Frank B. Walsh Session

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*12 minute presentation with no pathology and no neuroimaging
I Can’t See, Walk, Poop or Pee
David L. Knox, M.D., R. Nick Hogan, M.D., Ph.D.
Baltimore, MD, Dallas, TX

History and Exam
A 64-year-old Ashkenazi male, disably retired international business lawyer, presented to author, DLK, on August 28, 2002, for evaluation of several years of decreasing vision of both eyes.

Family history was medically and neurologically negative.

Severe constipation began at age 40. Rectal and colonic manometric studies led to a diagnosis of “inert colon” from both sensory and motor denervation. Neurologic consultation was advised. Urinary bladder and sexual function ceased by age 49.

Multiple neurologic consultations diagnosed peripheral neuropathy. Ankle reflexes were absent and Babinski positive. Mayo Clinic neurologists recommended two courses of oral corticosteroids which made him feel worse. Following diagnostic lumbar puncture, his legs rapidly became weaker (CSF protein 90 mg/dl, n = 15-45 ng/dl). Constipation persisted, urinary bladder emptying was accomplished by auto catheterization and he became wheelchair dependent at age 60.

He began using reading glasses at age 35. In his early 50’s right eye blurred vision was diagnosed at the National Eye Institute as “uveitis” and successfully treated with eye drops. At age 64, an episode of right eye blurred vision was diagnosed by a retinal specialist as “central serous retinopathy” and treated with oral carbonic anhydrase inhibitors.

The patient had no awareness of color vision impairment and neither of his two wives had ever complained about his poor color vision sense.

Examination, performed with the patient in his wheelchair, found by manifest refraction, 20/60- vision right eye, and 20/70 left eye. With a + 3.00 add he could read 1.00 M print, and with +6.00 add, 0.50 M print. He was only able to read the first “12” Ishihara color plate.

External examination revealed pale skin and reddish hair. Both pupils reacted sluggishly and incompletely to direct light. Ocular movements were full.

Slit lamp examination found nuclear sclerosis, posterior subcapsular cataracts and vitreous degeneration. Ocular pressures were 15 mm Hg in each eye.

Ophthalmoscopy found 20/40 media in the right eye and trace pallor of the temporal optic nerve head. Retinal arteries were narrow and the macular retina thick without a foveal reflex. The left media had 20/25 clarity. The optic nerve head had more pallor than the right disk. Retinal arteries were narrow, macula was thick without a foveal reflex. Goldman and automated perimetry found irregular contraction and suppression of visual fields.

What diagnostic tests should be performed on this patient?
I Can’t See, Walk, Poop or Pee

Answer

Final Diagnosis

Adult Polyglucosomal Body Disease

Summary of Case Including Pathology

Sural nerve and axillary skin biopsy established that this patient has Adult Polyglucosomal Body Disease. Neurologic and biopsy aspects of the case were reported in 2001. These ocular aspects were defined in August 2002.

Adult Polyglucosomal Body Disease, first described in 1971 and 1979 was established as a distinct clinical entity in the 1980 publication by Robitaille et al. in Brain. This was followed in 1982 by Okamoto et al.’s report in Acta Neuropathologica.

Since then many reports have confirmed a relatively clear clinical syndrome: mid 30’s to 40’s onset, mostly Ashkenazi Jews, gradual onset of central and peripheral nerve dysfunction which slowly progresses.

Histopathology and electron microscopy of peripheral nerves (e.g. sural) reveals varying sized PAS positive bodies which occupy and displace axonic material within myelin sheaths. For ease of biopsy, myoepithelial cells of skin apocrine glands, most accessible in axillae, contain pale blue staining inclusion material which is slightly positive to PAS staining. In autopsied cases, PAS positive bodies have been found in white matter of brain, astrocytes, liver, myocardium, smooth and skeletal muscle.

The disease has been seen in siblings and has been associated with a missense mutation in the ganglion branching enzyme gene on chromosome 3, leading to a deficiency of that enzyme. This mutation has not been seen in all cases tested. There is no established therapy.

Ocular involvement in this disease was identified by “poor vision” and “optic atrophy” in two of Robitaille et al.’s four cases. Okamoto et al., from Hirano’s lab at Einstein, in an autopsied case, described “gross atrophy of optic nerves.” Hirano kindly supplied stained sections of that chiasm which revealed multiple varying sized PAS positive bodies and diffuse atrophy.

Nick Hogan is preparing a report of a patient autopsied in Dallas. Ocular involvement is characterized by PAS positive bodies, most dense in the optic nerve just within and anterior to the cribriform plate. Scattered bodies are seen in the nerve fiber layer and in a few axons of the inner plexiform layer.

Jeff O’Dell is currently caring for a 50 + year old wheelchair bound lawyer who has slightly reduced acuity, color vision and mild optic atrophy.

By light and electron microscopy, the PAS positive bodies in this disease are similar and considered by some to be identical to the bodies seen in Lafora disease. Lafora disease begins in adolescence with seizures and mental deterioration with death in 5 to 7 years. Retinal histopathology of Lafora disease, as reported by Yanoff and Berard-Badier et al., demonstrate PAS positive bodies in ganglion cells and some bipolar cells, not axons. Cerebral grey matter cells are affected. From this, it must be concluded that, on both clinical and histochemical grounds, Lafora and APBD are two different entities. A long review article written by J.B. Cavanaugh was published in 1999.

References

4. Robitaille, Y, Carpenter, S., Karpati, G and DiMauro, S., A Distinct Form of Adult Polyglucosomal Body Disease With Massive Involvement of Central and Peripheral Neuronal Processes and Astrocytes, Brain, 1980, 103:315-336
History and Exam
A 61-year-old woman presented to the emergency room with sudden onset of left sided weakness and numbness. Her past medical history was notable for Waldenstrom’s macroglobulinemia diagnosed 10 years previously by urine protein electrophoresis and a bone marrow biopsy. She was treated with cytoxan and prednisone. Her other medical conditions included gastroesophageal reflux disease, fibromyalgia and depression. Her past neurological history was remarkable for an episode of acute inflammatory demyelinating polyneuropathy 2 years previously that was treated with intravenous immunoglobulin and plasmapheresis with complete recovery. Her medication list included prednisone 30 mg QOD, Cytoxan 100 mg QD, Zoloft 50 mg QD, metoprolol 50 mg QD and diazepam 2 mg QD. A review of symptoms was notable for a 20-pound weight loss over the past 2-3 months.

Two months prior to her presentation to our hospital, she began to experience severe headaches associated with nausea and vomiting. She was evaluated by a local neurologist and treated with pain medications. Within 1 month of the onset of headaches she also began to experience binocular horizontal double vision and soon after developed an episode of confusion, disorientation and hallucinations lasting approximately half a day. She was admitted to a local hospital and during the hospitalization had another episode of mental status changes. An electroencephalogram, cranial computed tomography and magnetic resonance imaging studies were reportedly normal. A lumbar puncture was also performed and reported to be normal. She was discharged home with acyclovir and levaxquin with a presumptive diagnosis of herpes encephalitis. Several weeks later, she developed a headache and the sudden onset of weakness and numbness of the left foot that progressed to involve her left leg, arm and face. A family member noticed her left face was drooping and the speech was impaired. Within 45 minutes the symptoms resolved, but on her way to the emergency room a similar episode occurred lasting 20 minutes.

On examination, she was oriented and alert but demonstrated poor attention span, poor recall and mild frontal lobe dysfunction. Language was normal. Neurological examination was non-focal. Visual acuity was 20/30 right eye and 20/25 left eye consistent with the level of the cataracts. Color vision, pupillary reflexes and visual field testing were all normal. Assessment of the extraocular movements demonstrated limitation of abduction of both eyes. In primary gaze there was a 25-prism diopter (PD) esotropia (ET). In right gaze there was a 20-PD ET and in left gaze there was an 18-PD ET. Dilated fundus examination was normal in both eyes.

Laboratory results:

<table>
<thead>
<tr>
<th>Serum PEP</th>
<th>CBC</th>
<th>ESR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein: 7.0 g/dl (6.3-8.2)</td>
<td>WBC: 3.4 thous/cu mm</td>
<td>31 mm/H</td>
</tr>
<tr>
<td>Albumin fraction: 3.5 g/dl (3.3-4.0)</td>
<td>HgB: 10.4 g/dl</td>
<td></td>
</tr>
<tr>
<td>Alpha-1 globulin: 0.3 g/dl (0.2-0.4)</td>
<td>IgG: 543 mg/dl (716-1554)</td>
<td></td>
</tr>
<tr>
<td>Alpha-2 globulin: 0.8 g/dl (0.6-1.1)</td>
<td>IgA: 93 mg/dl (71-377)</td>
<td></td>
</tr>
<tr>
<td>Beta globulin: 1.0 g/dl (0.7-1.3)</td>
<td>IgM: 153 mg/dl (45-259)</td>
<td></td>
</tr>
<tr>
<td>Gamma globulin: 0.8 g/dl (0.7-1.8)</td>
<td>IgD: &lt;0.8 mg/dl (0-14)</td>
<td></td>
</tr>
<tr>
<td>M spike: 0.2 g/dl</td>
<td>PLT: 192 thous/cu mm</td>
<td></td>
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</tbody>
</table>

A procedure was done.

Study supported by Research to Prevent Blindness
Discussion: Waldenstrom’s macroglobulinemia (WM), a disorder of plasma cells, is a low-grade lymphoplasmacytic lymphoma characterized by a monoclonal population of lymphocytes that produce monoclonal immunoglobulin M (IgM). WM occurs predominately in Caucasians and the elderly (median age at diagnosis 63 years).1 The clinical manifestations are protean and most commonly due to the infiltration of neoplastic cells in the bone marrow and lymphoid system. In addition, many of the complications of the disease occur as the result of the unique biological properties of the monoclonal IgM, in particular the development of the hyperviscosity syndrome. Patients can present with recurrent infections, bleeding diathesis, weakness, fatigue, anorexia and weight loss. Physical examination often demonstrates lymphadenopathy and hepatosplenomegaly. Laboratory findings include anemia, lymphocytosis, elevated erythrocyte sedimentation rate, low fibrinogen levels and high serum viscosity levels. Serum protein immunofixation electrophoresis demonstrates high levels of an IgM monoclonal protein. Treatment is reserved for those who are symptomatic and prognosis is variable depending on age, sex, hemoglobin level and neutrophil count. The median survival rate for most patients is 5 years.1,2

The ocular manifestations of WM have been well documented in the literature. The most common finding is venous stasis retinopathy (venous congestion, venous dilatation and tortuosity and retinal hemorrhages) due to an increase in serum viscosity.3 Other findings described include serous retinal detachment, conjunctival infiltration, corneal deposits, neovascular glaucoma, optic nerve edema, vitritis, scleritis, dry eye syndrome and neoplastic cell infiltration of the orbit, lacrimal gland and extraocular muscles.4-12

Neurological complications occur in approximately 25% of patients with WM.13 In the majority of cases a peripheral neuropathy occurs because of IgM reaction to glycoproteins and glycolipids of the peripheral nerves culminating in demyelination. However, the peripheral neuropathy can also occur from direct cellular infiltration of the peripheral nerves. Elevated serum viscosity resulting in ischemia can cause neurological disease in some patients with WM.1 Cerebrovascular permeability with intracerebral paraprotein infiltration may result in leukoencephalopathy.14 Eight years prior to Waldenstrom’s description of the disease that now bears his name,15 Bing and Neel described two patients with central nervous system (CNS) involvement from infiltration of plasma cell and lymphocytes that in retrospect was a form of WM.16 The Bing-Neel syndrome refers to direct CNS involvement of WM.17 Cytologic and immunohistochemical examination of the CNS cells identifies a monoclonal population of malignant B cells that are CD19, CD20 and CD22 positive and express cytoplasmic IgM, thereby excluding other lymphoproliferative and neoplastic diseases.1,18 The syndrome can be divided into a tumoral (intraparenchymal) and infiltrative form. Delgado et al. reviewed 8 cases in the literature of the tumoral form of the Bing-Neel syndrome.13 The presenting clinical manifestations were mental status changes, hemiparesis, seizure activity and aphasia. The clinical characteristics of the infiltrative form of the Bing-Neel syndrome are similar to neoplastic meningitis.19 The malignant cells infiltrate the perivascular spaces, leptomeninges, periventricular white matter and brainstem.13

Our patient’s sixth cranial nerve paresis may have been the result of elevated intracranial pressure or direct infiltration of the cranial nerves by the malignant cells of WM. Whatever the mechanism, bilateral sixth nerve paresis in a patient with WM warrants diagnostic consideration of the Bing-Neel syndrome.

