

Available online at www.sciencedirect.com

ScienceDirect

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

Clinical challenge

Masses in the membranes

**Sandip Suresh, BS^a, Anne S. Abel, MD^a, Brian R. Younge, MD^b,
Jurij R. Bilyk, MD^c, Michael S. Lee, MD^{a,*}**

^a Department of Ophthalmology, University of Minnesota, Minneapolis, Minnesota, USA

^b Department of Ophthalmology, Mayo Clinic, Rochester, Minnesota, USA

^c Wills Eye Hospital, Jefferson Medical College, Philadelphia, Pennsylvania, USA

ARTICLE INFO

(In keeping with the format of a clinical pathological conference, the abstract and key words appear at the end of the article.)

Article history:

Received 7 May 2015

Accepted 2 October 2015

Available online xxx

Peter Savino and **Helen Danesh-Meyer**, Editors

1. Case report

A 24-year-old woman from Liberia gave a 1-year history of progressively worsening painless vision loss in the right eye (OD). After a recent workup by her rheumatologist, he prescribed 60 mg of daily prednisone for presumed systemic lupus erythematosus with optic neuritis. Her past medical history, review of systems, and medication list were otherwise unremarkable. Despite corticosteroid therapy, her vision continued to deteriorate and, at that point, she was referred to an ophthalmologist for further evaluation.

Visual acuity was 20/20 in the left eye (OS), but counting fingers OD. Visual field testing showed a bitemporal hemianopia. Pupil examination was not recorded. Brain magnetic resonance imaging (MRI) demonstrated multiple homogeneous T1 isointense and uniformly gadolinium-enhancing dural-based masses, consistent with meningiomas (Fig. 1). These masses were noted in the falx, tentorium, occipital dura, and right planum sphenoidale, with compression of the chiasm.

What is the differential diagnosis and how would you like to proceed?

2. Comments

2.1. Comments by Jurij Bilyk, MD

The patient's unilateral visual loss and bitemporal visual field defect strongly suggest perichiasmal pathology, with possible asymmetric extension along the left optic nerve. Enhancement of the occipital dura would not cause a bitemporal defect. In this case, the lesion along the planum sphenoidale would explain her ophthalmologic findings. The diagnosis of multiple meningiomas, while certainly possible, should be approached with caution. There are many reports in the literature of inflammation (most notably sarcoidosis and

This work was supported in part by an Unrestricted Grant from Research to Prevent Blindness (MSL, New York, NY, USA).

* Corresponding author: Michael S. Lee, MD, Department of Ophthalmology, University of Minnesota, 420 Delaware Street S.E., MMC 493, Minneapolis, MN 55455-0501, USA.

E-mail address: mikelee@umn.edu (M.S. Lee).

0039-6257/\$ – see front matter © 2015 Elsevier Inc. All rights reserved.

<http://dx.doi.org/10.1016/j.survophthal.2015.10.001>

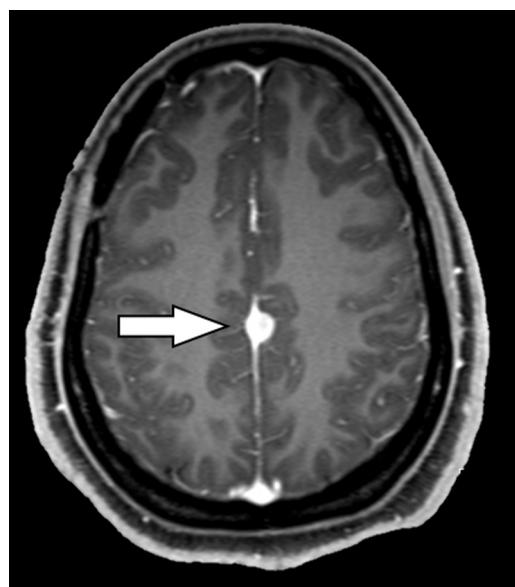


Fig. 1 – Brain MRI. Postgadolinium, axial T1-weighted image showing a dural-based, uniformly enhancing mass along the falk cerebri (arrow). Similar lesions were seen in the planum sphenoidale, tentorium, and occipital dura. MRI, magnetic resonance imaging.

