Published in final edited form as:

J Neuroophthalmol. 2014 December ; 34(4): 408–411. doi:10.1097/WNO.0000000000000194.

Mass Confusion in a 30-Year-Old Man

Edward A. Margolin, MD, Jasmine Gopwani, MBBS, Charles G. Eberhart, MD, PhD, and Ari M. Blitz, MD

Department of Ophthalmology and Visual Sciences (EM, JG), University of Toronto, Toronto, Canada; Department of Neurology (EM), University of Toronto, Toronto, Canada; Department of Ophthalmology (JG), Queen Elizabeth Hospital, Bridgetown, Barbados; and Departments of Pathology (CGE) and Radiology and Radiological Science (AMB), Johns Hopkins Medical Center, Baltimore, Maryland

Dr. Margolin

A 30-year-old previously healthy man who recently immigrated to Canada from Sudan presented to the emergency room with a seizure. Brain magnetic resonance imaging (MRI) was performed (Fig. 1) as was a lumbar puncture.

Dr. Blitz

The initial MRI demonstrates pachymeningeal, leptomeningeal, and subcortical parenchymal enhancement, principally within the right orbital frontal region (*arrow*, Fig. 1A). There is extensive surrounding hyperintensity on the accompanying fluid-attenuated inversion recovery image (FLAIR) images (Fig. 1B) extending into the genu of the corpus callosum (*arrow*) and with associated mass effect and leftward subfalcine herniation. There is no associated restricted diffusion. Differential diagnosis would include primarily infectious and inflammatory processes.

Dr. Margolin

Cerebrospinal fluid (CSF) analysis revealed a mild lymphocytosis with normal cytology and flow cytometry. A brain biopsy was performed with inconclusive results. Diagnoses considered included benign gliosis with no evidence of malignancy, gliomatosis cerebri, and lymphocytic meningitis with secondary chronic brain inflammation. The pathological slides from this biopsy were not available for review.

The patient left the hospital against medical advice. He was, however, readmitted 9 months later for increasing headaches and underwent repeat MRI (Fig. 2). During this admission, he developed psychosis and attempted to stab a floor nurse with a knife. He was transferred to the forensic psychiatry unit.

Copyright © North American Neuro-Ophthalmology Society

Address correspondence to Edward Margolin, MD, Division of Neurology, Department of Ophthalmology and Visual Sciences, University of Toronto, 801 Eglinton Avenue West, Suite 304, Toronto, ON M5N 2M7, Canada; edmargin@gmail.com.

The authors report no conflicts of interest.

Dr. Blitz

There has been interval surgery with a region of postoperative encephalomalacia in the right dorsolateral prefrontal cortex (*arrow*, Fig. 2A). The operative region does not seem to encompass the region of pathologic parenchymal enhancement previously noted in the orbital frontal cortex. There is minimal marginal enhancement of the operative cavity. There is persistent pachymeningeal enhancement subjacent to the orbital frontal cortex. The previously noted parenchymal enhancement and mass effect in the right orbital frontal region have resolved. There is minimal residual FLAIR hyperintensity (*arrow*, Fig. 2B), probably gliosis rather than the FLAIR hyperintense edema previously seen.

Dr. Margolin

An extensive evaluation for infectious and inflammatory conditions was performed. The following serologies were negative: syphilis (venereal disease research laboratory test and rapid plasma reagin), toxoplasma, HIV, herpes simplex virus, cytomegalovirus, Creutzfeldt-Jacob virus, candida, cysticercosis, Lyme, brucella, tularemia, ehrlichiosis, leptospirosis, histoplasmosis, schistosomiasis, Q-fever, and blastomycosis. Testing for collagen vascular diseases and vasculitides also was negative. Another MRI was performed (Fig. 3).

Dr. Blitz

This MRI shows that the pachymeningeal enhancement is more extensive. There now is thickening of the falx cerebri, and the process crosses the midline into the left orbital frontal region, where it is associated with new parenchymal enhancement (*arrow*), Fig. 3A), edema (*arrow*, Fig. 3B), and mass effect.