References
History and Exam

J.F. is a 34-year-old right-handed male with no significant medical history who developed the acute onset of vertigo one morning. The dizziness increased and he developed an unsteady gait. He went to an emergency room, and was prescribed meclizine. However, he developed intractable nausea and vomiting and returned several days later. A CT scan demonstrated hypoattenuation in the medial left cerebellum.

J.F. denied any headache, photophobia, fever, stiff neck or difficulty thinking. He worked as a financial consultant, was married and had two children. He quit smoking ten years earlier and drank a glass of wine daily. His hobbies included golf and travel.

On physical examination, the patient appeared uncomfortable and occasionally retched. He was afebrile and his vital signs were normal.

Neurological examination was remarkable for bilateral horizontal end-gaze jerk nystagmus, worse with left gaze, and terminal dysmetria on finger-nose-finger testing, especially on the left. There were no ocular dysmetria or pursuit abnormalities. He had a wide-based unsteady gait. The remainder of his exam was unremarkable including confrontation fields and funduscropy.

CBC, Panel 7, LFT’s, ESR and ACE were normal. His RPR and HIV test were negative. Cerebrospinal fluid protein and glucose were normal. The CSF had 110 white blood cells (WBC) and 1550 red blood cells with 4% neutrophils, 86% lymphocytes, 9% monocytes, 1% eosinophils. His stool was negative for ova and parasites.

His MRI scan demonstrated T-2 frond-like enhancement in the inferior cerebellar vermis and nodulus, the left superior cerebellar peduncle, the left more than right medial cerebellum and the medial aspect of the right brachium pontis.

The patient’s condition rapidly worsened. The patient was taken to neurosurgery where a diagnostic procedure was performed.
Final Diagnosis
Neuroschistosomiasis

Summary of Case Including Pathology
Due to the concern for malignancy and the patient’s deterioration, a brain biopsy was performed. The frozen section was consistent with “parasite.” On further questioning, the patient’s family noted that, five years earlier, they had gone swimming in Lake Victoria while on safari in Kenya.

On pathologic examination, sections of the cerebellum revealed scattered large necrotizing granulomas composed of eosinophils, histiocytes, lymphocytes and giant cells, ova within the granulomata, some with prominent lateral spines, consistent with *Schistosoma mansoni*. Most eggs had maturing larvae within, although occasional eggs were empty. No adult parasites were seen.

After malaria, schistosomiasis is the second most common parasitic infection worldwide, with an estimated 200 million people infected.1 Humans are the definitive hosts for the three main species of schistosoma and the complicated life cycle involves an intermediate host, the Biomphalaria snail. A fluke from the snail penetrates human skin, changes form and migrates through the pulmonary and systemic circulation, eventually to the portal veins.2 In the liver, the organisms mature into adults.2 The male and female forms pair and then, for *S. mansoni*, typically migrate to the mesenteric venules to mate. The female migrates further against venous flow and lays eggs that travel to the intestine and are shed in stool. Other eggs are carried into the hepatic microvasculature, where they lodge and cause a granulomatous inflammatory response.2 Eggs passed in stool hatch in freshwater and invade the intermediate snail host.2

There are two possible ways that Schistosomiasis can involve the CNS: aberrant migration of flukes followed by egg deposition or, more commonly, systemic embolization of eggs via the arterial system or retrograde venous flow.3,4 In this case, it was likely ectopic migration of the fluke pair to the cerebellar venous system, followed by prolific egg deposition that led to the large area of eosinophilic granulomata and mass effect. This “tumoral” form of neuroschistosomiasis is extremely rare with less than a dozen cases described.4 The cerebellum is the most common site reported in the literature.4 Our patient almost certainly was infected while swimming in Lake Victoria five years earlier. *S. mansoni* flukes can survive up to 30 years in a host, though average life span is estimated 5-10 years.2,5

The pathologic bilateral end-gaze nystagmus, finger dysmetria and intractable vomiting in our patient correspond with the anatomic location of the granulomatous lesion and mass effect. Other reported neuro-ophthalmologic findings in chronic CNS schistosomiasis include papilledema, optic neuritis, optic atrophy, homonymous visual field defects, cortical blindness, ocular motor pareses, ocular dysmetria, and vestibular nystagmus.4,5

After neurosurgery the patient was placed on high-dose dexamethasone. He had an acute deterioration of his mental status, developed hydrocephalus and cerebellar herniation. He had a ventriculostomy placed. He was treated with 5 days of praziquantel (45mg/kg/day) and high dose steroids. While on therapy, he had severe nausea, vomiting, photophobia and meningismus which began to resolve by post-operative day 6. Ten days post-operatively his ventriculostomy was removed, his mental status, cerebellar signs and symptoms substantially improved. He continues to improve with some rare nausea.

References
1. www.cdc.gov/ncidod/dpd/parasites/schistosomiasis/factsht_schistosomiasis
History and Exam
A 76-year-old woman presented to Mayo Clinic Jacksonville on 10-22-02 for complaints of intermittent horizontal diplopia and balance difficulties that began June 2002. She denied any other neurologic complaints.

General neurologic examination was completely normal for age except for tandem gait difficulties. Neuro-ophthalmologic evaluation revealed visual acuity with correction to be 20/30 OU, pinholing to 20/25 –2 on right, and no help with pinholing on the left. Near vision with correction was a brisk J1 on the right and a slow J2 on the left. Color vision was 8.5/10 HRR plates on the right and 9/10 on the left. Visual fields were full to confrontation bilaterally. Pupils were 4mm and 2+ reactive to near and there was no RAPD. The patient had a significant esophoria that was relatively comitant on up, down and lateral gaze, but would sometimes transiently break down to an esotropia. Eye movements revealed slow saccades in all planes but were otherwise normal and full. No eyelid abnormalities were evident. Cranial nerves V and VII were intact. Slit lamp examination showed 3+ nuclear sclerotic cataracts OU. Fundoscopic examination was normal. Laboratory studies included normal myasthenic and paraneoplastic panels.

Four months later, 1-1-03, the patient had 5-minute episode of blank stare, lack of speech, and transient amnesia. The patient was re-evaluated 1-9-03 and had periods of inattention and lack of speech. She was hospitalized for concerns of aphasic transient ischemic attacks. A MRI was performed and showed small vessel disease with no evidence of stroke or other abnormality other than a small left parafalcine meningioma. EEG showed periodic lateralized epileptiform discharges (PLEDS) emanating over the right hemisphere. Presumptive diagnosis was non-convulsive status epilepticus, and the patient was loaded with fosphenytoin. A lumbar puncture on 1/17/03 revealed a normal opening pressure, 1 WBC, 104 RBC, 71 glucose, protein 28, normal West Nile Virus antibodies, and negative HSV and VZV PCR’s. 14-3-3 protein was 4.0 ng/mL (positive > 4 to 8ng/mL). Repeat MRI’s on 1-15 and 1-22-03 were read and reported unchanged. EEG continued to show epileptiform discharges with a periodicity of approximately 1.4Hz, more prominent over the right hemisphere than the left hemisphere. The patient’s condition continued to worsen over the next month with progressive lack of speech (eventually mutism), stupor, left hemiparesis, and eventually coma despite several anticonvulsants (ativan, valproic acid, and phenobarbitalcoma) and steroids. The patient was discharge to a skilled nursing facility on depakote and lamotrigine.

A procedure was performed.
Final Diagnosis
Creutzfeldt-Jakob Disease (Sporadic)-MM1 type

Summary of Case Including Pathology
The patient died and underwent autopsy. The autopsy revealed spongiform changes in the basal ganglia, thalamus, cerebellum, and hippocampus consistent with Creutzfeldt-Jakob disease (CJD). Specialized immunostaining with 3F4, the monoclonal antibody to the prion protein, revealed granular deposits as seen in prion disease (CJD). Immunoblot pattern and Western Blot analysis revealed protease resistant scrapie protein (PrP\textsuperscript{sc}) confirming the diagnosis of prion disease. Codon 129 of the prion protein gene (PRNP) demonstrated homozygosity for methionine (ie., M/M1 type) consistent with sporadic CJD and excluded a familial inheritance.

CJD with classic visual complaints such as visual field loss progressing to cortical blindness is termed Heidenhain’s variant. The neuro-ophthalmologic abnormalities of CJD include geotropic ocular deviation with skew and absence of saccades, periodic alternating nystagmus, and slow vertical saccades, suggesting involvement of the cerebellar nodulus, uvula, and brainstem reticular formation. Periodic alternating gaze deviation (loss of saccades and quick phase of nystagmus) with cyclical tonic deviation of the eyes and the head side to side may occur. Supranuclear gaze palsy has been reported in familial CJD associated with codon 200 mutation.

Discussion: Sporadic CJD occurs worldwide with an incidence of 0.5 to 1.0 cases per million population per year. Sporadic CJD (sCJD) may be molecularly and phenotypically classified into six distinct variants based upon either methionine (M) or valine (V) alleles at codon 129 of the prion protein gene (PRNP): MM1, MM2 (types C, cortical and T, thalamic), MV1, MV2, VV1 and VV2 (Table 1). Historically, CJD that presents with progressive visual deterioration has been termed Heidenhain’s variant. Visual signs and symptoms (i.e., visual loss, visual field defects, visual distortion, abnormal color vision and cortical blindness, and excluding hallucinations) are only associated with MM1 and MV1 types.

14-3-3 protein sensitivity was previously reported to be 93-100% in detecting CJD but this value was recently challenged by pathologically-proven CJD cases and found to be only 53 to 61%. Further, the specificity of the 14-3-3 protein is highest when the value is greater than 8ng/mL. False positives of 14-3-3 protein (CJD-mimicking diseases) include rapidly-progressive dementias (Alzheimer’s, Lewy-body, and fronto-temporal), paraneoplastic limbic encephalitis, Hashimoto’s encephalopathy, vasculitis, intravascular lymphoma, toxic-metabolic encephalopathy, non-convulsive status epilepticus, and CNS Whipple’s disease.

Magnetic resonance imaging (MRI) sensitivity and specificity in the detection of CJD has been reported as 67% and 93%, respectively. The MRI abnormalities in sCJD typically include bilateral, symmetric signal intensities on T2-weighted, FLAIR, diffusion-weighted (DW) and proton density-weighted images in the basal ganglia (i.e., putamen, globus pallidus, caudate nucleus), insular cortex, thalamus, and in one case (with Heidenhain variant) occipital cortex. EEG findings in sCJD include periodic sharp wave complexes (PSWC), which are typically unilateral, focal, or absent, and seen in 88% of patients within 12 weeks of onset of clinical symptoms. Eight-three percent of patients with sCJD and those with typical PSWC’s recorded during the first four months of symptoms were exclusive to only the MM1 and MV1 types. The presence of PSWC with clinical, cerebrospinal, and MRI findings consistent with CJD are diagnostic.