hypertrophic pachymeningitis), lymphoproliferation, and metastatic disease being misdiagnosed as “multiple meningiomas.” Although uniform, vigorous gadolinium enhancement is the rule with meningioma, this can also occur with a variety of other processes. Serologic testing for sarcoidosis, granulomatosis with polyangiitis, and IgG4-related disease is reasonable, but should be delayed for a few weeks to minimize any residual effect of recent corticosteroid use on the results. I would also add a lactate dehydrogenase and serum protein electrophoresis for possible lymphoproliferative disease or blood dyscrasia. Hypertrophic pachymeningitis may also occur secondary to tuberculosis. Although this is admittedly rare in the United States, it is a well described phenomenon in other parts of the world. Since the patient is from Liberia, it would be prudent to either place a purified protein derivative or check a serum quantiferon gold. If any serologic abnormalities are found, lumbar puncture would be indicated. Given the duration of symptoms, it is unlikely that the patient’s findings are due to metastatic disease; however, it would be worth documenting any smoking history and results of a recent chest X-ray and mammogram.

3. Case report (continued)

The patient did not smoke. She did not undergo chest X-ray or mammogram. Lactate dehydrogenase was normal. Serum protein electrophoresis showed a mild, polyclonal elevation in the gamma fraction, which can be seen in inflammatory conditions. The MRI did not show evidence of optic nerve enhancement, and the prednisone was discontinued. The patient underwent excisional biopsy of the planum sphenoidale mass that was compressing the optic chiasm. The

histopathologic diagnosis was benign psammomatous meningioma. Surgical decompression of the chiasm failed to restore vision OD but seemed to halt further deterioration. She was lost to follow up.

Five years later, she presented with a 3-month history of painless, worsening vision OS and left upper lid ptosis. Visual acuity was now 20/400 bilaterally. Examination revealed 2-mm ptosis of the left upper lid, a decreased corneal reflex with diminished sensation in the frontal nerve (V1) distribution, and limited ability to adduct, elevate, or depress OS; the left pupil was large and minimally reactive to light and accommodation. There was no afferent pupillary defect.

What is your assessment of these deficits and how would you like to proceed?

4. Comments (continued)

4.1. Comments by Dr. Bilyk

In addition to vision loss in the OS, presumably from either a left optic neuropathy or progressive chiasmal pathology, the sensory and motor cranial neuropathy point to pathology along the left skull base involving the orbital apex, the cavernous sinus, or both. The patient needs a dilated funduscopic examination for assessment of the optic nerves, automated perimetry, and repeat, high-quality MRI of the skull base. Optical coherence tomography would be helpful in documenting a baseline nerve fiber thickness level for comparison with future serial testing.

5. Case report (continued)

Funduscopic examination showed bilateral optic atrophy. Optical coherence tomography nerve fiber layer thickness was not obtained. The patient was diagnosed with a left orbital apex syndrome involving cranial nerves II, III, and V1. Repeat MRI showed no interval changes in the falcine, tentorial, or occipital masses and no recurrence of the right planum sphenoidale mass; however, dural thickening was seen around the optic nerve in the orbital apex and cavernous sinus, concerning for recurrent occult meningioma versus inflammation. (Fig. 2). Lumbar puncture showed normal results and cytology. Laboratory medicine did not feel that flow cytometry was warranted based on the cytologic results. She was started on corticosteroids without benefit. She subsequently underwent craniotomy with optic nerve decompression and cavernous sinus biopsy. During gross dissection, the neurosurgeon noted that the macroscopic appearance of the lesion was much softer than that of a meningioma. Histologically, the mass was described as chronic inflammation in a dense amorphous material, most likely collagen, consistent with hypertrophic pachymeningitis (Fig. 3)

These results prompted a more thorough reexamination of the initial biopsy specimen from the outside institution. Immunostaining of the prior specimen revealed a dense population of CD138+ cells, a marker of B-cell differentiation toward plasmacytes. Interspersed among the plasmacytic infiltrate were CD20+, a marker for B-cell lymphocytes.

