American Journal of Clinical Neurology and Neurosurgery
Vol. 2, No. 1, 2016, pp. 1-4
http://www.aiscience.org/journal/ajcnn

Uveitis and Hypertrophic Pachymeningitis with Elevated Myeloperoxidase and p-ANCA Antibodies Secondary to IgG4 Disease

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Abstract

Objective: The objective of this paper is to present a case report of IgG4 disease with associated hypertrophic pachymeningitis and panuveitis that primarily presented to an eye clinic for evaluation of symptoms. The purpose of this paper is to help clinicians realize the broad clinical differential of panuveitis when presenting with concurrent systemic complaints. *Methods:* A 52-year-old Hispanic female with a history of panuveitis of the left eye presents with left eye pain, severe headaches, confusion and dizziness. Ophthalmic examination of the left eye revealed nongranulomatous panuveitis and optic disc edema. She was started on topical corticosteroids, however her vision continued to deteriorate and her systemic symptoms became more prevalent. She was admitted for further evaluation and for initiation of intravenous corticosteroids due to the severity of presentation. *Results:* She was diagnosed with idiopathic hypertrophic pachymeningitis after clinical, radiological, and laboratory evaluation. Dural biopsy was performed and histopathologic analysis revealed IgG4 cell population predominance consistent with IgG4-related disease. *Conclusion:* We report a case of uveitis and hypertrophic pachymeningitis as manifestations of systemic IgG4 disease with elevated p-ANCA and myeloperoxidase antibodies.

Keywords

IgG4 Disease, p-ANCA, Myeloperoxidase, Pachymeningitis, Uveitis

Received: Aguest 21, 2015 / Accepted: November 8, 2015 / Published online: January 8, 2016

1. Case

A 52-year-old Hispanic female with a history of panuveitis of the left eye for the past seven months was referred from another hospital for evaluation of severe headaches, dizziness and mild confusion in addition to persistent left eye pain and blurry vision. She was treated by many providers with an unclear history of multiple topical ocular medication use, including antibiotics and steroids, without resolution of symptoms. Past medical history was remarkable for previously treated systemic toxoplasmosis infection. Her visual acuity at presentation was 20/400 via Snellen with pinhole to 20/60 in the right eye and 20/70 in the left eye. Intraocular pressures were within an acceptable range. An afferent pupillary defect was present in the left eye. Ophthalmic examination of the left eye showed two clock hours of sectoral scleral injection, 3+ cells in the anterior chamber, posterior synechiae, a nuclear sclerotic cataract, and 2+ vitreous cells. No granulomatous keratic precipitates or granulomatous lesions were found on exam. Fundus examination showed grade II optic disc edema, cystoid macular edema, and tortuous vessels in the left eye. Anterior segment and dilated fundus examination of the right eye was unremarkable except for nuclear sclerotic cataract. There were no signs of anterior chamber or vitreous cell, keratic precipitates, or optic disc edema in the right eye. Prednisolone acetate and atropine drops were initiated to decrease inflammation, prevent posterior synechiae, and

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improve patient comfort.

Due to the patient's severe uveitis presentation and neurological symptoms, neuroimaging was performed. Magnetic resonance imaging (MRI) of the brain with and without gadolinium-chelated contrast showed significant leptomeningeal enhancement in the left parietal-occipital region and posterior fossa (Figure 1). CSF analysis demonstrated atypical lymphocytosis, low glucose, no organisms on Gram stain, no malignant cells on cytology, and few oligoclonal bands consistent with aseptic meningoencephalitis. Laboratory tests revealed elevated serum levels of myeloperoxidase (MPO) antibodies with a strongly positive perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) titer of 1:40 (reference < 1:20) and elevated IgG level of 1728mg/dL (reference 716-1554mg/dL). Given the severity of uveitis and inclusion of masquerade syndromes such as lymphoproliferative disorders on the differential diagnosis, a vitreous biopsy was performed and was confirmed negative for malignancy and infectious etiology. The patient was commenced on oral steroids after ruling out any inciting or concurrent systemic infection.

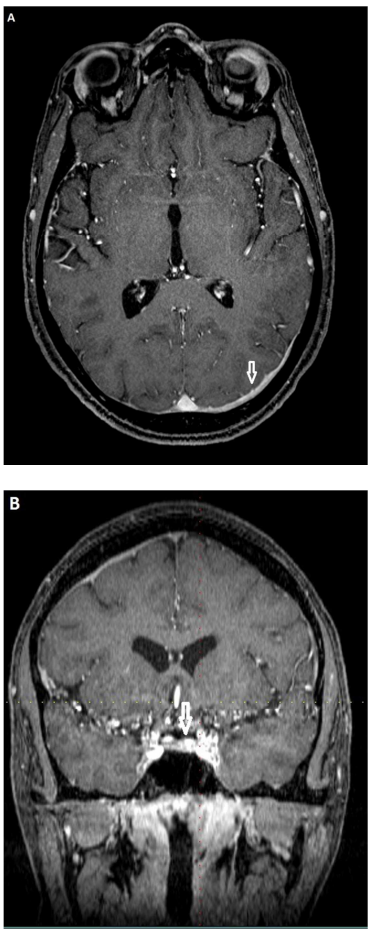

Figure 1. MRI of the brain showing significant leptomeningeal enhancement in the left parietal-occipital region (A) and posterior fossa (B). No abnormal enhancement of the orbit or optic nerves.