Conclusion: We present a case of sporadic Creutzfeldt-Jakob disease associated with the M/M1 type. Patients with this genotype often present with visual complaints and were historically called Heidenhain’s variant of CJD. MRI did not show evidence of typical patterns seen in CJD, and the 14-3-3 protein was not confirmatory. The EEG abnormality that was thought to represent status epilepticus likely represented PSWC.
Table 1: Characteristic Differences between the Different sCJD variants

<table>
<thead>
<tr>
<th>SCJD variant</th>
<th>MM1</th>
<th>MV1</th>
<th>VV1</th>
<th>MM2*(T &amp; C types)</th>
<th>MV2</th>
<th>VV2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of Cases</td>
<td>With MV1 70%</td>
<td>With MM1 70%</td>
<td>15.3</td>
<td>31</td>
<td>17.1</td>
<td>16</td>
</tr>
<tr>
<td>Age at Onset (y)</td>
<td>65.5</td>
<td>62.1</td>
<td>39.3</td>
<td>58.3</td>
<td>59.4</td>
<td>61.3</td>
</tr>
<tr>
<td>Duration (mo)</td>
<td>3.9</td>
<td>4.9</td>
<td>15.3</td>
<td>15.6</td>
<td>17.1</td>
<td>6.5</td>
</tr>
<tr>
<td>Previous Classification</td>
<td>Myoclonic, Heidenhain variants</td>
<td>Same as MM1</td>
<td>Not established</td>
<td>MM2 thalamic variant</td>
<td>Kuru plaques variant</td>
<td>Ataxic variant</td>
</tr>
<tr>
<td>Clinical Features</td>
<td>Rapid progressive dementia, myoclonus, visual or unilateral signs at onset in 40%</td>
<td>Same as MM1</td>
<td>Progressive dementia</td>
<td>MM2 insomina, psychiatric ataxia, progressive dementia</td>
<td>Ataxia and progressive dementia</td>
<td>Ataxia in onset, late dementia</td>
</tr>
<tr>
<td>Neuropathologic Features</td>
<td>“Classic CJD” prominent involvement of occipital cortex</td>
<td>Same as MM1</td>
<td>Severe involvement of neocortex, striatum, sparing brain stem</td>
<td>MM2 thalamic atrophy and inferior olives. Little pathology in other areas</td>
<td>Similar to VV2 but presence of amyloid-Kuru plaques in cerebellum</td>
<td>Prominent subcortical &amp; brainstem involvement, neocortex deep layers involved</td>
</tr>
<tr>
<td>EEG findings %</td>
<td>Typical changes in 4 mo.</td>
<td>Typical changes in 4 mo.</td>
<td>No typical EEG</td>
<td>No typical EEG</td>
<td>No typical EEG</td>
<td>No typical EEG</td>
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*MM2 types averaged, **Key: Ap=aphasia, At=ataxia, C=cognitive, D=dysarthria, M=myoclonus, O=ocular motor, P=psychiatric (includes insomnia), S=sensory, U=Unilateral, V=visual (one or more of visual loss, visual field defect, visual field distortion, abnormal color vision, cortical blindness). Adapted from Parchi P, et al. Classification of Sporadic Creutzfeldt-Jakob Disease Based on Molecular and Phenotypic Analysis of 300 Subjects. Annals of Neurology. 46:224-233.

References


History and Exam
A 31-year-old woman presented to the neuro-ophthalmology clinic with acute diplopia. The patient awoke with horizontal, binocular double vision and bilateral ptosis. Two weeks later, she noticed worsening ataxia and left-sided weakness.

The patient began walking at 18 months and was clumsy as a child. She complained of weakness and stiffness of her legs that had been chronic, frequently causing stumbling and falls. She had two prior episodes of worsening of her symptoms: the first associated with a viral infection and the second with hip surgery.

The general examination was unremarkable. Visual acuity and color vision were normal. Visual fields were full to confrontation. Both pupils measured 4.5mm, with minimal light response and near response. Lid fissures measured 9mm OD and 10mm OS. Levator function was 6mm OD and 7mm OS. There was a right exotropia noted in primary gaze. The right eye ductions were limited to 25% of normal elevation and adduction; depression was absent. The left eye had 75% of normal adduction, 25% of normal elevation; depression was absent. There was no vertical vestibular ocular reflex in the right eye. The left eye demonstrated a normal Bell’s phenomenon. Ocular saccades to the right were hypometric. The leftward saccades demonstrated poor initiation, velocity, and accuracy. Funduscopic examination was normal.

Neurologic examination was remarkable for decreased temperature sensation on the left face and decreased facial expression on the right. Tone was increased in the lower extremities. Strength testing showed 4/5 weakness in the left arm and both lower extremities. DTRs were 3+ at the knees and absent at the ankles with extensor plantar responses. High arches were present. Finger-to-nose and heel-to-shin testing demonstrated dysmetria, right greater than left. Gait was wide-based and mildly spastic with dystonic posturing of the right arm.
Final Diagnosis
T8993C mutation in the mitochondrial genome

Summary of Case Including Pathology

MRI of the brain showed an enhancing lesion in the dorsal midbrain and hypothalamus. Additionally, a left anterior basal ganglia lesion was present. EMG revealed a sensory-motor axonal polyneuropathy. Cerebrospinal fluid had two oligoclonal bands. Mitochondrial DNA testing showed a T8993C mutation in the ATPase 6 gene.

Our patient presented with neurogenic weakness, ataxia, neuropathy, ophthalmoplegia, and stroke (NANOS). The clinical presentations of mutations at nucleotide 8993 are heterogeneous and include Leigh’s disease (subacute necrotizing encephalopathy), NARP (neurogenic weakness, ataxia, retinitis pigmentosa), or a phenotype resembling spinocerebellar ataxia.1 Missense mutations include either a T to G or a rare T to C substitution. The T to C substitution results in a proline to leucine replacement in a strongly conserved helical domain in the proton channel of the ATP synthetase complex.2 Cell death may ensue secondary to either defective oxidative phosphorylation or superoxide overproduction and apoptosis.3,4 Clinical symptoms usually correlate with the severity of the biochemical defect and the amount of heteroplasm in the tissues. Phenotypes with a higher amount of mutant genomes tend to be more severe,5 with respiratory distress and rapid clinical evolution in infancy (Leigh’s disease). Ataxia, neuropathy, and retinitis pigmentosa appear more frequently in milder forms of disease (NARP).6 Exacerbations frequently occur with intercurrent illness.

Individuals with the rare NARP T8993C DNA mutation are predisposed to developing mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes.7 When compared to the more common T8993G mutation, the T8993C mutation is less likely to produce retinitis pigmentosa or optic atrophy.6 This case illustrates the difficulty of diagnosing mitochondrial disorders based on clinical acumen. Mutations at the 8993 locus result in a heterogeneous phenotype with symptoms of CNS and PNS injury and may masquerade as stroke in a young individual.

References

History and Examination
A 54-year-old Chinese male presented with gradual worsening of vision in the left eye over the last 6 months. The patient also noted his left eye progressively protruding. He had no past medical or surgical history and was not taking any medications.

Examination revealed visual acuities of 20/30 OD and finger counting at 1 foot OS. There was a 2+ APD and markedly diminished brightness sense OS. Color plates, normal in the right eye, could not be tested in the left. The left eye was proptotic, and Hertel exophthalmometry measurements were 19 mm OD and 21 mm OS, over a base of 108 mm. There was mild resistance to retropulsion of the left eye. The patient had normal ductions and full motility OU. Palpebral fissures were 10 mm OD and 12 mm OS. Funduscopy revealed mild temporal pallor in the left eye.

Thyroid function tests were unremarkable. CT and MRI scanning of the orbit revealed bilateral extraconal soft tissue masses superior to the levator palpabrae superioris and superior rectus muscles, extending posteriorly and intracranially. The mass on the left side involved the cavernous sinus and left petrous portion of the temporal bone. There was also a left inferior orbital mass causing bone remodeling of the orbital floor with extension into the maxillary sinus. The masses were isointense on T1 and hypointense on T2 with homogenous enhancement post-contrast.

A diagnostic procedure was performed.
Final Diagnosis
Maxillary/orbital lymphoid tumor

Summary of Case Including Pathology
A transantral approach was used to biopsy the large inferior orbital mass on the left side. The biopsy specimen revealed aggregates of lymphoid cells separated by abundant collagen matrix. There were well-defined follicles and nodules of small lymphoid cells. The follicles had features of benign germinal centers and were composed of a variety of large and small lymphocytes, follicular dendritic cells, and phagocytic histiocytes. The lymphoid nodules showed a combination of B-cell and T-cell populations, as seen on CD3 and CD20 staining. Positive kappa and lambda stains are consistent with the polyclonal nature of this mass.

This case shows the features of a benign lymphoid proliferation that is loosely referred to as orbital pseudotumor. Idiopathic orbital inflammation, or orbital pseudotumor, was first described by Gleason in 1903 as an orbital mass that simulated a neoplasm but was histologically inflammatory. It is the third most common orbital disease, following Graves’ orbitopathy and similar lymphoproliferative disorders. The presentation is often unilateral with periorcular pain, conjunctival injection, lid erythema, chemosis, and diplopia. Symptoms usually develop over days to weeks, and take a benign course. Thus, this case was atypical in that the patient had a painless development of multiple discrete masses bilaterally over a period of 6 months. These masses extended intracranially and led to bone remodeling as well as a compressive optic neuropathy on the left side.

The patient responded to systemic steroids and regained 20/30 vision in the left eye.

References
History and Exam
A 43-year-old woman was referred for bilateral restricted eye movements found incidentally on pre-op assessment by a LASIK eye surgeon. She was able to carry out her daily activities although she had been noticing easy-fatiguability for several months. She had occasional vertical diplopia on looking upward. She noticed gradual difficulty moving her eyes for the past two years. Upon direct questioning, she noted she has muscle cramps in shoulders and legs in doing simple tasks like drying her hair, reaching for a book and climbing stairs.

Past medical history includes paroxysmal tachycardia in the past few years. She also had meningitis at age 27, psoriasis, osteoarthritis, cirrhosis of liver, cholecystectomy and positive Factor V Leiden (asymptomatic). Medications include Atenolol for tachycardia and Celebrex for arthritis. Family history is positive for DVT in a sister, Factor V Leiden in her father and all her siblings, as well as multiple sclerosis in her mother.

Examination revealed normal visual acuity, fields, color vision and fundi. Pupils were normal. Ductions were severely restricted on upgaze but full on downgaze in both eyes. Abduction and adduction were about 50% of normal in each eye. There was no ptosis nor proptosis. The remainder of neurological exam was normal.

Laboratory tests, imaging and finally a diagnostic procedure were performed.
Frozen Eyes and Muscle Cramps
Answer

Final Diagnosis
McArdle’s disease (Glycogen Storage Type V) causing chronic progressive external ophthalmoplegia (CPEO).

Summary of Case Including Pathology
Blood work including free T3, T4, antithyroglobulin, anti-microsomal antibodies, CK and lactate were normal. CT scan of the orbits were normal. Magnetic resonance imaging of the brain was normal except for a small non-specific focus of abnormal signal in the right parietal subcortical white matter. Repetitive nerve stimulation study and single fiber EMG were normal.

A left deltoid muscle biopsy was performed. Areas of isolated muscle fibers with subsarcolemmal accumulation of glycogen were seen. Only one ragged red fiber was seen among multiple sections stained with modified Gomori trichrome. PAS showed increased glycogen content throughout the cytoplasm. Phosphorylase stain showed markedly diminished enzyme activity when compared with control. The endomyosial connective tissue and mitochondria were normal on EM.

McArdle’s disease (Glycogen Storage Type V) is also known as Cori’s syndrome, Cori’s type V glycogenosis and McArdle-Schmid-Pearson syndrome. It is a rare condition caused by an inborn abnormal accumulation of glycogen in muscle tissue due to phosphorylase deficiency, an enzyme which initiates the breakdown of glycogen in skeletal muscle. Onset is usually in the first two decades of life, but can occur in infancy or adulthood. Presenting symptoms include exercise intolerance secondary to severe muscle cramps during exercise, and stiffness shortly afterwards associated with rhabdomyolysis and myoglobinuria. “Second wind” phenomenon, described as a sudden, marked improvement in exercise capacity following a brief rest, is characteristic.