Dr. Margolin

A second biopsy of the right frontal region was performed that was interpreted as chronic meningitis and encephalitis, possibly due to infection. Again, however, the pathological slides from this biopsy were unavailable for review. MRI was repeated 1 month later and was unchanged.

Six months after admission to the forensic psychiatry unit, the patient complained of decreased vision in the right eye that had developed over a period of 1 month. On examination, visual acuity was no light perception in the right eye and 20/20 in the left eye. There was a marked right afferent pupillary defect. The right optic disc was pale; the left disc appeared normal. A fourth MRI was performed (Fig. 4).

Dr. Blitz

Postcontrast T1-weighted coronal images show even more pachymeningeal thickening and enhancement than previously, and there is now a nodular focus on the right (*arrow*, Fig. 4A), elevating the prechiasmatic optic nerve and extending anteriorly into the right optic canal (*arrow*, Fig. 4B).

Dr. Margolin

The patient was treated with a 5-day course of intravenous methylprednisolone (1 g/d), followed by an oral taper over 4 weeks without improvement in visual acuity.

Two months after completion of steroid therapy, the patient began to experience deterioration of vision in the left eye. On examination, his visual acuity was now no light perception in the right eye and 20/70 in the left eye, associated with mild left optic disc pallor. Intravenous steroids were administered again followed by oral taper. Computed tomography of the chest, abdomen, and pelvis revealed no abnormalities. Repeat CSF analysis was unchanged. Total body bone scan was normal. MRI of the brain and orbits with contrast was reportedly unchanged.

Within 1 month of onset of the new visual symptoms in the left eye, the vision in the right eye improved slightly to light perception, but the vision in the left eye worsened to no light perception. A third course of intravenous steroids was administered without visual improvement. Another MRI of the brain and orbits was performed (Fig. 5).

Dr. Blitz

There is extension of enhancement into the left optic canal (arrowhead, Fig. 5A) and persistent enhancement in the right optic canal (*arrow*, Fig. 5A). Bulky soft tissue thickening and enhancement were seen within the left cavernous sinus (*arrow*, Fig. 5B), demonstrating T2 hypointensity (*arrow*, Fig. 5C) and appearing continuous with pachymeningeal enhancement over the left middle cranial fossa (*arrow* and arrowhead, Fig. 5D). T2 hypointensity with enhancement in the absence of neoplasm suggests fibrosis, granulomatous or nongranulomatous inflammation, or both.

Dr. Margolin

Quantiferon gold testing was performed and was positive. A presumptive diagnosis of tuberculous meningoencephalitis was made, the patient was started on triple therapy for tuberculosis, and he was transferred to our center where a third brain and dural biopsy was performed (Fig. 6).

Dr. Eberhart

Microscopic examination demonstrates dura with mixed inflammation, including lymphocytes and plasma cells forming lymphoid follicles with germinal centers and some macrophage-rich vaguely granulomatous regions (Fig. 6A). Fibrosis is present as well, but there is no evidence of neoplasia, infection, or vasculitis. Immunohistochemical stains reveal a mixed population of CD3⁺ and CD20⁺ lymphocytes (Figs. 6B and 6C). CD138⁺ plasma cells and CD68⁺ macrophages were also present. Immunostains highlight regions with increased numbers of immunoglobulin G4 (IgG4)-positive plasma cells (Fig. 6D), although IgG-positive plasma cells were 3–4 times more numerous.

Final Diagnosis

IgG4-related hypertrophic pachymeningitis.

Dr. Margolin

The patient was lost to follow-up after he was discharged from the hospital.

Hypertrophic pachymeningitis (HP) is an inflammatory condition in which the dura mater of the cranium or spine becomes thickened. IgG4-related disease is a recently described entity that can cause tumefactive lesions at multiple locations and that has been proposed as the most common etiology of noninfectious HP, although differential diagnosis includes infections (neurosyphilis, tuberculosis, cryptococcosis, bacterial meningitis), inflammatory processes (neurosarcoidosis, polyarteritis nodosa, granulomatosis with polyangiitis, Behçet's disease, rheumatoid arthritis), and neoplastic entities (meningeal metastasis, central nervous system lymphoma) (1,2).