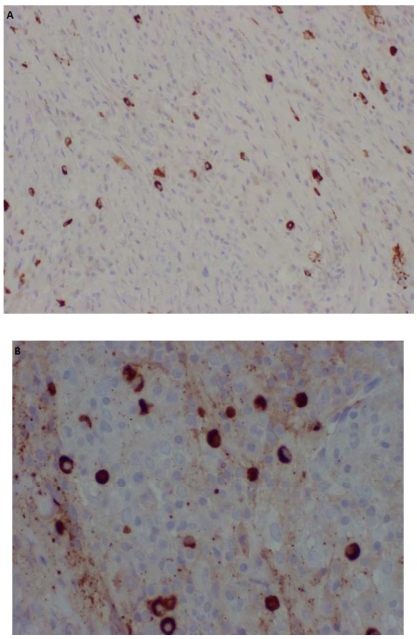

Figure 2. Immunohistochemistry showing an increased number of IgG4-positive plasma cells (IgG4+: 33.6/HPF), consistent with hypertrophic pachymeningitis due to IgG4 disease. A. IgG4-IHC low magnification. B. IgG4-IHC high magnification.

One week post-operatively, the patient's visual acuity failed to improve in the left eye while on oral steroid therapy. She continued to have worsening headache, confusion and left eye pain which were associated with persistent nausea in the setting of normal intraocular pressures. She was admitted for further evaluation and for intravenous pulse-dosed corticosteroids. Biopsy of the left dura was subsequently performed to evaluate the radiographic finding of hypertrophic pachymeningitis. Histopathologic examination confirmed hypertrophic pachymeningitis with an increased number of IgG4-positive plasma cells, meeting the diagnostic criteria of IgG4-related disease (Figure 2). The patient moved out of state immediately following completion of her hospitalization and her continued medical care was transferred to her local institution.

2. Discussion

IgG4-related disease is an autoimmune condition first recognized in autoimmune pancreatitis and later found to affect virtually any organ system with an infiltration of IgG4-positive plasma cells [1]. The pathogenesis of IgG4-related hypertrophic pachymeningitis remains unclear. Recent studies have hypothesized that IgG4-related disease involves CD4-positive T cells and activated IgG4-positive B cells in response to an antigen [2]. The consequent activation of CD4-positive T cells causes an inflammatory response and facilitates fibroblast activation [3]. The trigger responsible for stimulating B-cell to produce IgG4 antibody is not fully understood. The immunoregulatory cytokine interleukin-10

has been shown to induce the class switching of B cells to secrete IgG4 antibodies [4, 5].

IgG4 disease has certain characteristics that can help to point the clinician towards diagnosis; however, these characteristics are somewhat vague and can mimic several other disease processes. These characteristics include hyperplasia or fibrosis causing enlargement of various organs, multi-system involvement, varying symptoms depending on organ involvement, IgG4 infiltration of organs, and responsiveness to steroid therapy [6].

Hypertrophic pachymeningitis is a rare condition described as thickening of the cranial or spinal cord dura mater, which can be caused by a wide spectrum of diseases including vasculitides, autoimmune disorders, malignancies, and infections.[7] When there is no clear etiology, the disease is termed idiopathic hypertrophic pachymeningitis. Recently, Wallace et al. showed that up to 67% of hypertrophic pachymeningitis cases that were initially thought to be idiopathic are actually related to IgG4 disease [7]. The dura mater, also called the pachymeninges, is believed to be primarily affected in IgG4-related disease but concomitant involvement of the pia and arachnoid mater, making up the leptomeninges, may also play a role [1, 7].

The diagnosis of hypertrophic pachymeningitis is dependent on histopathological examination of the dura. In addition to an increased number of tissue IgG4-positive plasma cells, the recently published 2012 consensus criteria for IgG4-related disease requires at least one of the following histopathological features: dense lymphoplasmacytic infiltrate, fibrosis and obliterative phlebitis [8]. MR imaging of the brain with contrast can be helpful in visualization of the affected lesion; however, radiologic imaging is not necessary for diagnosis due to the variation of appearance among cases [7]. CT scan with contrast may be beneficial to visualize dural lesions and evaluate for concurrent bone involvement [9].