Proximal muscle weakness in the upper and lower limbs can also be seen in older patients. Unlike other types of glycogenosis, the disease is not fatal. Inheritance is autosomal recessive (chromosome 11q 13). More than 30 different mutations have been identified. Allelic heterogeneity is common. Common mutations include Arg49 stop (nonsense) in exon 1 (in Britain, US and Germany), a skipped codon 708/709 (in Japan), and G204S (10%).

A triad of progressive ophthalmoplegia, glycogen storage and abnormal mitochondria was first described by Sluga and Moser 1 in four cases. Since then, three additional cases have been reported. 2 4 DiMauro et al. 2 reported a 40 year old man with bilateral ptosis and ophthalmoplegia at age 12, together with muscle weakness of the arms. Muscle biopsy showed increased glycogen and large number of mitochondria with paracrystalline inclusions. Moggio et al. 3 described a 43 year old man with painful cramps after muscular efforts, progressive bilateral ptosis, limitation of eye movements in all directions, and weaknesses of the orbicularis, facial and shoulder muscles. Muscle biopsy revealed many ragged red fibers in type I fibers with abnormal mitochondria. Increased glycogen content was found between myofibrils and beneath the sarcolemmal membrane in type II fibers, which contained normal mitochondria. Scelsi et al. 4 reported a 66 year old woman with bilateral ptosis, marked limitation of eye movements, weakness of the sternomastoid and proximal muscles of the upper and lower limbs. Muscle biopsy showed ragged red fibers and abnormal mitochondria on EM. Abnormal glycogen accumulation was found within the mitochondria, between myofibrils, and beneath the sarcolemmal membrane. In all three cases 2 -4 , phosphorylase activity was normal.

Our patient represents a unique case in which external ophthalmoplegia is associated with abnormal glycogen storage as a result of phosphorylase deficiency (McArdle’s syndrome), without any mitochondrial abnormality.

References
History and Exam
A 57-year-old healthy female was referred for persistent postoperative edema/inflammation and blepharoptosis 18 months following bilateral upper and lower blepharoplasty performed in conjunction with a full facelift. Initial facial edema partially resolved leaving persistent swelling of all four eyelids and slowly progressive bilateral blepharoptosis. Past medical history was significant only for seasonal allergies.

Examination revealed infiltration of all four eyelids, which were rubbery to palpation, bilateral blepharoptosis, with an “S-shape” configuration, and palpably enlarged lacrimal glands. Ophthalmologic examination was otherwise unremarkable including visual acuity correctable to 20/20 OU, normal anterior and posterior segments, normal pupil examination, full confrontational visual fields, normal symmetric exophthalmometry measurements and full extraocular motility.
Another Plastic Surgery Disaster?
Answer

Final Diagnosis
Xanthogranuloma

Summary of Case Including Pathology
Orbital magnetic resonance imaging demonstrated bilateral diffuse periorbital infiltration with lacrimal gland involvement. On surgical exploration, via inferior anterior orbitotomy, all tissue planes, from dermis to anterior orbit fat, were involved and obscured with diffusely infiltrative, firm, bright yellow material. Histopathology demonstrated lipid-laden histiocytes, Touton-giant cells and reactive follicles consistent with xanthogranuloma. Addition evaluation questionably identified a monoclonal cell population. Follicles, judged benign, were CD20 positive, contained few CD3 and CD43 positive cells and were kappa, lambda and bcl-2 negative. Mantle cells were IgD negative, with scattered CD3 positive cells, and had a kappa to lambda positive plasma cell ratio of 5:1. Flow cytometry suggested a kappa monoclonal B-cell population (ratio 10:1). Polymerase chain reaction using three sets of primers (FR3A/VLJN, FR2A/VLJH, FR2B/VLJH) detected no heavy chain gene rearrangements. No lymphoproliferative disorder was detected on systemic evaluation including full body imaging, bone scan and serum and urine protein electrophoresis. Oral prednisone achieved a temporary partial response, with recurrence upon taper. External beam radiation (2080 Grad in 13 divided doses) resulted in complete clinical resolution, which persists six months later.

Discussion: Xanthogranulomatous inflammation is encountered in juvenile xanthogranuloma, Erdheim-Chester disease and occasionally in association with lymphoproliferative disorders. Rare isolated occurrences in adults have been reported. It is a histiocytic proliferation often involving the eyelids and orbits with the potential for local destruction including extraocular muscle abnormalities and optic neuropathies. Equally concerning is the possible association with lymphoproliferative disorders. Jakobeic et al., in the initial description of six patients, suggested that xanthogranuloma might be a benign variant of necrobiotic xanthogranuloma, histologically distinguished by interstitial collagen degeneration and almost invariably associated with lymphoproliferative disorders. In fact, one of their patients developed paraproteinemia 25 years after diagnosis and in another a separate focus with necrobiosis was found. In a recent series, one patient died of leukemia 12 years following treatment for xanthogranuloma. In our patient, although judged unlikely, concurrent lymphoma cannot be definitively excluded and periodic evaluation will continue indefinitely. Given the rarity of xanthogranuloma, ideal treatment is difficult to determine. Limited short-term benefit with steroids and variable responses to external beam radiation have been described.

The exact association with blepharoplasty can only be speculated. An entirely causal relationship seems unlikely; however, surgical insult might have stimulated/amplified subclinical disease. Although the temporal correlation may prove coincidental, xanthogranuloma should be considered in the setting of apparent persistent postoperative edema following blepharoplasty.

References
History and Exam
A 51-year old Caucasian woman presented to emergency ophthalmology clinic with bilateral sequential vision loss. She developed a sudden “dark spot” in the right eye on the morning of presentation, which she attributed to her longstanding migraines. She denied any positive visual phenomena at the time of her vision loss, and denied any significant pain or discomfort. She opted to sleep for an hour in hopes that she would abort the onset of her typical migraine headaches. When she awoke 90 minutes later, she was “blind in both eyes.” She denied pain or retrobulbar discomfort other than her longstanding chronic daily headaches, which she experienced for years. She also denied scalp pain, jaw tenderness, or constitutional symptoms of giant cell arteritis. On further inquiry, the patient had previous medical problems, which began 6 years ago. She developed symptoms of xerostomia, rash, and arthralgias at that time. She saw a rheumatologist, and was diagnosed with hypersensitivity vasculitis and then Sjogren’s syndrome, based on the findings of an elevated serum sedimentation rate (70 mm per hour) and rheumatoid factor (606 KU/L, normal <35). Cell count with differential, electrolytes, Sjogren’s specific antibodies (SS-A and SS-B), serum protein electrophoresis, anti-nuclear antibody (ANA) and anti-neutrophil cytoplasmic (ANCA) titres were normal, anti-DNA antibodies and complement levels were normal. The creatinine kinase (700) and aldolase (10) levels were elevated. Hepatitis serology was negative. Schirmer’s testing was normal at the time. Urinalysis showed trace protein, and mild hematuria. A chest x-ray and abdominal ultrasound were normal. Electromyography and nerve conduction studies were normal. The patient was treated with oral prednisone (1 mg per kg daily) with a slow taper for approximately one and half years, until her symptoms resolved. The patient remained well, except for symptoms of arthralgias 4 years later. The aforementioned serological tests were all within normal limits, as was the urinalysis. Three months prior to her vision loss, the patient developed pain, bilateral upper eyelid orbital swelling and diplopia. At that time, a CT scan of the orbits and orbit echography demonstrated enlarged lacrimal glands. The patient was treated with oral prednisone (1 mg per kg per day) at the time of her vision loss.

The examination demonstrated normal vital signs. Blood pressure was 130/70 mm Hg. The visual acuity measured hand motion vision in both eyes. Pupils measured 4.5 mm in both eyes, and constricted to 3 mm in bright light. There was no relative afferent pupil defect in either eye. The external ocular examination showed bilateral lacrimal gland enlargement, with proptosis in the left eye more so than the right eye. There was injection of the conjunctival and episcleral vessels of both eyes. Slit lamp biomicroscopy was normal, and the intraocular pressures measured 15 mm Hg by applanation tonometry in both eyes. There was mild limitation of abduction in both eyes. Dilated ophthalmoscopy demonstrated bilateral central retinal artery occlusions, with cherry red spots. The remaining cranial nerves were within normal limits, except for diminished auditory acuity in both ears. The patient wore hearing aids. There were no carotid bruits. The motor, sensory, coordination, and gait systems were normal. The cardiac examination was normal, and the only additional clinical findings included splinter hemorrhages in the distal nail beds of the upper and lower limbs.

Fundus angiography confirmed the presence of bilateral central retinal artery occlusions with partial reperfusion. A chest x-ray, carotid Doppler ultrasound testing, cranial magnetic resonance imaging and an echocardiogram were normal. Serum cell count with differential, electrolytes, ANA, complement levels, angiotensin converting enzyme, anti-phospholipid antibodies were within normal limits. Renal studies and urinalysis were normal. The serum sedimentation rate (60 mm per hour) was elevated.

A diagnostic procedure was performed.
Final Diagnosis
A limited form of Wegener’s Granulomatosis

Summary of Case Including Pathology
A left eyelid and orbital biopsy was performed, which demonstrated acute neutrophilic infiltrate and necrosis. There was evidence of chronic granulomatous inflammation, but unfortunately the results were non-specific. Repeat serological studies were of greater diagnostic value, because the c-ANCA level was positive with a markedly positive PR-3 EIA titre (100 units, normal 0-10). The p-ANCA and MPO EIA levels were negative.

Wegener’s granulomatosis (WG) is an inflammatory systemic vasculitic disorder affecting the upper airways, lungs, and kidneys with both classical and limited forms of expression1,2,3. In the classical form, both the pulmonary and renal systems are involved. In limited forms of the disease, the renal system is spared, and ocular involvement may be the presenting feature1. In our case, the diagnosis of WG was a diagnostic challenge, as the patient demonstrated neither pulmonary nor renal involvement. The eye may be involved in 52% of cases during the course of the disease 1,4,7 and in 8-16% of cases, ophthalmic disease is the presenting feature1,4. Ophthalmologic manifestations include conjunctivitis, scleritis, episcleritis, optic neuritis, retinitis, central retinal artery ischaemia, and cranial nerve paresis1,2,7. Vision loss may occur through a number of mechanisms including vascular occlusion macular edema, inflammation of the retina, glaucoma and damage to the optic nerve or corneoscleral tissue7,9. Our patient developed permanent vision loss from bilateral central retinal artery occlusions secondary to WG, which has been infrequently reported in the English language literature5,8,15.

In addition to the clinical presentation, the diagnosis of WG is suggested by laboratory and radiological findings. Three major histopathological findings define WG including parenchymal necrosis, vasculitis, and granulomatous inflammation. The classical clinical findings may not be present in WG1, and the absence thereof does not preclude the diagnosis, as was evident in our case13. Additional serological tests may also be abnormal in WG, but not diagnostic. Non-specific findings of systemic inflammation may include normochromic anemia, leukocytosis, thrombocytosis, and decreased serum albumin. Creatinine clearance, urine chemistry, and examination of urine sediment may be useful to diagnose glomeronephritis, as three-fourths of patients with WG will develop renal involvement. In our case, and limited forms of WG, the renal screen may be negative13.

Autoantibodies directed against cytoplasmic neutrophil antigens or proteinase 3 anti-PR3 have been well described in patients with WG. These antibodies are called antineutrophil cytoplasmic antibodies or ANCA. Of all the ANCA found in WG, 80-95% are C-ANCA antiPR3,1,4. Most of the remaining 5-20% are p-ANCA anti-myeloperoxidase (MPO). The absence of c-ANCA does not preclude the diagnosis of WG, as 5-10% of cases of WG may be serum c-ANCA negative5,13. These autoantibodies are less common in limited forms of the disease, as was apparent in our case. The ANCA titre may parallel the course of the disease, and in our case the patient was seropositive for c-ANCA at the time of vision loss. The disappearance of ANCA can be associated with clinical remission, and patients who maintain negative or decreasing titres after therapy are at lower risk for clinical relapse (5-20%). However this relationship is not absolute and the ANCA titre may be discordant with the disease process in one-third of patients1.

