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Treatment of IgG4-related pachymeningitis in a patient with steroid intolerance: The role of early use of rituximab

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ABSTRACT

IgG4-related pachymeningitis is a serious inflammatory condition that can present with symptoms of mass effect and focal deficits. The first-line therapy is steroids and second-line is chemotherapy (methotrexate, azathioprine, etc.). We describe a patient with IgG4-related pachymeningitis in whom steroid use was contraindicated and methotrexate was ineffective. During the course of treatment, the patient presented to the emergency department with receptive and expressive aphasia, slurred speech, right-sided neglect, and loss of sensation. After a single infusion of rituximab and anticonvulsants, her symptoms resolved. Our unique case suggests that patients with IgG4-related pachymeningitis might benefit from early initiation of rituximab.

1. Introduction

Although initially reported in cases of Type I autoimmune pancreatitis, IgG4-related disease, an inflammatory condition, has recently been implicated in a wide range of pathologies. The disease is a "great mimicker" of numerous disorders. Seemingly unrelated medical conditions including, but not limited to, Riedel's thyroiditis, idiopathic tubulointerstitial nephritis, autoimmune pancreatitis, and inflammatory aortic aneurysm are now known to be part of the IgG4-related disease spectrum (Stone et al., 2012). IgG4-related disease typically exhibits pathological characteristics of $IgG4^+$ plasma cell-rich lymphoplasmacytic infiltrate, storiform fibrosis, as well as mild to moderate eosinophilia and obliterative phlebitis (Kamisawa et al., 2015; Mahajan et al., 2014; Perez Alamino et al., 2013; Stone et al., 2012). While the pathophysiology of the disease is not fully understood, involvement of cytokine imbalances, T helper cells, and T regulatory cells has been proposed (Akitake et al., 2010; Detlefsen et al., 2008; Kanari et al., 2010; Miyoshi et al., 2008, p. 4; Suzuki et al., 2010). Descriptive studies have found an imbalance of T helper type 2 cells (Th2) with overproduction of Th2 derived cytokines in affected tissue from patients with IgG4-related disease (Akitake et al., 2010; Kanari et al., 2010; Suzuki et al., 2010). Cytokine imbalances may underlie the allergic manifestations of IgG4-related disease (Kamisawa et al., 2009). Other studies have implicated that an increase in transforming growth factor β driven by T regulatory cells may lead to development of fibrosis in late disease (Detlefsen et al., 2008; Miyoshi et al., 2008). Historically, the first cases of IgG4-related disease were described over 100 years ago; however, a clear description and nomenclature did not get formulated until the last 10 years. IgG4-related pachymeningitis is a rare fibroinflammatory condition affecting the dura mater, resulting in neurological symptoms such as headaches, cranial nerve palsies, visual problems, motor weakness, numbness, sensorineural hearing loss, and less commonly, seizures (Lu et al., 2014; Wallace et al., 2013). Histologically, it is characterized by the predominance of IgG4-positive plasma cells and CD4+ T lymphocytes. Disease progression and response to treatment are best monitored with serial imaging, although recent studies have also demonstrated that analysis of IgG and IgG4 production in cerebrospinal fluid are safe potential diagnostic and monitoring tools (Della-Torre et al., 2014, Della-Torre et al., 2013; Li et al., 2015). Despite the recent increase in the number of confirmed cases of IgG4-related pachymeningitis, no consensus on its optimal treatment has yet been reached. Steroids are currently the first-line treatment followed by other immunosuppressants, such as methotrexate, mycophenolate mofetil, and finally, rituximab, which although expensive, has been shown to be most effective (Bosco et al., 2013; Ebbo et al., 2012; Hyun et al., 2014; Khosroshahi et al., 2015, Khosroshahi et al., 2012, Khosroshahi et al., 2010; Moss et al., 2012). We describe a patient

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with IgG4-related pachymeningitis in whom steroids were contraindicated. Treatment with methotrexate did not show any clinical or radiological response and as a result, the patient experienced a significant exacerbation of her symptoms that may have been prevented with early institution of rituximab treatment.

2. Case report

A 54-year-old woman presented to her neurologist with a three-year history of gradual onset sensorineural hearing loss, right side greater than left, and worsening left sided headaches and dizziness. Initially, the right-sided hearing loss was thought to be due to eustachian tube dysfunction since a middle ear effusion was discovered upon right myringotomy; however, placement of a pressure equalization (PE) tube did not improve the patient's hearing. The patient's neurologic exam was normal aside from hearing, and the rest of the comprehensive physical exam was unremarkable. The neurologist ordered a Magnetic Resonance Imaging (MRI) of the brain, which revealed a small, thin, left subdural fluid collection on the axial and sagittal T2 flair images. A lumbar puncture (12 cc) was also performed, the results of which were negative for cancer and infection. Thereafter, her headaches resolved for 4 weeks. Four months later, she returned to her neurologist with debilitating left sided headaches radiating to her neck and lower back. A second brain MRI was performed which revealed enlargement of the left holohemispheric dura, with enhancement and slight nodularity in the left temporal region (Fig. 1B).

Given the patient's increasingly debilitating headaches, dizziness, and lack of diagnosis despite an exhaustive evaluation, she underwent a left temporal craniotomy and biopsy of the dural lesion. The craniotomy was planned with stereotactic navigation. A burr hole was placed and a bone flap was turned. Aided by stereotactic navigation, the most thickened and abnormal dura was identified. The dura was then opened 1 cm from the edge of the craniotomy, and a 2.5 × 3 cm dural biopsy was taken. Grossly, the dural sample was white, thick and avascular.