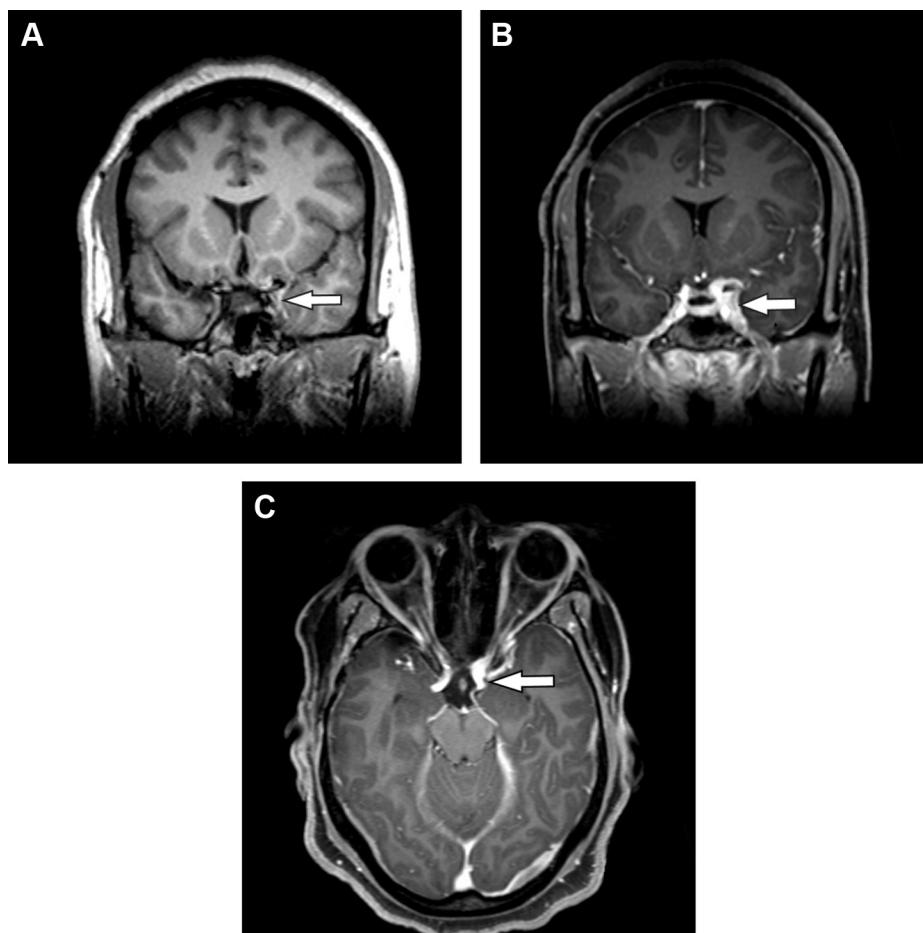


Fig. 2 – Brain MRI. A: precontrast coronal T1-weighted image showing isointense lesion in left cavernous sinus (arrow), B: postcontrast coronal T1 image showing enhancing mass in left cavernous sinus (arrow), and C: postcontrast axial T1 image showing enhancing mass in left cavernous sinus (arrow). MRI, magnetic resonance imaging.

Negative S100 and CD1a stains ruled out Langerhans cell histiocytosis and Tolosa-Hunt syndrome. IgG4 stain was negative, and the ALK-1 fusion protein was absent. Negative Congo red stain excluded amyloid deposition diseases. Reinterpretation of this initial specimen was now deemed most consistent with hypertrophic pachymeningitis, with no evidence of meningioma.

How would you manage the patient at this point?