Untreated, WG is fatal. Treatment with corticosteroids and immunosuppressive agents such as cyclophosphamide has improved the prognosis of the disease. For this reason, early recognition of atypical forms of WG is imperative to prevent serious morbidity and mortality among patients.

References
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The Eye That Went to the Dogs

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History and Exam
A 48-year-old white woman presented to the ophthalmologist with four days’ history of droopy right eyelid.
She was in her usual state of health until three weeks ago at which time she was treated for right foot infection with Avelox.
One day prior to the development of ptosis OD, she complained of right eye pain associated with photophobia and right-sided headaches. All of these symptoms were worsening.
Past medical, surgical and family history was unremarkable.
On initial physical examination she was afebrile, BP 104/78, P 96 and RR 16. Her ophthalmological examination was unremarkable except for 2mm, non-fatiguing ptosis OD with palpebral fissures 8mm OD and 10mm OS. Her best-corrected visual acuity was 20/20 OU and there was no proptosis or relative afferent pupillary defect. She had full extra-ocular movements, equal pupils, normal slit lamp and fundus examination. Her visual fields were full OU. Neurological examination was unremarkable. Laboratory tests were obtained, including CBC, thyroid function tests and ESR. All of these were normal.
MRI scan of the brain and orbits with gadolinium and fat suppression showed enhancement and enlargement of the extraocular muscles, enhancement of the anterior and posterior orbital structures and optic nerve OD.
She was started on high dose prednisone and by day five her ptosis resolved and was asymptomatic.
Thirty-one days after her initial right eye pain, while still on prednisone, she developed right facial weakness with inability to close her right eye. Her neuro-ophthalmic examination was consistent with right peripheral seventh nerve palsy. Lumbar puncture showed opening pressure of 17cm of CSF, WBC 168, differential: seg-2, lymph-91, RBC 476, protein 253, glucose 44 and Gram’s stain negative. Repeat MRI of brain and orbits with gadolinium and fat suppression showed complete resolution of the previous changes but some new findings.
She was admitted to the hospital for treatment.
The Eye That Went To The Dogs

Answer

Final Diagnosis
Central nervous system Lyme disease

Summary of Case Including Pathology
48-year-old woman presented with right eye pain and one day later developed ptosis OD. There were no signs of orbital/ocular or systemic infection. She had normal CBC, thyroid function tests and ESR.

*Initial MRI* of the brain and orbits on the T1-weighted post contrast, fat suppression thin views showed enhancement of the right anterior and posterior orbital structures, optic nerve sheath and all extra-ocular muscles. The right extra-ocular muscles were also enlarged. There was no enhancement of the cranial nerves. There was a small right maxillary sinus cystic lesion, most likely an inclusion cyst.

High dose prednisone was recommended for the presumed diagnosis of orbital pseudotumor. However, initially only 20 mg of prednisone was started on which ptosis OD resolved by day five but there was continued mild-to-moderate right eye pain. Therefore, her prednisone was increased to 60mg QD on which she became asymptomatic. Her prednisone was tapered by 10mg q 3 days down to 5 mg a day. During this time she also developed some joint and back pain for which she saw a chiropractor.

While still on prednisone 5mg QD developed right peripheral VIIth nerve palsy. Social history of living in a wooded area and “pulling ticks from the dogs” were obtained.

*Laboratory test* showed positive serum Lyme IgM antibodies: 39, 23 KD and IgG: 58, 45, 41, 39, 30, 23 and 18 KD by Western blot.

Lumbar puncture was also positive for Borrelia burgdorferi IgM: 1:1 and IgG: 1:32 by IFA but negative for HSV and VDRL.

*Repeat MRI* of the brain and orbits with gadolinium and fat suppression showed resolution of the previous right orbital findings but enhancement of the seventh cranial nerve.

She was admitted to the hospital for treatment with ceftriaxone 2gr IV QD for the presumed diagnosis of CNS Lyme disease. The patient by the next morning was noted to have mild left Bell’s palsy. She received four weeks of IV antibiotic treatment and showed gradual improvement with mild residual right seventh nerve palsy.

References
History and Exam
A 55-year-old male developed left temporal headaches in February 2002. Past medical history consisted of hypertension, diabetes, and hyperlipidemia, treated with terazosin hydrochloride (Hytrin), hydrochlorothiazide and bisoprolol (Ziac), rosiglitazone maleate (Avandia) and pravastatin (Pravachol). Four months following headache onset, on 6/22/02, he developed binocular oblique diplopia. A brain MRI on 6/25/02 showed increased T2 signal within the splenium of the corpus callosum and contiguous left enhancing periventricular white matter, while an LP 6/27/02 revealed a normal formula including protein 50.

Ophthalmologic exam 7/1/02 revealed VA 20/20 OU, a 2 prism diopter LHT in left gaze which increased to 14 PD LHT in right gaze, with 8 degrees relative cyclotropia, disc edema OS, and nonspecific changes in the right hemifield on Humphrey 24-2 computerized perimetry. Repeat brain MRI on 7/13/02 showed slight interval progression of the increased T2 signal seen in the previous imaging. Repeat exam 7/18/02 revealed VA 20/20 OU and disc edema OS>OD. Repeat brain MRI 8/21/02 showed the lesions described earlier with a new 5 mm nodular enhancing area in the medial-most aspect of the left temporal lobe.

He was admitted 8/22-26/02 and LP 8/23/02 revealed protein of 106 mg/dL, with otherwise normal formula, and negative high volume cytology. MBP, oligoclonal bands, AFB, CMV, HSV, viral, fungal and CSF cultures were negative. ANA, HIV, RPR, CEA and PSA were normal. Chest and abdominal CT scans were negative. Exam 8/26/02 revealed VA 20/20 OD and 20/30 OS with an RAPD OS and disc edema OS>OD. Humphrey 24-2 computerized perimetry showed a nasal field defect OU. IVMP 1 gm qd x 3 days was administered and followed by prednisone 40 mg po qd x 2 weeks upon hospital discharge, with no improvement.

Repeat MRI 9/02 showed enhancement of the left optic nerve and relatively stable intracranial findings. Evaluation on 9/17/02 revealed visual acuity 20/20 OD and HM OS, an RAPD OS, and disc edema OS>OD. Vision OD subsequently worsened, followed by slight dysarthria and dysphagia in late September 2002. Exam 9/26/02 demonstrated VA 20/25 OD, NLP OS, with 8/10 HRR plates OD and an amaurotic pupil OS. A temporal hemianopia was present OD. Disc edema OS>OD was evident, with peripapillary heme OS and a superotemporal branch retinal vein occlusion. Right trigeminal hypoesthesia was noted.

A diagnostic procedure was performed.
Double Then None from More Than One
Answer

Final Diagnosis
Glioblastoma Multiforme

Summary of Case Including Pathology
Stereotactic biopsy of the left splenium of the corpus callosum was performed on 10/11/02. Histopathology revealed a grade 4 fibrillary astrocytoma (WHO, glioblastoma multiforme).

Subsequent History: The patient noted episodic tingling in his left arm, anorexia and a 13-pound weight loss over two weeks in October 2002. On 12/10/02, the patient completed six weeks of external-beam cranial radiation and started his first cycle of systemic chemotherapy with BCNU and benzyl guanine, but subsequently expired on 12/19/02.

Discussion: Glioblastoma multiforme (GBM) is the most common and aggressive of adult glial tumors, usually in the 5th-6th decades of life. GBM can present with multiple tumor foci, either with microscopic connections or CSF spread (“multifocal”), or as isolated, anatomically-distinct tumors (“multicentric”).1-2 Leptomeningeal dissemination was a presenting feature in 14% of malignant astrocytoma cases in one series.2 The proximity of the radiographic epicenter of the tumor to the lateral ventricle in this patient could explain the CSF spread of tumor cells from the splenium of the corpus callosum to the optic nerves. Cells penetrating into the CSF can form secondary leptomeningeal deposits throughout the neuroaxis.4 Solid tumor deposits disseminated in this manner usually appear as plaque-like foci in the leptomeninges invading Virchow-Robin spaces or with nodular deposits on nerve roots. Cranial nerves most commonly involved in leptomeningeal gliomatosis include II, VI, and VII, probably due to their long intracranial tracts, although there are reports of GBM affecting CN III and IV.5

Multicentric gliomas are widely separated lesions in different lobes or hemispheres with an absence of histological continuity, and can be separated by time of occurrence. This is found in 2-10% of patients with malignant gliomas.1-7 Willis8 suggested that multicentric lesions could result from a two-step process. In the first stage, “initiation,” a large area or perhaps the entire brain undergoes neoplastic transformation, becoming more susceptible to neoplastic growth. In the second stage, “promotion,” neoplastic proliferation in multiple sites occurs following various kinds of stimulation (biochemical, hormonal, mechanical or viral).

The question of whether this patient has a multifocal or multicentric glioblastoma could be aided by autopsy findings; however, this was not performed in our case. Nonetheless, if patients present with multiple lesions within the brain and varied neurological symptoms, GBM should be included in the list of clinical considerations.

References
History and Exam
A 47-year-old right-handed Caucasian woman presents with a chief complaint of intermittent vision loss in her left eye. She had diabetes, hypertension, hypothyroidism, hypercholesterolemia, allergic sinus disease, and no significant past surgeries. Her medications were Synthroid, Metformin, Avandia, Metoprolol, Paxil CR, Lipitor, and Naproxen. She occasionally drank alcohol and did not smoke tobacco. Family history was remarkable for a father with glaucoma and aneurysm.

Two months prior to presentation, she began to notice intermittent blurry vision in her left eye. She had some sinus congestion but was otherwise in good health. She did not experience any double vision or headache.

On presentation, she had a visual acuity of 20/30 in the right eye and 20/40 in the left eye. In the left eye, she had diminished color vision and constriction of her visual field on confrontational testing. Humphrey visual field (24-2) in the right eye was normal. In the left eye, there was general depression with a mean deviation of -23.28. Pupils were 5 mm bilaterally with a 1.8 log unit left relative afferent pupillary defect. External examination disclosed left-sided proptosis with mild conjunctival chemosis. A palpable mass was present in the left superior orbit. Lid examination disclosed no paralysis or lagophthalmos. She had 3 mm of proptosis of the left eye on exophthalmometry. She had symmetric facial sensation and strength. Extraocular motility was full in the right eye while the left eye had a -2 deficit of elevation, depression, abduction, and adduction. In primary gaze, she had a 10 prism diopter left hypertropia and a 6 prism diopter exotropia. Intraocular pressures were 16 in each eye. Slitlamp examination of the left eye showed mild conjunctival injection. Dilated fundus examination of the right eye was normal while the left eye had a swollen optic nerve with some peripapillary optic nerve hemorrhages. The veins were mildly engorged. There were no cotton-wool spots.

MRI of the brain and orbits with contrast showed a large extra-axial, lobular, dural based homogeneously enhancing mass, extending to the left superior intraorbital extraconal space with bony erosion of the left orbital roof and lateral wall of the left orbit. This mass was mostly isointense to the gray matter on both T1 and T2 weighted images. This mass did not appear to extend to the adjacent paranasal sinuses.
Feel Like a Giant
Answer

Final Diagnosis
Hemangiopericytoma

Summary of Case Including Pathology
Pathology demonstrated a highly cellular neoplasm with prominent nuclei. “Staghorn” vessels were present. The tumor was immunostain positive for CD34 and Factor XIIIa and negative for GFAP and smooth muscle actin. These findings were consistent with a hemangiopericytoma.

Giant Tumors of the Anterior Skull Base: Giant anterior cranial base tumors are defined as those with a tumor equivalent diameter of greater than 4.5 cm. Giant tumors involving the anterior skull base arise from the bony skull base itself, intracranially, or from the sinonasal tract and orbit. It may be difficult to determine the site of origin of giant tumors as anatomical boundaries are frequently breached. The presence of dural and perineural invasion influences both prognosis and surgical planning.

The differential diagnosis of giant tumors of the anterior skull base from common to rare includes epithelial sinonasal malignancy, meningioma, chondrosarcoma, benign fibro-osseous lesions, esthesioneuroblastoma, and hemangiopericytoma.