The dural biopsy revealed several evenly-spaced, well-developed, reactive lymphoid follicles surrounded by a dense lymphocytic and highly plasma cell-rich inflammatory process. The plasma cell component was morphologically normal, and no atypical or immature lymphoid component was seen. The differential diagnosis included infection, plasmacytoma, IgG4-related disease, low-grade B-cell lymphoma, and autoimmune disease. The initial work-up was inconclusive, suggesting a chronic non-specific meningitis, but further investigations, including immunohistochemical stains, supported reactive follicular hyperplasia. A striking number of IgG4-positive plasma cells were identified (greater than 200 per high-powered field in more than 5 high-powered fields; IgG4/IgG ratio estimated at 58%). In-situ hybridization assays did not reveal light chain restriction in the plasma cell population (Fig. 2C, D). Renal and liver function tests were unremarkable, and other organ system involvement was ruled out. Findings were therefore consistent with isolated IgG4-related meningeal disease. Serum IgG4 levels were elevated (122.7 mg/dL; reference range 4–86 mg/dL), which further supported the diagnosis. After the diagnosis was established, the patient was placed on oral steroids (40 mg), as well as methotrexate (12.5 mg per week). One month later, during her follow-up appointment, the patient stated that although her headaches had improved significantly, her gastroenterologist advised against continuing prednisone due to her history of multiple gastric surgeries. An MRI, 3 months post-surgery, demonstrated some improvement in her left frontal and temporal dural enhancement (Fig. 1D). Since she was tolerating methotrexate well and could no longer continue a significant dose of oral steroids, her weekly methotrexate dose was increased to 25 mg per week. At a follow-up appointment 6 weeks later, the patient complained of progressive debilitating headaches on her left side which now also included the back of her head. At this point, she had completed her oral steroid taper, and was solely relying on a weekly 25 mg dose of methotrexate along with folic acid (1 mg daily) for disease control. Frustrated that she could no longer maintain her two businesses, the patient sought a second opinion for other treatment options. Considering the severity of her condition, the ineffectiveness of methotrexate, and the contraindication to steroids, she was advised to begin rituximab therapy. Returning to her original treatment team, she received an infusion of rituximab (2 × 1000 mg), but within 24 h, before rituximab could have significant effect, her symptoms worsened prompting her presentation to the emergency department with receptive and expressive aphasia, slurred speech, right-sided neglect, and hemianesthesia. CT of the head and neck without contrast showed no evidence of stroke. Although brain MRI revealed prominent left-sided parieto-occipital-temporal dural enhancement and thickening measuring up to 5 mm (Fig. 1E), no imaging findings of cerebral hemorrhage or infarct were found. Routine EEG revealed marked left hemispheric slowing, mild right hemispheric slowing with frontal intermittent rhythmic delta activity (FIRDA) and no evidence of epileptic discharges. Serum IgG4 levels were further elevated (164 mg/dL). After work-up for stroke was negative, anticonvulsants were initiated for seizures secondary to pachymeningitis with progressive cerebral irritation. A day later, serial serum IgG4 levels were down trending (130 mg/dL), and the patient was discharged 7 days later with resolution of symptoms. The patient received additional rituximab infusions 6 months (2 × 1000 mg) and 1 year (2 × 1000 mg) following the initial rituximab infusions. One year post-discharge, the patient has not experienced seizure-like symptoms and continues taking Keppra and Topamax. Daily headaches have improved with nonsteroidal anti-inflammatory drugs.

3. Discussion

The general consensus on treatment of IgG4-related diseases is that administration of steroids generally produces a favorable response with attenuation of clinicoradiological signs and symptoms (Choi et al., 2010; Khosroshahi et al., 2015; Kosakai et al., 2010; Lindstrom et al., 2010). However, there have been cases in which steroids were not effective, and clinicians had to rely on other means of immunosuppression in order to resolve the disabling neurological symptoms that are associated with uncontrolled hypertrophic pachymeningitis (Hyun et al., 2014; Shapiro et al., 2012). Methotrexate, an antagonist of folic acid known to inhibit lymphocytes and B-cell function (Gutiérrez-Ureña and Espinoza, 1995; Rosenthal et al., 1988), has recently been shown to be effective in

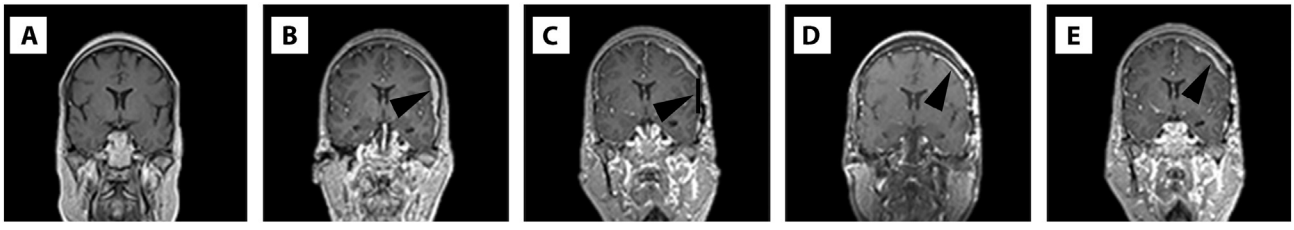

Fig. 1. MRI. A: Two years prior to diagnosis, coronal T1 with contrast of the brain demonstrating no obvious enhancement in the left temporofrontal dura. B: Significant pachymeningeal enhancement in the left temporofrontal dura (arrowhead). C: Status post left temporal craniotomy for dural biopsy, note (arrowhead and vertical line) the area of left temporal dural biopsy. D: Improvement of the patient's dural enhancement (arrowhead), after prednisone treatment. E: Recurrence of the patient's dural enhancement (arrowhead). At this time, the patient returned with worsening neurological symptoms while on methotrexate alone.