6. Comments (continued)

6.1. Comments by Dr. Bilyk

Hypertrophic pachymeningitis is a descriptive term encompassing any process that causes inflammatory thickening of the meninges. Most commonly in the United States, this is idiopathic, but as already mentioned, other noninfectious (e.g., sarcoidosis, granulomatosis with polyangiitis, IgG4-related disease) and infectious (e.g., tuberculosis) inflammations must be considered and ruled out. The histopathology shows no evidence of granulomatous inflammation, vasculitis, or IgG4 staining. The pathologist should also perform staining to rule out acid-fast and fungal

organisms. Once all other specific etiologies for hypertrophic pachymeningitis are ruled out, it is reasonable to conclude that the inflammation is idiopathic. Therapy typically begins with systemic corticosteroids, and if no improvement is noted, antimetabolite therapy is instituted.

7. Case report (concluded)

Her vision failed to improve postoperatively. Her left cranial nerve III palsy worsened, and she developed a new left cranial nerve VI palsy. Rheumatologic workup undertaken to ascertain an etiology for the pachymeningitis revealed an elevated erythrocyte sedimentation rate and elevated titers of antinuclear antibodies, Sjögren syndrome A, Sjögren syndrome B but negative Lyme and hepatitis serologies, rapid plasma reagins, anti-ribonucleoprotein, anti-double stranded DNA, anti-Smith, rheumatoid factor, and antineutrophil cytoplasmic autoantibody. HIV testing, angiotensin-converting enzyme and QuantiFERON Gold were negative. Serum IgG4 was not tested. She had not experienced any shortness of breath, cough, pleuritic chest pain, or sicca symptoms. She did have chronic fatigue, intermittent subjective fevers, and occasional painless oral blisters. She was started on high-dose