Epithelial sinus malignancies comprise 39% of cases and include squamous cell carcinomas and adenocystic carcinomas. Meningiomas arising from the olfactory groove or tuberculum sella account for 12–22% of all meningiomas. They are calcified in 10-20% of cases, and a linear enhancing “tail” extending away from the tumor mass is a characteristic feature in 60% of cases. Skull base chondrogenic tumors are more commonly malignant than those elsewhere in the head and neck. Benign fibro-osseous lesions encompass both fibrous dysplasia and ossifying fibromas. Esthesioneuroblastomas are rare, slow growing malignant neoplasms which usually arise from the basal layer of olfactory mucosa in the region of the olfactory plate or superior nasal cavity.

Hemangiopericytomias account for 1% of giant tumors involving the anterior skull base and arise from neoplastic pericytes. Hemangiopericytomias were formerly thought to represent a subclass of meningiomas referred to as angioblastic meningiomas. On neuroimaging, they are often mistaken for meningiomas. On CT scanning hemangiopericytomias are moderate to intensely enhancing, well defined, hyperdense masses. Although they may resemble meningiomas as in this case, these tumors tend to erode bone instead of inducing hyperostosis. They rarely contain calcification. MR images demonstrate low to intermediate $T_1$ signal and intermediate to high $T_2$ signal intensities. There may be some $T_2$ heterogeneity and there is always marked gadolinium enhancement.

Distinguishing hemangiopericytomias pre-operatively is advantageous as treatment consists of total surgical excision with careful maintenance of the tumor capsule. Incomplete excision may lead to local infiltrative growth. Postoperative adjuvant radiotherapy is often recommended. Local recurrence and metastases outside the central nervous system can develop years after diagnosis and adequate treatment of the primary tumor. Both radiation and chemotherapy have been used for recurrences.

References
The Cavernous Sinus Is Normal?

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History and Exam
This is the case of a 61-year-old male, seen initially on June 28 by neuro-ophthalmology for diplopia and facial numbness. In May he developed tingling and numbness on the left chin progressing to involve the entire left side of the face over one month. A brain MRI was interpreted as “inconclusive” although that scan is unavailable. In late May the left eye “froze,” “it moved hardly at all.” This led to repeat MRI on June 1 that was said to be negative for lesions. An MRA showed an 80% stenosis of the Lt ICA. A spinal tap was done at that time. CSF showed a low-grade pleocytosis but was otherwise normal. Cytology was not performed but no malignant cells were appreciated on smear. Lyme serology done because of recent travel to CT was negative as were IgG studies. Because of the carotid stenosis the patient underwent carotid endarterectomy (CEA).

While in the hospital he was found to be anemic, leading to diagnosis of colon cancer. Colectomy was performed for stage C, invasive, moderately to poorly differentiated adenocarcinoma with 4 of 9 nodes positive. Imaging of the abdomen and chest revealed no metastatic lesions in liver or lungs. The patient started on chemotherapy (Camptosar 125 mg/M2, leucovorin 20/mg/M2, 5-FU 350 mg/M2 on a three week on, fourth week off treatment) beginning in early June, completing one course by the time of his evaluation and completing a second course during the next month.

PMH: unremarkable other than as detailed above.

On exam, visual acuity, color vision, pupil reactions, anterior segment and fundi were all normal. There was age-related ptosis with mild but symmetrically weak eye closure. Eye movements OD were normal. In primary position OS was fully deviated medially, moved to the midline but not past it on left gaze and had full vertical movements. The general neurologic examination was unremarkable. Specifically there was no facial motor weakness, hearing was normal, and tongue, soft palate function and gag were intact.

The patient’s findings localized to the left cavernous sinus region. The patient’s oncologist was enthusiastic about the patient’s prognosis with chemotherapy, stating that the absence of any metastatic disease in the liver or lungs argued strongly against metastatic colon cancer. She agreed, however, that another MRI was appropriate and on July 16 a repeat study was also interpreted as negative, no metastases. Both MRI’s were obtained for review.

On review the initial MRI on June 1 was found to have marked, symmetric enlargement of both cavernous sinuses. There was some extracavernous extension on the left in the region of the petroclival region where the fifth nerve crosses over the petrous apex and the sixth nerve enters the cavernous sinus. Interestingly, the MRI of July 16 showed marked resolution of the cavernous sinus enlargement but persistence of the petroclival mass adjacent to the cavernous sinus. In addition, the trigeminal nerve could be seen to enhance. A reading without history by our neuroradiologist indicated infiltrative or inflammatory conditions as the most likely diagnosis, specifically lymphoma or sarcoid. With the history of cancer the neuroradiology comment was that metastatic cancer was always a possibility. The oncologist remained skeptical and continued chemotherapy. A spinal tap with cytology was normal in all respects.

Management choices: Repeat CSF cytologies; biopsy; observation?
Final Diagnosis

Since this is a neuro-ophthalmology-pathology symposium the answer must be biopsy. At the time, however, the radiologic findings had improved and therefore the patient was followed with planned repeat MRI one month later. He finished the second course of chemotherapy but was clinically unchanged. Repeat MRI showed return of cavernous sinus enlargement with enhancement of additional cranial nerves. A biopsy/decompression of the extravascular extension in the petroclival region was done. The pathology report was metastatic poorly differentiated adenocarcinoma of colonic primary with essentially identical morphology as that of the original colon tumor.

Summary of Case Including Pathology

In an earlier time, Thomas and Yoss reviewed 102 cases of parasellar syndrome at the Mayo Clinic and found 13 cases of inflammation (Herpes zoster, Tolosa Hunt, arachnoiditis, giant cell arteritis, Wegener’s granulomatosis and Lu’s), 19 neuritis, and 70 neoplasms. Of the neoplasms, four were lymphoma or multiple myeloma and 23 were distant metastases, two from the GI tract. The majority, two-thirds, of neoplastic parasellar syndromes at the cranial base are the result of a primary intracranial tumor (pituitary adenoma, meningioma, craniopharyngioma, neurofibroma, chordoma) or local spread of a sinus or nasopharyngeal tumor, a figure likely to remain valid in today’s world of sensitive neuroimaging. Thomas and Yoss did not note how in many patients the neurologic syndrome was the presenting problem in the cases with distant metastases. In a review of 17 patients with cavernous sinus metastases, Lanning Kline, Joel Glaser and others had six patients in whom the cavernous sinus syndrome was the presenting complaint but did not specify which primaries these patients had; in any case, none of their patients had GI malignancies. There has been one report of acute bilateral ophthalmoplegia secondary to cavernous sinus metastases from a known colon cancer primary in a patient with known liver metastases. Cavernous sinus syndrome as a presenting symptom of unknown GI malignancies is rare.

Bilateral symmetric cavernous sinus changes raised the possibility of lymphoma. Lymphoma was responsible for two of 17 cases in Kline and Glaser’s series and, along with multiple myeloma, four of Thomas and Yoss’ cases. Three of four of Roman-Goldstein et al.’s cases of primary lymphoma at the cranial base involved the cavernous sinus with periorbital pain and diplopia. Cavernous sinus involvement by lymphoma is not common (see reviews by Galetta and Nakatomi) and primary cavernous sinus lymphoma makes up only a minority of these cases. Bilaterality also does not appear to be very helpful: reviewing cavernous sinus syndrome related to lymphoma, Kasner et al. found only one bilateral case out of 16 cases. Bilateral metastases from distant sites to the cavernous sinuses are also uncommon but probably occur with sufficient frequency that this is not a useful distinguishing feature.

Pain is common in cavernous sinus syndrome whether from distant metastases or lymphoma, sometimes leading to a misdiagnosis of Tolosa-Hunt syndrome. Nevertheless, it is a small majority with non-painful cases being common. A CT scan might have been useful in looking for bony erosion suggesting metastases, but only 8/17 of the patients reported by Kline and Glaser had bony erosion on CT imaging.

The development of metastases without involvement of the liver and lungs certainly occurs with GI malignancies although it is notably unusual. Further it would be highly unusual for adenocarcinoma of the colon to present initially as metastases to the CNS or to the cavernous sinuses or other meningeal structures. The neuroradiologic pitfall in our case may have been the symmetric involvement of the two cavernous sinuses that lured the radiologists into believing there was no disease there.

Initial response to his chemotherapy regimen is not especially helpful. Camptosar and related compounds are used primarily for GI tumors but have been studied in late, refractory hematologic malignancies. The response of meningeal metastases to any systemic chemotherapy is usually not promising so the improved MRI findings were surprising when seen.

References


History and Exam
A 44-year-old previously healthy man presented with one-day history of loss of depth perception and vision loss in his right eye upon awakening. There was no history of pain on eye movements, no other neurologic symptoms and no headaches. Past medical history was notable for Lyme disease five years ago and Bell’s palsy on the right, eight months prior to presentation.

Visual acuity was notable for NLP acuity in the right eye and 20/50 in the left eye with presence of dyschromatopsia on the left and a right afferent pupillary defect. Eye movements were normal. Goldmann perimetry disclosed an inferior temporal visual field defect in the left eye. Funduscopic examination revealed healthy optic discs bilaterally without any evidence of swelling or pallor. The remainder of neurologic examination was normal.

MRI of the brain demonstrated an extensive dural-based mass involving the floor of the anterior cranial fossa along the olfactory groove bilaterally. Radiologic differential diagnosis of the lesion suggested a meningioma, lymphoma, glioblastoma, esthesioneuroblastoma and metastasis.

The patient was admitted to the hospital and started on intravenous steroids. During the next 24 hours there was progressive deterioration of visual acuity in the left eye to 20/200, with worsening color vision and visual fields.

A procedure was performed.
When Small Is Big

Answer

Final Diagnosis
Primary sinonasal small cell carcinoma

Summary of Case Including Pathology
Patient underwent endoscopic sphenoethmoidectomy with biopsy; right optic canal decompression and repair of skull base defect with fascia.

Intraoperatively, the mass was seen to involve the ethmoid sinuses and the olfactory bulb. Bony involvement was also noted posteriorly along the wall of the sphenoid in the region of the optic chiasm.

Pathologic examination of the tissue fragments revealed a poorly differentiated carcinoma with small cells and numerous mitoses. Immunohistochemical and cytomorphological features were most consistent with a poorly differentiated small cell carcinoma.

Oncology work-up including a CT scan of the chest and abdomen, bone scans, bone marrow aspiration and biopsy were negative for primary and metastatic disease. The patient underwent palliative treatment with conventional radiotherapy and chemotherapy (cisplatinum and etoposide). Vision remained NLP OD and counting fingers OS. He ultimately succumbed to his illness, secondary to systemic metastases 18 months later.

Primary sinonasal small cell cancer is an extremely uncommon, highly aggressive neoplasm with very few cases reported in literature. These tumors are histologically identical to the small cell carcinoma arising in the lung. However, review of literature suggests a different clinical behavior for sinonasal small cell cancers, with a propensity for local invasion, rather than early metastatic spread. Although the exact cell of origin is still debatable, sinonasal small cell cancers are believed to arise within the minor salivary glands.

The most common symptoms at presentation of sinonasal small cell cancers are epistaxis, pain, and nasal obstruction. Our case represents a unique, previously unreported presentation of rapidly progressive bilateral vision loss secondary to chiasmal compression/ischemia, occurring as an isolated symptom of this rare aggressive tumor.

Treatment for sinonasal small cell tumors involves a multidisciplinary approach combining surgical extirpation when feasible, along with radiation and adjuvant chemotherapy. Extrapulmonary small cell carcinoma is usually a fatal disease with a 13%, 5-year survival rate. In a recent study from the Mayo clinic, the median survival was only 14.5 months from presentation.

Our case represents a rare presentation of chiasmal visual loss, secondary to an extraordinarily rare tumor. Aggressive malignancies of the paranasal sinuses should be considered in the differential diagnosis of sudden visual loss.

