis pachimeningitas (IHP) yra būklė, kuriai būdingas difuzinis ar lokalus kietojo smegenų dangalo sustorėjimas ir fibrozė, kurią sukelia neaiškios kilmės uždegiminis procesas. Dažniausiai IHP yra diagnozuojamas tik atmetus galimas antrines hipertrofinio pachimeningito (HP) priežastis. Autoimuninės ligos (dažniausiai ANCA asocijuoti vaskulitai (AAV) ir su IgG4 susijusi liga), ypač kai pasireiškia lokalizuota forma (tik CNS), apsunkina HP diferencinę diagnostiką. Paprastai norint atmesti minėtas patologijas kaip antrines HP priežastis, reikia atlikti biopsiją, kadangi, esant lokaliai HP formai, specifinių klinikinių, radiologinių ir kraujo pokyčių, padedančių diferencinėje diagnostikoje, nėra. Šiame straipsnyje aprašoma 63 metų pacientė, kuriai HP pasireiškė galvos skausmu ir dvejinimusi akyse. Pacientei atlikti išsamūs laboratoriniai, instrumentiniai tyrimai, tačiau pirminė HP priežastis nebuvo identifikuota. Remiantis turimais duomenimis, suformuluota IHP diagnozė. Pacientė atsisakė smegenų kietojo dangalo biopsijos, todėl nebuvo galima užtikrintai atmesti AAV ir su IgG4 susijusios ligos diagnozių. Kadangi pacientai su IHP ir antriniu HP dažnai turi panašius klinikinius simptomus, o iš radiologinių vaizdų yra sunku nustatyti tikslią diagnozę, smegenų kietojo dangalo biopsija yra būtina. Pristatytas klinikinis atvejis ir parodo kietojo dangalo biopsijos svarbą, atmetant antrines HP priežastis ir nustatant tikslią diagnozę.

Raktažodžiai: idiopatinis hipertrofinis pachimeningitas, antrinis hipertrofinis pachimeningitas, su IgG4 susijusi liga, ANCA asocijuotas vaskulitas.

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