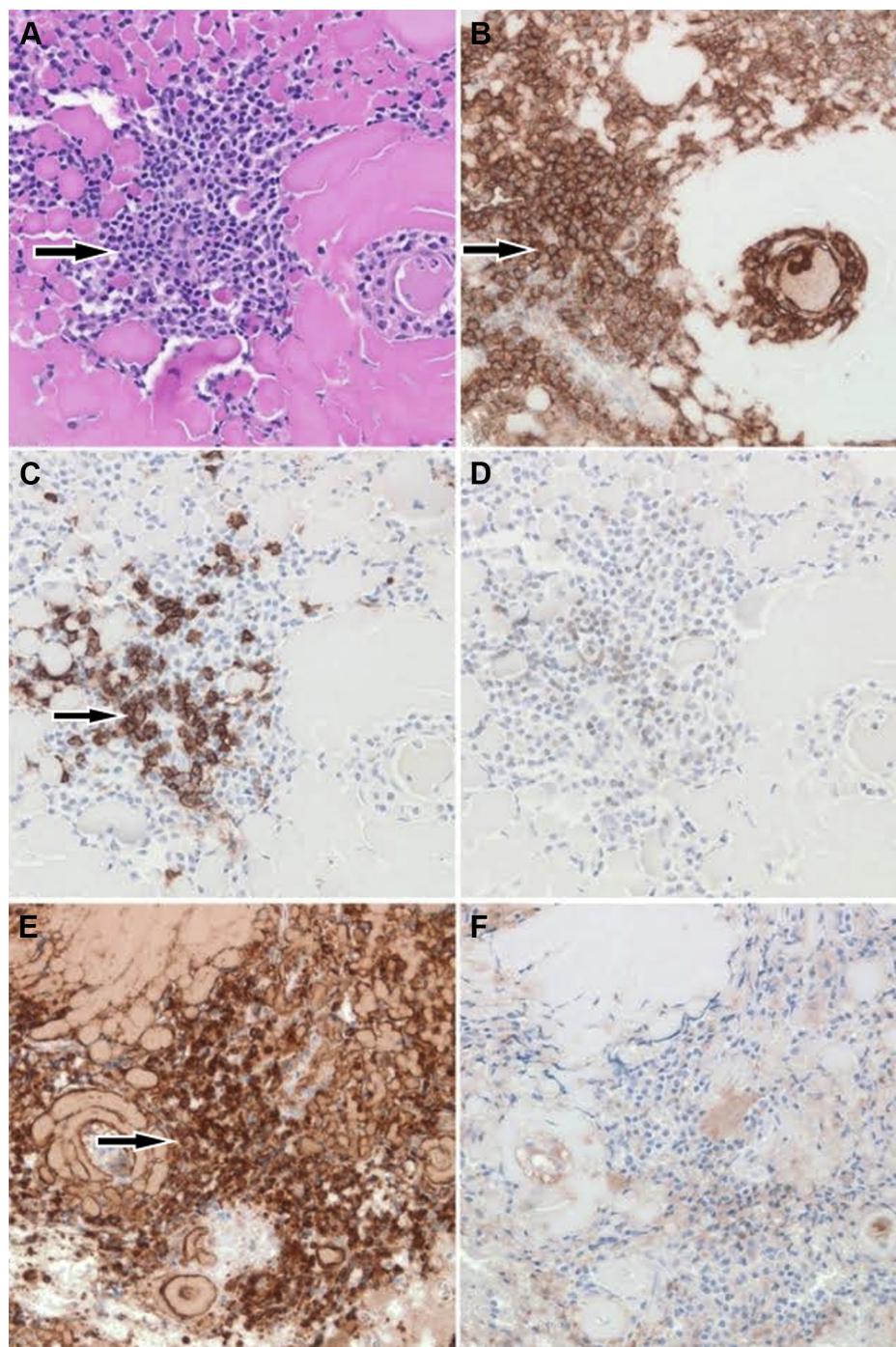


Fig. 3 – Initial biopsy specimen. A: hematoxylin and eosin stain shows small-sized lymphocytes (arrow) in a dense extracellular medium. B: immunohistochemistry shows predominantly CD138+ plasma cells (arrow), C: sparse CD20+ B-cells (arrow), D: absent CD3+ T-cells, E: abundant kappa light chain (arrow), and F: and minimal lambda light chain. These results indicate a monoclonal low-grade B-cell population with plasmacytic differentiation and extracellular immunoglobulin deposition, most consistent with a diagnosis of mucosa-associated lymphoid tissue lymphoma.

corticosteroids in combination with imuran and cytoxan for atypical SLE-induced pachymeningitis.

Repeat MRI of the head done 3 months later showed stable, persistent dural thickening and atrophy of the optic nerve along with stable posterior meningiomas. Given the worsening cranial nerve palsies and lack of improvement on treatment, the 2 biopsy specimens were reexamined, this time

by 2 hematopathologists. Immunostaining once again revealed a plurality of CD138+ plasmacytes with a minority of CD20 B-cells (Fig. 3). Rare CD3+ T-lymphocytes and CD68+ histiocytes were also present. Kappa and lambda light chain staining unveiled a kappa light chain restricted specimen, indicative of a monoclonal population of plasmacytes and lymphocytes. A definitive diagnosis of low-grade B-cell

lymphoma with plasmacytic differentiation and extensive extracellular immunoglobulin deposition was made by both hematopathologists. These findings were consistent with extranodal marginal zone lymphoma (EMZL).

Systemic workup detected no systemic involvement. The final diagnosis was primary central nervous system (CNS) EMZL. The patient declined therapy.

