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Case Report

A Case of Hypertrophic Pachymeningitis Associated with Immunoglobulin-G4 and c-ANCA

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Hypertrophic pachymeningitis · IgG4 · c-ANCA · IgG4-related disease

Abstract
Hypertrophic pachymeningitis (HP) is characterized by inflammation of the dura mater. It has been described in the setting of numerous systemic inflammatory diseases including immunoglobulin G4 (IgG4)-related disease as well as granulomatosis with polyangiitis (GPA). In this case report, we describe a 48-year-old man presenting with headache who was found to have HP and had systemic features of both GPA and IgG4-related disease as well as seropositivity for both cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) and IgG4. He was treated with prednisone and rituximab with improvement in his symptoms. Co-occurrence of IgG4 and ANCA against myeloperoxidase has been reported in other cases of HP. The overlap between IgG4 and ANCA has also been described in other systemic manifestations of the diseases. These reports suggest a clinical overlap between ANCA and IgG4-related disease, and the case presented herein suggests an overlap between GPA and IgG4-related disease.

Introduction

Hypertrophic pachymeningitis (HP) is defined as inflammation and thickening of the dura mater [1]. Etiologies include: systemic inflammatory diseases such as sarcoidosis,

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granulomatosis with polyangiitis (GPA), rheumatoid arthritis, and immunoglobulin G4 (IgG4)-related disease; infectious diseases including syphilis, tuberculosis, and Lyme disease; intracranial hypotension; and reactive change to tumor in the surrounding bone [1]. The most common presenting features of HP are headache and cranial nerve dysfunction [1]. IgG4-related disease is a group of immune-mediated inflammatory diseases, commonly with multiple organ involvement, characterized by lymphoplasmacytic infiltration of IgG4-rich plasma cells, formation of swellings or masses resembling tumors, and elevated IgG4 levels in serum [2, 3]. Cases usually present with a mass or nodule in the orbit, kidney, or lungs; or diffuse enlargement of the pancreas. The disease is commonly associated with meningitis and cranial nerve dysfunction and may produce focal neurologic deficits by compressing nerves or vascular structures [3]. Presentation of IgG4-related HP is not usually distinguishable from other etiologies of HP; however, clinical manifestations beyond the meninges may be important in diagnosis [2]. Diagnostic pathologic criteria for IgG4-related disease include dense lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis [2]. GPA (previously Wegener's granulomatosis) is one of the described antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides [4]. These are typically characterized by necrotizing small vessel vasculitis and in GPA may involve systemic granuloma formation, causing a variety of manifestations including upper respiratory, sinus, or ear disease leading to hearing loss; lung involvement ranging from pulmonary nodules to pulmonary infiltrates and alveolar hemorrhage; and necrotizing glomerulonephritis [5]. An overlap has been described between ANCA-associated vasculitis and IgG4-related disease in other manifestations of the disease including tubulointerstitial nephritis, periaortitis, and prevertebral fibrosis [4]. This overlap has also been reported in cases of HP associated with IgG4-related disease and ANCA against myeloperoxidase [6–8]. In one of these cases, the patient was successfully treated with high-dose methylprednisolone pulse therapy followed by taper [6]. In another case report, the patient had disease progression despite therapy with high dose steroids, cyclophosphamide, and azathioprine but responded well to rituximab [7]. In a case describing this overlap with HP of the spine, the patient responded incompletely to steroids and so was treated with rituximab, which unfortunately led to infection secondary to immunosuppression [8].

Case Report

A 48-year-old man presented with a 4-month history of headache, 25-lb weight loss, bilateral ear pressure, hearing impairment, and frontal sinusitis. He had a history of severe left mastoiditis and bilateral myringotomy tube placement prior to presentation. He also had bilateral pulmonary lung nodules found incidentally on chest computed tomography (CT), and chronic sinusitis for which he had completed a course of steroids and amoxicillin. The biopsy of his lung nodule was completed prior to presentation, revealing atypical lymphohistiocytic infiltrate with increased IgG4 plasma cells. Exam findings were significant for bilateral hypoacusis, but otherwise unremarkable for neurologic deficits.

