Journal of the Neurological Sciences 318 (2012) 31–35

Contents lists available at SciVerse ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

# IgG4-related inflammatory pseudotumor of the central nervous system responsive to mycophenolate mofetil

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ARTICLE INFO

*Article history:*
Received 1 March 2012
Received in revised form 3 April 2012
Accepted 9 April 2012
Available online 28 April 2012

*Keywords:*
IgG4-related disease
Mycophenolate mofetil
Intracranial mass
Optic neuropathy
Inflammatory pseudotumor

ABSTRACT

Orbital apex and skull base masses often present with neuro-ophthalmic signs and symptoms. Though the localization of these syndromes and visualization of the responsible lesion on imaging is typically straightforward, definitive diagnosis usually relies on biopsy. Immunohistochemistry is important for categorization and treatment planning. IgG4–related disease is emerging as a pathologically defined inflammatory process that can occur in multiple organ systems. We present two patients with extensive inflammatory mass lesions of the central nervous system with immunohistochemistry positive for IgG4 and negative for ALK-1 as examples of meningeal based IgG4-related inflammatory pseudotumors. In both patients, there was treatment response to mycophenolate mofetil.



## 1. Introduction

The term inflammatory pseudotumor has been applied to a heterogeneous group of mass-forming lesions in various anatomic regions and organs characterized by a proliferation of fibroblasts or myofibroblasts admixed with an inflammatory infiltrate composed mainly of lymphocytes and plasma cells. The term is sometimes used interchangeably with plasma cell granuloma and inflammatory myofibroblastic tumor (IMT), which leads to confusion both clinically and in the literature. Unlike IMT, which is considered neoplastic with ALK-1 expression as a distinguishing feature [1], many inflammatory pseudotumors of the orbit and central nervous system likely represent a manifestation of inflammatory fibrosclerosis or idiopathic sclerosing inflammation. This process is analogous to retroperitoneal fibrosis, sclerosing mediastinitis, sclerosing cholangitis, Riedel sclerosing thyroiditis and sclerosing pancreatitis, which have been linked to IgG4 sclerosing diseases [2]. IgG4 staining in inflammatory mass lesions has been proposed as a marker of lesions with an autoimmune or primary inflammatory etiology [3].

## 2. Case reports

### 2.1. Patient 1

A 36-year-old woman presented with headaches, double vision worse in left gaze, and numbness of the left forehead and cheek. Visual acuity, color vision and computerized static perimetry were normal. There was 1 mm of anisocoria (left larger than right) with brisk reaction bilaterally and no ptosis or ocular misalignment. There was a partial left VIth nerve palsy. MRI of the orbits revealed a T1 isointense, T2 isointense, homogenously enhancing extra-axial mass in the left middle cranial fossa involving the left cavernous sinus. Partial resection of the mass was performed. Pathology was felt to be nonspecific and non-diagnostic. Post-operative MRI of the brain revealed additional meningeal based masses in the right posterior fossa, left frontal region and left occipital region (Fig. 1, top row). Chest CT did not show any masses. Cerebral spinal fluid (CSF) contained 4 wbc/μL (44% lymphocytes), 1 rbc/μL (tube 4), 42 mg/dL protein and 30 mg/dL glucose. CSF cytology did not reveal malignant cells and CSF flow cytometry did not reveal a monoclonal B-cell population

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doi:10.1016/j.jns.2012.04.010