8. Discussion

Primary CNS EMZL is the most common primary dural lymphoma, but is certainly an exceedingly rare primary CNS lymphomas.⁶ Most primary CNS lymphomas are high-grade, diffuse, large B-cell lymphomas occupying the brain parenchyma. EMZL are low-grade non-Hodgkin B-cell lymphomas originating from the marginal zone of secondary follicles.⁸ Up to 50% of cases present with multiple CNS lesions.² CNS EMZLs typically develop as discrete masses in the dural convexities and are known to mimic meningiomas radiologically and clinically.¹¹ Both of these entities have a predilection for middle aged women and both can present with seizures, headaches, vomiting, or symptoms of focal compression.^{2,10,12} Radiologically, CNS EMZLs are dural-based lesions and can have a dural-tail, a sign typically suggestive of meningiomas.⁶ Both entities appear isointense or hypointense on T1-weighted MRI and diffusely enhance with contrast.^{6,10} A restrictive pattern of diffusion weighted imaging, when present, can help distinguish dural lymphomas from meningiomas.⁹

Although most frequently associated with *Helicobacter pylori* antigenic stimulation in the stomach, EMZL also occur in nonmucosal sites such as the thymus, thyroid, salivary gland, breast, liver, and CNS.^{4,9} Certain anatomic locations of EMZL have been associated with specific etiologies, such as *H. pylori* gastritis with the stomach, Sjögren syndrome with salivary glands, and Hashimoto thyroiditis with the thyroid.⁴ There is also some evidence to suggest a higher incidence of EMZL in patients with severe, long-standing rheumatoid arthritis.^{3,7} No single causative agent has been definitively associated with primary CNS EMZL, but case reports have implicated several different autoimmune and infectious precursors.^{2,6} The pathogenesis of this process is not clearly understood, as the dura does not have a native lymphocyte population.^{5,10} One hypothesis posits that a monoclonal population arises from the lymphocytic infiltrate induced by chronic inflammation.^{6,10,11} It remains a possibility that this patient's autoimmune syndrome predisposed her to developing this lymphoma.

All EMZL are histologically characterized by proliferation of B-cells in the interfollicular marginal zones.⁸ They are typified by positivity of B-cell markers (CD19, CD20, CD79a) and are notably negative for CD3, CD5, CD10, CD23, and cyclin D1.¹¹ Plasmacytic differentiation, as seen in this case, can be identified by CD138+ cells and occurs in approximately one-third of EMZL. It can range from sparse clusters of plasma cells to plasmacyte dominant neoplasms.⁸ The presence of B-cells helps distinguish the latter from true plasma cell neoplasms⁴; however, the combination of lymphocytes and plasma cells also raises concern for a lymphoplasmacytic lymphoma. This

is further confounded by the fact that these plasma cells often secrete IgM resulting in a paraprotein gap that closely resembles a lymphoplasmacytic lymphoma.⁸ Bone marrow biopsy, bone scans, and immunoglobulin levels can help distinguish an EMZL with plasmacytic differentiation from a medullary process such as myeloma or lymphoplasmacytic lymphoma.⁸

Primary dural EMZL has an excellent prognosis with a 5-year survival greater than 86%, similar to gastrointestinal EMZL.⁶ Transformation to diffuse large B-cell lymphoma has not been reported.² Staging requires MRI of the brain and spine to look for multiple tumors and leptomeningeal involvement.⁶ Patients with EMZL can have systemic involvement at the time of diagnosis. One series of 180 patients with nongastric EMZL found that 23% had involvement at more than one site at diagnosis.¹³ Thorough systemic workup is needed to exclude a metastatic source. Systemic relapse can also occur years after treatment, even with complete response of the primary tumor.⁶

Owing to the scarcity of cases, there are no published guidelines for the management of CNS EMZL. These tumors are typically radiosensitive and responsive to low-dose radiation (20–45 Gy), avoiding neurotoxicity.^{1,2} Intervention occasionally necessitates surgical resection or chemotherapy as well. As no definitive etiologies for CNS EMZL have been elucidated, it is unclear whether amelioration of any underlying cause results in remission of CNS EMZL, a phenomenon that has been noted with *H. pylori* and gastrointestinal EMZL.¹¹

9. Literature search

An extensive literature search using the PubMed database was conducted in English using variations of the following search terms: multiple meningioma, lymphoplasmacytic meningioma, hypertrophic pachymeningitis, CNS marginal zone lymphoma, CNS MALT lymphoma, and dural lymphoma. Articles were analyzed and those germane to this patient's case were included in this report.