Symptoms of HP usually result from mass effect, nerve compression, or vascular compromise of the surrounding structures by the thickened and inflamed dura (2). The most common clinical manifestations are headaches, cranial nerve palsies, visual disturbances (either decreased central acuity from the involvement of the dura covering the optic nerves or diplopia from the involvement of ocular motor nerves), motor weakness, limb numbness, hearing loss, and seizures (2). Some patients may exhibit the symptoms of IgG4-related involvement of other structures including retroperitoneal fibrosis, orbital involvement with proptosis, pulmonary involvement, facial or neck swelling from lacrimal or salivary gland involvement, and lymphocytic pancreatitis (3).

The inflammatory infiltrate in IgG4-related disease consists of B and T lymphocytes and plasma cells with variably admixed eosinophils and macrophages. This infiltrate activates fibroblasts and leads to collagen deposition, causing hypertrophy of the dura matter (4). Some data suggest that a yet unknown antigen causes interaction of CD4-positive T cells and oligoclonal IgG4-positive B cells. Activated T cells then lead to the production of interleukin (IL)-4 and IL-10 that cause the switch of the autoreactive B cells to IgG4 and IgE subclasses and subsequent differentiation and proliferation of IgG4-positive plasma cells (5,6).

Serum IgG4 levels are elevated in 70%–90% of patients with IgG4-related pachymeningitis (serum IgG4 levels were not measured in our patient as he was lost to follow-up by the time the diagnosis was established) (7). CSF analysis usually demonstrates mild pleocytosis and increased serum to CSF IgG4 ratio (8). Meningeal biopsy is critical for the diagnosis. According to international consensus criteria, it must demonstrate 2 of the following 3 features: 1) dense lymphoplasmacytic infiltrate, 2) fibrosis with storiform features, 3) obliterative phlebitis. If only one of the findings is present, either increased serum IgG4, elevated IgG4 to IgG plasma cell ratio in the tissue, or multiorgan involvement with typical IgG4-related disease manifestations must be present (2,4,9,10). However, the specific thresholds used for IgG4-positive plasma cells can vary in different tissues and are still a matter of debate.

In our case, there was an increased number of IgG4-positive cells on dural biopsy and fibrosis, confirming the diagnosis of IgG4-related intracranial and orbital disease.

This case represents a rare presentation of HP with progressive bilateral frontal lobe lesions and severe bilateral optic neuropathy, no response to several courses of steroids, and brain biopsies with dramatically different interpretations. A positive QuantiFERON tuberculosis (TB) Gold test lead to the erroneous diagnosis of tuberculous meningitis, which was likely due to latent infection as the patient is from a region pandemic for TB.

The diagnosis of IgG4-related disease as a cause of HP in this case was made only after the third brain biopsy with staining for IgG4, by which time, our patient had significant visual and neurological dysfunction. Familiarity with this disease, which can produce both intracranial tumefactive lesions and HP (3), could have lead to an earlier diagnosis, appropriate treatment, and possibly a better clinical outcome.