References
History and Exam
A 41-year-old woman presented with new onset headaches in December 2001. The headaches were throbbing, increasing in intensity and severity, occipital, and debilitating. Her son was mosaic for the interstitial deletion on 15q (e.g., Prader-Willi syndrome). She was taking Phenobarbital for seizure prophylaxis. Past surgical history, review of systems, and social history were non-contributory. CT and MR scans showed a large right parieto-occipital/tentorial lesion that was dural based with adjacent edema of the occipital lobe. A presumptive diagnosis of “occipital meningioma” was made. Pre-operative cerebral angiography showed a vascular mass with feeders from the right posterior cerebral artery, petrosal and occipital branches of the external carotid artery, and the posterior meningeal branch of the right vertebral artery. She underwent a 90% devascularization via embolization of the lesion. After the embolization procedure, the patient developed diffuse cerebral edema and a CT scan showed an intraparenchymal hematoma in the right occipital lobe with surrounding vasogenic edema, subdural hemorrhage along the right frontal and temporal lobes, and subarachnoid hemorrhage along the right occipital sulci. The patient underwent an emergent occipital lobectomy. Her hospital course was complicated by a lower extremity superficial venous thrombophlebitis that required vein excision and systemic antibiotics. Post-operatively she had a mild right hemiparesis in the upper extremity greater than lower extremity and visual field loss. On neuro-ophthalmic exam, the visual acuity was 20/25 OU. Goldmann perimetry showed a complete left homonymous hemianopsia. Motility was full, and she was straight in the diagnostic positions of gaze. The pupils measured 4 mm in the dark and 2 mm in the light and there was no relative afferent pupillary defect. Slit lamp exam, intraocular pressure, and ophthalmoscopy were normal OU.
Final Diagnosis
Occipital lobe meningeal hemangiopericytoma

Summary of Case Including Pathology
Pathology showed a hypercellular, vascular spindle cell neoplasm characterized by staghorn, thin walled vascular spaces. Reticulin, CD34, smooth muscle specific actin and muscle specific actin were positive. CD31, desmin, and epithelial membrane antigen were negative consistent with occipital hemangiopericytoma. The patient underwent stereotactic radiosurgery (1750 cGy) and fractionated radiotherapy (5,940 cGy in 33 fractions) two months later. Post-operative MR scans showed a large resection cavity with a pseudomeningocoele, nodular residual enhancement of the right posterior tentorium cerebelli and right occipital encephalomalacia. Bone scan showed no bony metastasis. Chest radiograph was normal. There was no evidence for recurrent or metastatic disease at last follow-up 18 months after initial diagnosis.

Hemangiopericytomas usually occur in the deep soft tissues of the thigh and the pelvic retroperitoneum and are rare in the orbit or intracranial cavity (less than 1%). They are composed of pericytes of blood vessels. These rare tumors may be mistaken for meningioma and formerly were believed to be a type of “angioblastic meningioma.” Immunocytochemistry and morphologic differences allow differentiation from atypical meningioma. Histologic features such as increased mitotic activity, areas of necrosis and hemorrhage, and high nucleocytoplasm ratio may suggest a more aggressive tumor. The CT features are nonspecific with a broad-based dural attachment, variable attenuation, and homogenous enhancement. On MR, the lesion is isointense on T1; slightly hyperintense on T2; and shows diffuse, heterogeneous enhancement. Half of the cases have an irregular or lobulated margin. Unfortunately, the neuroimaging may be indistinguishable from meningioma. MR spectroscopy (high myoinositol) might be able to differentiate the tumors from meningioma but further study is needed. They may occur in the suprasellar space and mimic pituitary adenoma or may involve the dural venous sinuses or cavernous sinus. The treatment of choice is complete surgical excision. Pre-operative embolization may be helpful. Radiation therapy and radiosurgery have shown some benefit especially for residual tumor after resection. Chemotherapy including interferon alpha and doxirubicin has been used in some patients. Recurrences are common and may occur years later even after gross total resection. Extranodal metastases may also develop years later (up to 25% of cases), and occur most frequently in bone and lung. The 10-year survival is only 30%. Although the clinical and radiologic findings may mimic meningioma, differentiation of the two lesions is important because the prognosis, evaluation, and treatment are different. In summary, hemangiopericytoma is a rare intracranial lesion; the prognosis is dependent on completeness of surgical resection; hemorrhagic complications may occur before, during, or after therapy; radiation therapy may be a useful adjunctive therapy; recurrent or metastatic disease is common; and vigilant serial follow up for recurrence or metastasis is recommended.

References
History and Exam
A 37-year-old woman presented in June 2002 when she noticed some drooping of her left lid as well as diplopia. There was no associated pain or headache. Symptoms progressed over several days. She went to a local emergency room, where she was diagnosed with a left third nerve palsy. Head CT was normal. Cerebral angiogram was normal. Lumbar puncture revealed normal opening pressure and normal constituents. MRI demonstrated abnormal signal bilaterally in the pons extending to the medulla, much greater on the right. It was felt to be consistent with chronic ischemic changes, chronic inflammation, or demyelination. A repeat scan in October 2002 did not demonstrate a significant change in this abnormality.

Her past medical history was significant for a recent diagnosis of hypertension, with a diastolic pressure noted to be 115. A prolactinoma was diagnosed at the age of 9 when she presented with vision loss and a field defect OS. The tumor was resected and she received a course of radiation therapy. Her follow-up examination revealed resolution of her field defect and no evidence of optic atrophy.

In February 2003, she presented for a second neuro-ophthalmologic opinion. VA was 20/20 OU, visual fields were full to confrontation, and color plates were full. There was no afferent pupillary defect. Dilated funduscopic exam was unremarkable. There was a complete left third nerve palsy. The remainder of her neurologic exam was normal.
Tracking Down the Third Nerve
Answer

Final Diagnosis
Post-radiation poorly differentiated malignant neoplasm

Summary of Case Including Pathology
Repeat imaging revealed two focal areas of enhancement; one in the left cavernous sinus and suprasellar region, the other in the left pons and midbrain at the site of exit of the left third nerve. MR spectroscopy was consistent with a primary neoplasm of the brainstem. She was given a presumptive diagnosis of a post-radiation brainstem glioma and was treated with temozolomide. After eight weeks, the brainstem lesion continued to progress despite the chemotherapy. The sellar lesion was biopsied.

The final pathology revealed a poorly differentiated malignant neoplasm with pleomorphism and bizarre mitoses. In some areas the tumor appeared spindled, in others it had epithelioid features. Immunohistochemical stains were positive for S100, NSE, and vimentin. The S100 positivity suggested some neuroectodermal or nerve sheath differentiation to an otherwise poorly differentiated tumor.

Radiation-induced neoplasms are a well-recognized complication of radiation therapy. A strong dose-response relationship has been demonstrated, with a relative risk approaching 20 after estimated dosages of 2.5 Gy.1 The most commonly reported secondary tumors are meningiomas. Other secondary tumors include gliomas and sarcomas. Sarcomas are the rarest of post-radiation tumors and include osteosarcoma, fibrosarcoma, and malignant fibrous histiocytoma. The latency period for post-radiation tumors ranges from as short as 1 year to over 30 years1-10 and tends to be shorter for the more malignant tumors. Higher dosages of radiation are also associated with shorter latency periods.7,8 Brada et al. looked at the risk of secondary brain tumors after radiation for pituitary adenomas and found a cumulative risk of 1.3% in the first 10 years and 1.9% over 20 years, with an overall relative risk of 9.38 compared to the general population.9 They also looked at the previously reported cases to assess the latencies. They noted a median latency of 7.0 years (range 1-22) for glioma, 9.7 years (range 5-27) for sarcoma, and 13.8 (range 7-33) for meningioma.9 Although single-fraction radiosurgery is thought to carry a lower risk for secondary tumors, recent reports have demonstrated secondary tumors after radiosurgery, with malignant tumors occurring as early as six years and benign tumors between 16 and 19 years later.10 Our case is unusual given the isolated nature of the neuro-ophthalmic findings despite the extensive abnormalities on neuro-imaging, the multifocal location of the tumor, and the long latency period for such an aggressive, malignant tumor.

References
You Say Neuritis and I Say Neuropathy –
You Say Myelitis and I Say Myelopathy

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History and Exam
A 15-year-old black female presented with a four month history of visual loss in her right eye. Her visual loss initially was progressive over a seven day period, and associated with right periorbital pain, pain on eye movement, and headache. She also complained of left arm and leg heaviness. Because of her symptoms and mild optic nerve swelling on the right side a CT and MRI of the head and C spine were performed and were negative. Despite treatment with IV corticosteroids, the patient reported no improvement in her vision prior to our examination.

In August 1993, our examination showed a visual acuity of counting fingers out of her right eye and 20/15 out of her left eye. A 3.0 log unit afferent pupillary defect was measured on the right. Optic nerve pallor and atrophy was present on the right, intraocular pressures were normal, and no evidence of retinopathy or vascular sheathing was noted. A repeat MRI of the head and orbits was negative.

In December 1995, because of subjective decrease in visual acuity to 20/40 in the left eye, and nonspecific left upper arm pain the patient was retreated with IV methylprednisolone and started on oral methotrexate at a dose of 7.5mg per week. Bloodwork at that time was significant only for an ANA of 1:320 and a Rheumatoid factor of 1:160. The patient's symptoms significantly improved until September 1994, when the patient suffered significant visual loss in her left eye to 20/60, and new paresthesias in her left arm and leg. An MRI of her brain, C-Spine and orbits was significant only for bilateral optic nerve enhancement of the left side greater than the right side. VER testing was performed on 9/8/95 and 9/16/95, which was significant for progressive delay in the P100 value from 109 msec to 125 msec on the left side, despite high dose corticosteroid treatment. No recording was elicited on the right side. Cytoxan was started at a dose of 4 gm over four days, with the patient noting dramatic improvement in her visual acuity on the left side. VER testing showed normalization of the P100 value on the left side to 108, over a 14 day period. The patient was maintained on Cytoxan (150mg per day), and a tapering dose of prednisone.

In March 1995, the patient was readmitted to the hospital because of right sided weakness and numbness. A lumbar puncture revealed a mild lymphocytosis, in the presence of a normal protein, negative oligoclonal bands and normal myelin basic protein. MRI imaging studies were significant for severe periventricular white matter disease and a large cord lesion extending from C2 to C4.

A brain biopsy was performed.
Final Diagnosis
Autoimmune Optic Neuropathy and Associated CNS Vasculitis

Summary of Case Including Pathology
Autoimmune optic neuropathy is diagnosed rarely, and is often misdiagnosed as idiopathic optic neuritis of demyelinating disease. We present the case of a 15-year-old female with progressive bilateral optic neuropathy, and subsequent CNS vasculitis with “variable” laboratory evidence of collagen vascular disease.

Biopsy of parietal white matter revealed small vessel necrotizing vasculitis. Electron microscopy revealed IGG, IGM, and complement within the vessel walls. No demyelination was noted.

Autoimmune optic neuropathy in contrast to idiopathic optic neuritis often leads to severe irreversible visual loss if not treated promptly with high dose steroid and immunosuppressive therapy. The pathology of autoimmune optic neuropathy is disputed in the literature, but because of its response to treatment, it is believed to be at least in part due to an inflammatory etiology.

We evaluated a patient with autoimmune optic neuropathy and subsequent progressive central nervous system involvement. Her signs, symptoms and imaging studies mimicked demyelinating disease, while her laboratory studies, family history, and clinical course suggested a collagen vascular disease. A brain biopsy of cerebral white matter and dura showed diffuse perivascular inflammation in the absence of demyelination. Though long-term secondary ischemic demyelination may occur, the pathogenesis appears to be vaso-occlusive disease in small vessels of the central nervous system.

Primary and Secondary Devic’s Neuromyelitis Optica and Neuromyelitis Optica Plus (i.e., cortical involvement) will be discussed.

References
Another Steroid Responsive Optic Neuropathy?