10. Disclosure

The authors report no proprietary or commercial conflict of interest with any product or concept discussed in this article.

REFERENCES

1. Aqil B, Rouah E, Verstovsek G. Primary CNS marginal zone lymphoma: a case report and review of the literature. *Open J Pathol*. 2013;03(02):55
2. Bayraktar S, Stefanovic A, Montague N, Davis J, Murray T, Lossos IS. Central nervous system manifestations of marginal zone B-cell lymphoma. *Ann Hematol*. 2010;89(10):1003–9
3. Dasanu CA, Bockorny B, Grabska J, Codreanu I. Prevalence and pattern of autoimmune conditions in patients with marginal zone lymphoma: a single institution experience. *Conn Med*. 2015;79(4):197–200

4. Ferry JA. Extranodal lymphoma. *Arch Pathol Lab Med*. 2009;132(4):557–65
5. Huang H, Buhl R, Hugo HH, Mehdorn HM. Clinical and histological features of multiple meningiomas compared with solitary meningiomas. *Neurol Res*. 2005;27(3):324–32
6. Iwamoto FM, Abrey LE. Primary dural lymphomas: a review. *Neurosurg Focus*. 2006;21:E5
7. Mikuls TR, Endo JO, Puumala SE, et al. Prospective study of survival outcomes in Non-Hodgkin's lymphoma patients with rheumatoid arthritis. *J Clin Oncol*. 2006;24(10):1597–602
8. Molina TJ, Lin P, Swerdlow SH, Cook JR. Marginal zone lymphomas with plasmacytic differentiation and related disorders. *Am J Clin Pathol*. 2011;136:211–25
9. Sebastian C, Vela AC, Figueroa R, Marin MA, Alfaro J. Primary intracranial mucosa-associated lymphoid tissue lymphoma. *A report of two cases and literature review*. *Neuroradiol J*. 2014;27:425–30
10. Smith AB, Horkayne-Szakaly I, Schroeder JW, Rushing EJ. From the radiologic pathology archives: mass lesions of the dura: beyond meningioma-radiologic-pathologic correlation. *Radiographics*. 2014;34(2):295–312
11. Tu PH, Giannini C, Judkins AR, et al. Clinicopathologic and genetic profile of intracranial marginal zone lymphoma: a primary low-grade CNS lymphoma that mimics meningioma. *J Clin Oncol*. 2005;23:5718–27
12. Whittle IR, Smith C, Navoo P, Collie D. Meningiomas. *Lancet*. 2004;363:1535–43
13. Zucca E, Conconi A, Pedrinis E, et al. Nongastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. *Blood*. 2003;101(7):2489–95

A B S T R A C T

Keywords:
multiple meningioma
hypertrophic pachymeningitis
CNS MALT lymphoma
EMZL
dural lymphoma
systemic lupus erythematosus

A 24-year-old woman with systemic lupus erythematosus presented with a 1-year history of painless vision loss in the right eye. Examination was notable for a bitemporal hemianopia. Brain imaging revealed multiple contrast enhancing dural masses, including one along the planum sphenoidale. She underwent excisional biopsy for a presumed diagnosis of multiple meningiomas. Five years later, she developed worsening vision in the left eye, hypesthesia in the V1 distribution, and oculomotor nerve palsy. Repeat imaging showed an enhancing mass in the cavernous sinus and orbital apex. Biopsy demonstrated a lymphoplasmacyte rich infiltrate in dense extracellular material. She was diagnosed with lupus-induced hypertrophic pachymeningitis and started on immunosuppressive therapy. On further worsening of symptoms, her initial biopsy was reexamined and revealed a kappa light chain restricted B-cell and plasmacyte population. This led to the final diagnosis of central nervous system extranodal marginal zone lymphoma.

© 2015 Elsevier Inc. All rights reserved.