Brain magnetic resonance imaging (MRI) and magnetic resonance venography revealed pachymeningeal enhancement predominantly in the posterior fossa and bilateral posterior cerebral hemispheres as well as a remote left subinsular lacunar infarct and findings consistent with mastoiditis and pansinusitis (Fig. 1). Serum laboratory findings and peripheral blood smear showed mild neutrophil-predominant leukocytosis, thrombocytosis, and normocytic anemia. Renal function was normal, and routine urinalysis showed proteinuria of 300 mg/dL and moderate blood. Workup for infections including blood cultures, respiratory viral

polymerase chain reaction, human immunodeficiency virus, and *Aspergillus* galactomannan antigen were negative. Rheumatologic workup included antinuclear antibody, cyclic citrullinated peptide IgG antibody, and angiotensin-1 converting enzyme, which were subsequently negative. Serum erythrocyte sedimentation rate, C-reactive protein, and rheumatoid factor were elevated. Serum was also positive for cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) with significantly elevated anti-proteinase 3 antibodies (AP3 Ab) and elevated IgG subclass IgG4 (245 mg/dL, normal 4–86 mg/dL), although total IgG level was normal. Cerebrospinal fluid (CSF) showed mild lymphocytic pleocytosis (5.6 cells/mm^3) and 3 well-defined gamma restriction bands present in both CSF and serum. CSF infectious workup was unremarkable. Bone marrow biopsy was obtained, showing hypercellularity with mature tricellular hematopoiesis and increase in IgG4 plasma cells in bone marrow as well as in the attached soft tissue.

Immunotherapy was initiated with prednisone 60 mg daily and rituximab with 375 mg/mL weekly for a total of 4 weeks' induction, with intravenous methylprednisolone 100 mg administered on days receiving rituximab in lieu of oral steroid dose. Maintenance of rituximab was planned for 6, 12, and 18 months after induction therapy with prednisone taper. The patient reported improvement of headache and hearing at 6-month follow up. Repeat chest CT showed interval decrease in the largest pulmonary nodule size seen on the previous scan, resolution of mediastinal and hilar lymphadenopathy, and no evidence of new nodules. At this date, he has not yet followed up with neurology, and he has not had an interval brain MRI.

Discussion

The initial presentation of the patient above is common for HP; however, unique to the case is that the patient's overall clinical picture appears to be consistent with two pathologic processes. He had many of the common features of GPA, such as recurrent sinus infections. In addition, he was positive for serum markers suggestive of the disease including c-ANCA with elevated AP3 antibodies. However, he was also found to have elevated serum IgG4, and pathology of his lung nodule showed lymphohistiocytic infiltrate with IgG4 plasma cells, consistent with IgG4-related disease. Though classically GPA- and IgG4-related diseases have been pathologically distinct, they have been described to have atypical presentations, including pachymeningitis, suggesting there is a clinical overlap between the two conditions. GPA predominantly produces a leukocytoclastic vasculitis with granulomatous inflammation with the typical presentation of pulmonary nodules and/or renal involvement, whereas IgG4-related diseases have been largely associated with lymphoplasmacytic infiltrates and pseudotumors that often manifest with inflammatory disease [3, 5]. The case above describes both GPA and IgG4-related disease which may represent disease pathogenesis to be a spectrum instead of two distinct processes.