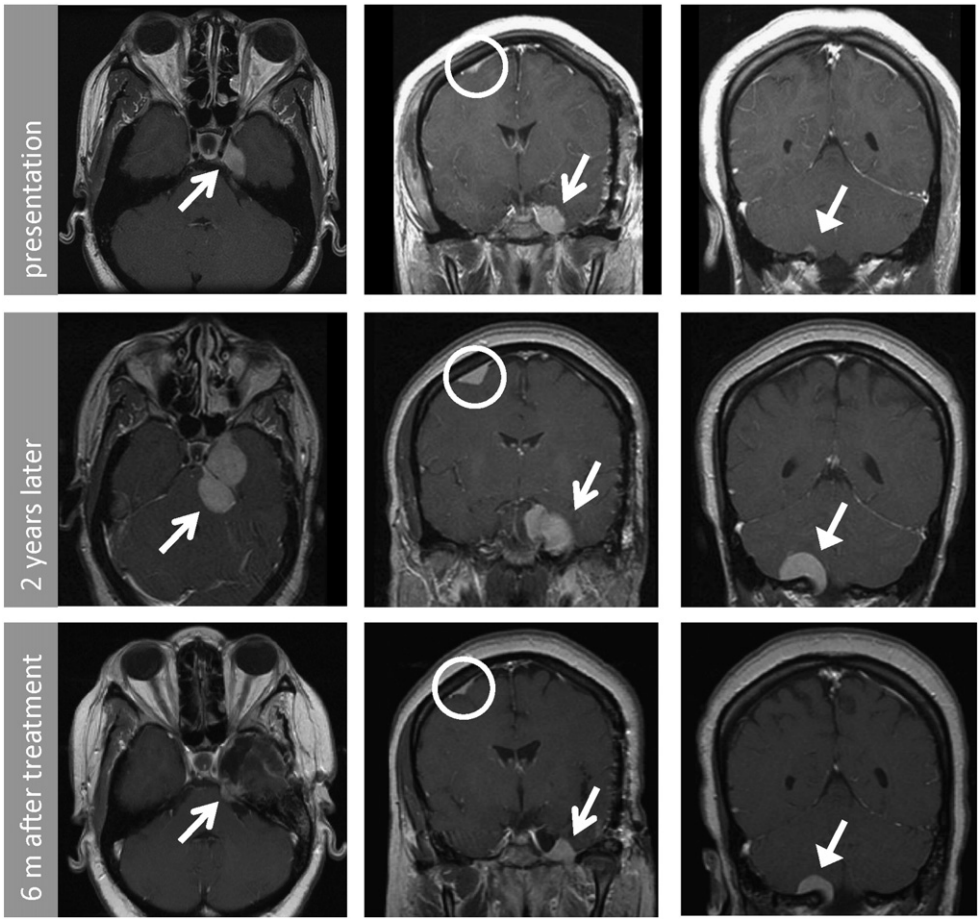


**Fig. 1.** Post contrast T1 MRI of brain axial (left column) and coronal (center and right column) images from patient 1. These demonstrate multifocal extra-axial lesions including middle cranial fossa (closed arrow), foramen magnum (open arrow) and superior frontal (circle). Top row shows initial imaging, middle row shows imaging obtained at representation 2 years later, and bottom row shows imaging 6 months after repeat resection of cavernous sinus lesion and medical therapy.

or aberrant expression of T-cell antigens. She was evaluated by the pulmonary and neuro-oncology services. A second biopsy was recommended. However, the patient's symptoms had resolved following the surgery and post-operative steroid taper (dexamethasone 40 mg daily tapered over 6 weeks), so she declined.

Two years later, she presented with blurred vision in the left eye and pain in the left cheek and chin that evolved over 3 months. MRI of the brain demonstrated enlargement of all the meningeal masses and segmental dural enhancement (Fig. 1, middle row). MRI of the spine did not reveal additional abnormalities. Repeat partial resection of the left cavernous sinus mass was performed.

Microscopic examination of both biopsy specimens showed fragments of leptomeninges and dura involved by dense chronic inflammatory infiltrates composed predominantly of plasma cells with abundant macrophages and lymphocytes (Fig. 2). The inflammatory infiltrates were organizing with moderate leptomeningeal fibrosis, but granulomatous inflammation was not observed. Gram, Grocott and Ziehl-Nielsen stains for bacterial, fungal and acid fast microorganisms were negative. The lymphocytic infiltrates consisted largely of CD3-positive T-cells with scattered CD79a and CD20-positive B-cells. Immunohistochemistry for kappa and lambda light chains, and flow cytometry of representative biopsy tissue did not reveal a monoclonal B-cell cell population. Moreover aberrant expression of T-cell antigens was not observed. An immunohistochemical stain for anaplastic lymphoma kinase-1 (ALK-1) was negative. IgG4 staining was prominent. Examination of multiple high power fields (10 fields at 40×) revealed up to 43 plasma cells with strong IgG4 staining per high power field (range 27–43), and an IgG4/IgG ratio of 20%. She

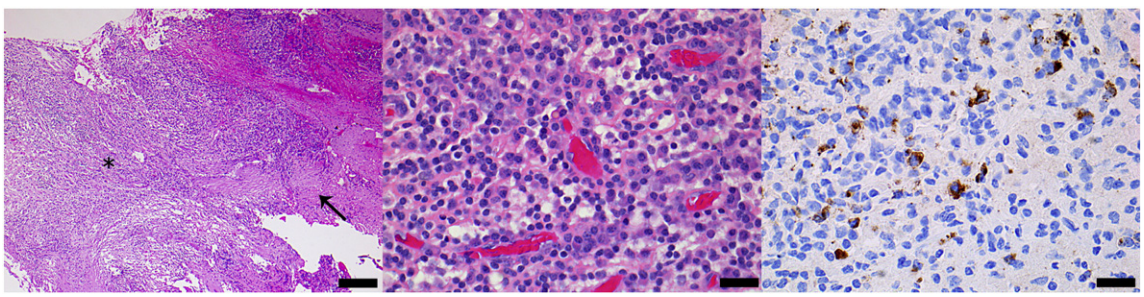

**Fig. 2.** Histologic features of middle cranial fossa biopsy from patient 1. Hematoxylin and eosin stain at low (10×) (left) and high (middle) (40×) power depict abundant macrophages, lymphocytes and plasma cells. Immunohistochemical stain for IgG4 (right) demonstrates multiple immunoreactive plasma cells. (Scale bars: left 200 μm, middle, right 50 μm).