REFERENCES

1. Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med*. 2012; 366:539–551. [PubMed: 22316447]
2. Lu XL, Della-Torre E, Stone JH, Clark SW. IgG4-related hypertrophic pachymeningitis clinical features, diagnostic criteria, and treatment. *JAMA Neurol*. 2014; 71:785–793. [PubMed: 24733677]
3. Wallace ZS, Carruthers MN, Khosroshahi A, Carruthers R, Shinagare S, Stemmer-Rachamimov A, Deshpande V, Stone JH. IgG4-related disease and hypertrophic pachymeningitis. *Medicine (Baltimore)*. 2013; 92:206–216. [PubMed: 23793110]
4. Mahajan VS, Mattoo H, Deshpande V, Pillai SS, Stone JH. IgG4-related disease. *Annu Rev Pathol*. 2014; 9:315–347. [PubMed: 24111912]
5. Jeannin P, Lecoanet S, Delneste Y, Gauchat JF, Bonnefoy JY. IgE/IgG4 production can be differentially regulated by IL-10. *J Immunol*. 1998; 160:3555–3561. [PubMed: 9531318]
6. Satoguina JS, Weyand EM, Larbi J, Hoeraug A. T regulatory-1 cells induce IgG4 production by B cells: role of IL-10. *J Immunol*. 2005; 174:4718–4726. [PubMed: 15814696]
7. Carruthers MN, Khosroshahi A, Augustin T, Deshpande V, Stone JH. The diagnostic utility of serum IgG4 concentrations in IgG4-related disease. *Ann Rheum Dis*. 2014; 20:1136.
8. Della-Torre E, Passerini G, Furlan R, Roveri L, Chieffo R, Anzalone N, Doglioni C, Zardini E, Sabbadini MG, Franciotta D. Cerebrospinal fluid analysis in immunoglobulin G4-related hypertrophic pachymeningitis. *J Rheumatol*. 2013; 40:1927–1929. [PubMed: 24187161]
9. Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, Klöppel G, Heathcote JG, Khosroshahi A, Ferry JA, Aalberse RC, Bloch DB, Brugge WR, Bateman AC, Carruthers MN, Chari ST, Cheuk W, Cornell LD, Fernandez-Del Castillo C, Forcione DG, Hamilos DL, Kamisawa T, Kasashima S, Kawa S, Kawano M, Lauwers GY, Masaki Y, Nakanuma Y, Notohara K, Okazaki K, Ryu JK, Saeki T, Sahani DV, Smyrk TC, Stone JR, Takahira M, Webster GJ, Yamamoto M, Zamboni G, Umehara H, Stone JH. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol*. 2012; 25:1181–1192. [PubMed: 22596100]
10. Lindstrom KM, Cousar JB, Lopes MB. IgG4-related meningeal disease: clinico-pathological features and proposal for diagnostic criteria. *Acta Neuropathol*. 2010; 120:765–776. [PubMed: 20844883]

Fig. 1. Initial magnetic resonance imaging. **A.** Postcontrast T1 coronal MRI demonstrates pachymeningeal, leptomeningeal, and subcortical parenchymal enhancement principally in the right orbital frontal region (*arrow*). **B.** Axial fluid-attenuated inversion recovery image shows extensive hyperintensity extending into the genu of the corpus callosum (*arrow*) with mass effect and subfalcine herniation.

Fig. 2.

Nine months after presentation. **A.** T1 coronal image with gadolinium postoperative encephalomalacia (*arrow*) and minimal marginal enhancement of the operative cavity. **B.** Axial fluid-attenuated inversion recovery image has minimal residual hyperintensity (*arrow*) likely representing gliosis.

Fig. 3. Eleven months after presentation. **A.** Postcontrast T1 coronal scan shows more extensive pachymeningeal enhancement and new parenchymal enhancement (*arrow*). **B.** Axial fluid-attenuated inversion recovery image demonstrates more extensive edema (*arrow*) and mass effect.

Fig. 4. Sixteen months after presentation. **A** and **B**. Postcontrast T1 coronal images reveal progression of pachymeningeal enhancement and a new nodular focus of enhancement on the right (*arrow*) (**A**), elevating the prechiasmatic optic nerve and extending into the optic canal (*arrow*) (**B**).

Fig. 5. Nineteen months after presentation. **A** and **B**. Postcontrast T1 coronal images show extension of enhancement into the left optic canal (*arrowhead*) (**A**), persistent enhancement in the right optic canal (*arrow*) (**A**), and soft tissue thickening and enhancement in the left cavernous sinus (*arrow*) (**B**). **C**. T2-image demonstrates parasellar hypointensity (*arrow*). **D**. T1 axial image reveals pachymeningeal enhancement in middle of left cranial fossa (*arrowhead*) contiguous with the region of T2 hypointensity (*arrow, as seen in C*).

Fig. 6.

Specimen of third brain biopsy. **A.** There is a mixed inflammatory dural infiltrate including lymphocytes and plasma cells and macrophage-rich areas suggestive of granulomatous inflammation (hematoxylin & eosin, $\times 25$). Immunostaining reveals CD3⁺ (**B**) and CD20⁺ (**C**) lymphocytes (**B** and **C**, $\times 200$). **D.** There are abundant IgG4-positive plasma cells (immunostain, $\times 100$).