If IgG4-related disease and GPA are indeed a spectrum of disease rather than two separate entities, this may have implications for treatment. First line for both typically includes glucocorticoids [2, 5]. There is no consensus for the use of steroid-sparing agents in IgG4-related disease [2]. In GPA, initial therapy also includes an immunosuppressant such as cyclophosphamide or rituximab. In the case reports described previously involving an overlap between IgG4-related disease and ANCA, the approach to treatment in all cases initially involved high-dose steroids [6–8]. In 2 of the cases reported, steroids were insufficient to prevent disease progression and the patients were treated with rituximab [7, 8]. In our case, the patient

responded well to initial treatment with high dose steroids and rituximab. These reports suggest that rituximab may be a good option for first-line treatment of HP related to both IgG4-related disease and ANCA-related disease.

Statement of Ethics

This case report did not involve human research.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Stephanie Wyrostek and Satabdi Chakrabarti were the primary authors of this paper. Editing and revision assistance was provided by Kelly Baldwin and J. David Avila.

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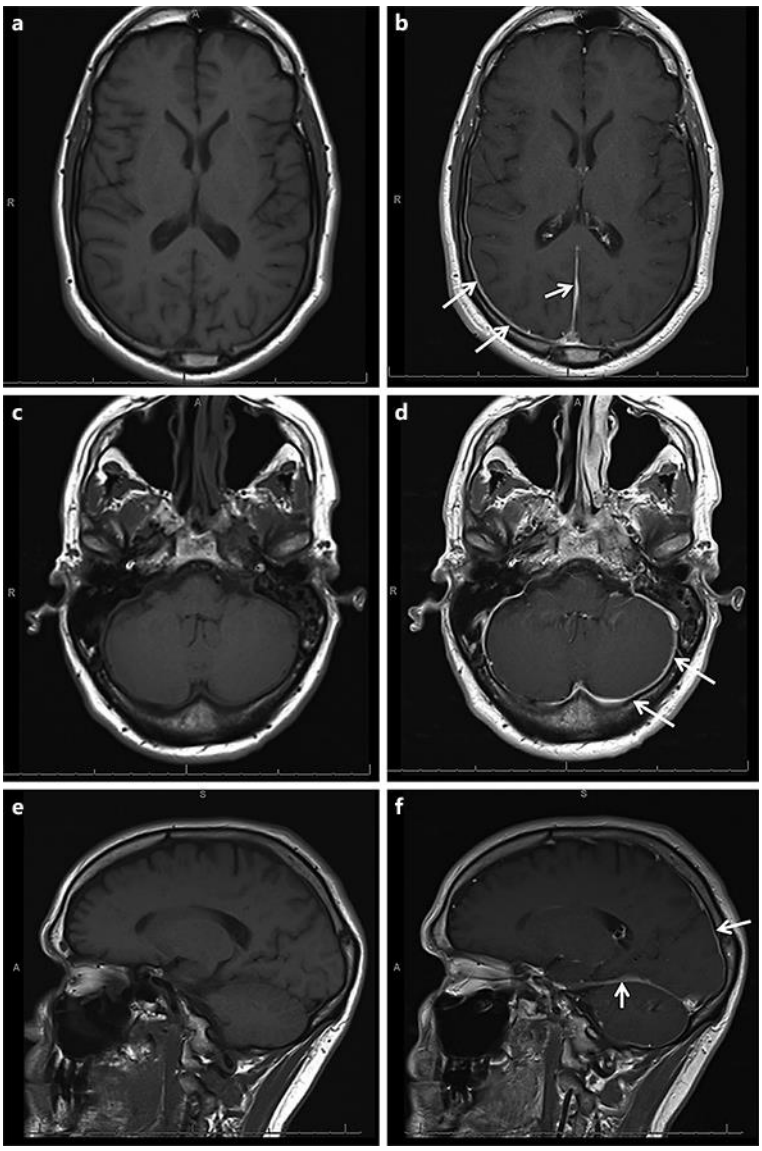

Fig. 1. T1-weighted pre- and post-contrast sequences showing contrast enhancement of pachymeninges (arrows). **a**, **c** Axial T1 pre-contrast. **b**, **d** Axial T1 post-contrast. **e** Sagittal T1 pre-contrast. **f** Sagittal T1 post-contrast.