The neurological manifestations of IgG4-related hypertrophic pachymeningitis usually stem from active compression of nerve or vascular tissue from the thickened dura mater leading to neurological deficits [9]. The neurological symptoms from most common to least common include headaches, cranial nerve palsies, visual deficits such as diplopia or vision loss, decreased strength and numbness. A recent literature review of the disease epidemiology suggests a predilection for men with a mean diagnosis of 53 years (range 32-82 years) [3, 9].

Serum IgG4 levels are elevated in 70%-90% of patients with IgG4-related disease, including Ig-G4-related hypertrophic pachymeningitis. Since the inflammation in hypertrophic pachymeningitis occurs at the dura mater close to the blood-brain barrier and CSF, IgG4 concentrations in the CSF may rise while serum IgG4 concentrations remain normal.[9] If serum levels of IgG4 increase, this usually suggests an underlying systemic disease beyond the meninges [9]. Therefore, an elevation of IgG4 is not specific for the diagnosis of IgG4-related hypertrophic pachymeningitis, and histopathological examination remains the gold standard [10]. Lumbar puncture and CSF analysis are important to exclude neural infections and malignancies.

The treatment of hypertrophic pachymeningitis relies on identification of the underlying condition. For cases of hypertrophic pachymeningitis that are associated with IgG4 disease, the treatment recommendation is glucocorticoids without a defined optimal regimen or maintenance dose [11]. Although the initiation of glucocorticoids often results in rapid remission, the symptoms usually return once the prednisone is tapered [11]. The increased resistance to corticosteroid therapy prompts the use of immunosuppressive therapy such as azathioprine or mycophenolate mofetil with limited data on efficacy [12]. Rituximab, an anti-CD20 monoclonal antibody, has recently been used as a promising option with significant clinical improvement in corticosteroid-refractory cases [7, 13, 14]. The drug targets B-cells that produce IgG4, resulting in a reduction of the IgG4 subclass alone [13, 14]. Spontaneous remission without treatment has also been reported in a few cases [7].

While there is a multitude of cases on pancreatic IgG4 disease, there is currently no meaningful data on the relapse rate of extrapancreatic IgG4-related disease. Monitoring serum IgG4 levels have produced ambiguous results in studies on pancreatic IgG4 disease. According to Kamisawa et al, only 63% of patients achieve normal serum IgG4 levels with treatment and of those who have persistently elevated IgG4 levels, only 30% have relapses [15]. Although an inexact indicator of disease recurrence, elevated serum concentrations of IgG4 during the remission phase require close clinical follow-up [11].

The ocular manifestations of IgG4 disease ranges from inflammation of the orbit and lacrimal gland that mimics Sjogren's disease to unusual ocular involvement causing scleritis, uveitis, bilateral optic neuropathy, optic nerve perineuritis, and pseudotumor of the orbit [16]. The case presented here demonstrates hypertrophic pachymeningitis with associated panuveitis in the setting of elevated IgG4 and p-ANCA antibodies against MPO. To our knowledge, there has been no other reported case with the combination of both ocular and meningeal involvement with our laboratory profile. The co-occurrence of elevated c-ANCA antibodies and IgG4-related disease, such as in granulomatosis with polyangiitis, is not uncommon. However, an elevated p-ANCA level in IgG4-related disease is rather rare with only

two other cases reported, neither of which had ocular involvement [17, 18]. Although the presence of MPO antibodies is specific to microscopic polyangiitis in the presence of positive p-ANCA, our patient had normal renal function and hypertrophic pachymeningitis, which can also present with positive p-ANCA. Given the limited data on the correlation between p-ANCA and IgG4-related disease, further studies are necessary to define the role of p-ANCA positivity and IgG4 elevation in the pathogenesis of hypertrophic pachymeningitis.

This case emphasizes the broad differential for panuveitis presenting to the ophthalmology clinic with accompanied systemic complaints and the importance of a multidisciplinary approach to obtaining the diagnosis and managing treatment. Limitations of this case presentation include the lack of long term follow up and post-treatment clinical course.

3. Conclusion

IgG4-related disease is increasingly being recognized as a systemic process of autoimmune origin, although definitive pathogenesis has not been established. The association between hypertrophic pachymeningitis and IgG4 disease has recently been recognized based on the new consensus diagnostic criteria. While IgG4-related disease can affect any organ system, the histopathological features remain similar. Corticosteroids are the first-line treatment for pancreatic IgG4 disease; however, rituximab has recently shown to be effective in treating extrapancreatic IgG4-related disease. With the rising data on IgG4 disease, physicians may gain familiarity in recognizing clinical manifestations of rare autoimmune causes.

Acknowledgements

The authors would like to acknowledge Dr. Marie Rivera-Zengotita, MD, University of Florida's Department of Pathology for providing the histopathological images of the patient's dura biopsy.

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