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History and Exam
In November 2002, a 58-year-old healthy woman was evaluated locally for blurred vision in the left eye for two months. Best corrected visual acuity was 20/20 OD and 20/25 OS with trace RAPD OS and normal Ishihara color plate responses. Visual field was normal OD, and OS had a cecocentral scotoma. The left optic disc had trace temporal pallor with nasal hyperemia. Brain and orbital MRI showed enlargement and enhancement of the intracanalicular and prechiasmatic portions of the left optic nerve. CBC, ESR, RPR, ANA, ACE, thyroid function tests, urinalysis, and PPD were normal. Spinal tap was normal and negative for oligoclonal bands.

In January 2003 she reported worsening vision OS. The patient was treated with IV methylprednisolone 250 mg q6hr for three days followed by oral Prednisone. The vision improved initially and the cecocentral scotoma improved after one week of therapy. The vision then worsened to 20/40 OS, and the visual field showed bigger central and nasal nerve fiber layer related defect. The Prednisone was discontinued after 23 days. Repeat MRI revealed increased thickness and enhancement of the intracanalicular and prechiasmatic and chiasmatic portions of the left optic nerve.

In March 2003, the patient was referred to Bascom Palmer. Best acuity was 20/20 OD and 20/40 OS with a 0.9 log unit RAPD OS. The left eye had central and nasal nerve fiber related defect, and had +3 diffuse optic disc edema. The patient preferred to pursue further work-up locally. CBC, ANCA, ANA were negative. Gallium scan was normal. MRI showed further increase in thickness and enhancement of the left optic nerve. Spinal tap with CSF flow cytometry was normal. Further work-up performed locally included chest CT suspicious paratrachial enhancing lymph node, and fine needle biopsy showed no malignancy. Bone marrow aspirate revealed normal cytology.

In April 2003 the patient was treated again with IV methylprednisolone 250 mg q6hr for three days, and the left eye improved to 20/25 with less RAPD. The patient was placed on Prednisone 100 mg daily with gradual taper. Two weeks later while on Prednisone 60 mg daily, acuity OS worsened to 20/40 with worse RAPD. The Prednisone was subsequently discontinued in June 2003 by patient due to side effects.

The patient returned to Miami for evaluation on June 2003, visual acuity was 20/20 OD and count fingers OS. Visual field OS revealed a central scotoma. The left optic disc showed +3 diffuse edema with +1 pallor. MRI showed further increase in thickness and enhancement of the left optic nerve.

A procedure was performed.
Another Steroid Responsive Optic Neuropathy?

Answer

Final Diagnosis
Optic nerve glioma

Summary of Case Including Pathology
Biopsy of the left optic nerve showed pilocytic astrocytes, with positive GFAP stain. The nuclei were surrounded by vacuolated spaces that appear microcystic with myxomatous change. The findings are consistent with optic nerve glioma.

Optic pathway glioma accounts for 1% to 5% of intracranial tumors and less than 1% of orbital tumors. In about 25% of cases, the tumor is confined to the optic nerve; in 20% to 40% it involves the chiasm; and in 33% to 60% it is posterior to chiasm. Approximately 68% to 78% of optic gliomas occur during the first decade of life, and up to 90% occur by age 20 with 11% to 33% being associated with Neurofibromatosis type I. Occurrence of optic glioma after the fourth decade is rare, and tumors in older age groups tend to be malignant and more progressive.

The clinical course of our 58-year-old patient suggested a steroid responsive optic neuropathy. The transient improvement of her vision with steroid treatment obligated an extensive work-up. Steroid responsive optic neuropathy associated with optic glioma is rare. Pfaffenbach and associates in 1972 reported an 11-year-old boy with optic nerve glioma, who was initially misdiagnosed as optic neuritis with good but transient response to steroid treatment. The mechanism of this improvement is not clear; steroid treatment presumably reduces inflammatory and edematous elements of the glioma.

On follow-up one month after the procedure, the patient’s visual acuity was 20/20 OD and counting fingers OS, visual field was normal in OD with lower nasal defect in OS. The left optic disc showed temporal pallor with no elevation.

There is no consensus for treatment of optic glioma. Observation is recommended in silent lesions. Evidence of tumor enlargement with visual deterioration may support partial or total resection with or without radiation therapy or chemotherapy. Spontaneous regression or regression after optic nerve glioma biopsy or partial resection is well documented in young patients.

References
History and Exam

A 31-year-old African American woman presented with “blurry and jumpy vision.”

Her past medical history was notable for hypertension since childhood, complicated by end-stage renal disease. She was on hemodialysis (right supraclavicular line) from the age of 28 (2000). On 8/02/2002, she underwent an uncomplicated cadaveric renal transplant with ureteroneocystostomy and placement of double J transplant ureteral stent. She did well immediately post-operatively and was treated with clonidine, hydralazine, lopressor, pepcid, magnesium chloride, K-Phos, prednisone (20 mg qd), and prograf (6 mg bid). She was discharged four days later (8/06/2002) to her Georgia home.

On 8/16/2002, she developed fever (39.4 degrees C), diarrhea, upper respiratory symptoms, cutaneous rash, and low back pain. Two days later, she complained of blurry vision, dizziness and unsteady gait. Her condition rapidly worsened and she became confused and obtunded. She was intubated on 8/18/2002 and transferred to the ICU. A brain CT without contrast was unremarkable. Chemistry was unremarkable. CBC showed 15.8 white cells (90% neutrophils, 8% lymphocytes, 2% other), hemoglobin 10.0 g/dl, platelets 237 (10^3/mm^3). A lumbar puncture showed elevated protein (87 mg/dl), 675 white cells per mm^3 (92% neutrophils, 6% lymphocytes, 2% other), and glucose 67 mg/dl. Tacrolimus level was 6.7 ng/ml (within normal limits). She was started on ceftriaxone, vancomycin, and ampicillin for possible bacterial meningitis. However, cultures remained negative. Her prednisone and prograf were discontinued.

She improved and was extubated a week later. A brain MRI with contrast was unremarkable. She was discharged on 9/4/2002, at which time prednisone and prograf were restarted.

At discharge, she complained of persistent gait imbalance and blurry vision. She also noticed that everything was jumping when looking to the side. On examination, she had normal visual function and fundus examination. She had bilateral gaze-evoked horizontal nystagmus and a comitant 4 prism-diopter esotropia. Her nystagmus did not resolve.
Final Diagnosis
West Nile virus encephalitis transmitted through organ donation

Summary of Case Including Pathology
Commercial-laboratory testing of serum collected on 08/23 for West Nile virus IgG and IgM antibody with the use of the indirect fluorescent antibody method was equivocal, with a neutralizing antibody titer of 1:16 (a titer of less than 1:16 was considered to indicate that no antibody was detected); similar testing of the patient’s CSF showed no evidence of West Nile virus antibody. However, CSF specimens collected August 22 and 29 were positive for West Nile virus IgM antibody on IgM antibody capture ELISA at the CDC laboratories. Serum collected 09/11 was positive for West Nile virus IgM and had a neutralizing antibody titer of 1:5120. The patient’s clinical condition improved, and she was discharged to a rehabilitation center on 09/11/2002.

It was determined that the cadaveric kidney used for her transplant was the source of her infection. The organ donor was a previously healthy 20-year-old woman from Georgia who sustained injuries from unintentional trauma on July 30, 2002. On July 30 and July 31, she received 53 units of blood components and 1 pool of cryoprecipitated antihemophilic factor. She was declared brain dead July 31, and her organs were recovered August 1. Screening of the organ donor by the procurement agency revealed no symptoms or laboratory findings suggestive of infection before the fatal injury. Medical records and interviews with family members indicated potential exposure to mosquitoes, but no symptoms of infection were noted before the injury. The donor lived in and traveled through areas of Georgia that had epizootic West Nile virus activity in 2002. Two serum samples collected at the time of admission on July 30, before blood transfusion, had no detectable West Nile virus IgM antibody or nucleic acid. Although a serum sample obtained July 31, after the receipt of all transfusions, had no detectable levels of West Nile virus nucleic acid, serum and plasma samples collected August 1 at organ recovery yielded West Nile virus nucleic acid on quantitative PCR (13 and 5 plaque-forming units per milliliter, respectively) and West Nile virus on culture (Iwamoto et al.).

The other 3 patients who received the other organs (kidney, heart and liver) from the same donor also developed West Nile Virus encephalitis (Iwamoto et al.). The other kidney recipient died from West Nile encephalitis and autopsy was performed (Iwamoto et al.). Extensive evaluations of the other 3 patients as well as from the organ donor and the persons who donated blood to the organ donor were performed (Iwamoto et al.). They identified West Nile virus infection in the organ donor and in all four organ recipients. Encephalitis developed in three of the organ recipients, and febrile illness developed in one. The 3 recipients became seropositive for West Nile virus IgM antibody; the fourth recipient had brain tissue that was positive for West Nile virus by isolation and nucleic acid and antigen assays. Serum specimens obtained from the organ donor before and immediately after blood transfusions showed no evidence of West Nile virus; however, serum and plasma samples obtained at the time of organ recovery were positive on viral nucleic acid testing and viral culture. The organ donor had received blood transfusions from 63 donors. A review of blood donors and follow-up testing identified one donor who had viremia at the time of donation and who became seropositive for West Nile virus IgM antibodies during the next two months. This observation confirms the transmission of West Nile virus by organ transplantation. Blood transfusion was the probable source of the West Nile virus viremia in the organ donor. These cases raise the question of screening donors of organs and blood for West Nile virus.

West Nile virus belongs to a group of flaviviruses that include Japanese encephalitis, St Louis encephalitis, Dengue, and Yellow fever. West Nile virus infects over 150 species of birds as well as mammals such as squirrels, dogs, wolves, horses, and mountain goats. Flaviviruses (arboviruses) are transmitted to humans through mosquito bites. Since its arrival in New York in 1999, West Nile virus has spread rapidly across the United States and into Canada, and has become an expanding pandemic in the Western Hemisphere. Recent experience with the virus has led to new information on viral transmission through organ transplantation, blood transfusion, breast-feeding, and intrauterine infection, along with reports of associated poliomyelitis-like syndrome.

Most persons infected with West Nile virus are asymptomatic or have only mild symptoms. Meningitis or encephalitis develop in approximately 1 of 150 infected persons. Limited data suggest that immunocompromised patients (such as organ recipients) may be at risk for death after West Nile virus infection. Our patient had confirmed West Nile virus encephalitis and developed nystagmus as part of this encephalitis. It is a unique case in which the encephalitis was transmitted — not by a mosquito — but by an organ donor for a cadaveric renal transplant.

Reported ophthalmologic manifestations of West Nile virus include uveitis, optic neuritis, and multifocal chorioretinitis. Ophthalmologic findings are usually associated with fever, headache, myalgia, arthralgia, and a maculopapular rash.

References
History and Exam
A 45-year-old sports coordinator was seen for painless sequential visual loss.

In early May 2003 he had recurrent cold sores treated with valacyclovir. In the middle of May he developed vertigo with earache and tinnitus on the left, which resolved after several weeks. Evaluation was unremarkable. On June 6th he developed flashes of light followed by gradual painless loss of vision in the left eye. When seen on June 18th, he had a large central defect and a swollen optic nerve OS, and normal vision OD. He was treated with oral steroids without benefit. On July 14th he had 20/50 vision OS and a pallid non-edematous optic nerve. Perimetry showed an inferior altitudinal defect with involvement of fixation OS. His vision and field defect in the left eye remained stable. However, on July 18th, he developed flashing in the right eye followed by a visual field defect. The vision in the right eye seemed to worsen daily. It continued to decline through a course of IV methylprednisolone.

He drank alcohol sparingly and did not smoke cigarettes. His medical history was notable for asthma, headaches, and possible hepatitis eight years ago. He was currently taking lansoprazole, prednisone, finasteride (Propecia), aspirin, and vitamins. He had no medication allergies. Review of systems was notable for a cough from November through February, and some difficulty in the last year with nausea, constipation, and diarrhea. Family history was noncontributory. Past ophthalmic and neurologic histories were unremarkable apart from LASIK OU six years ago.

On examination on July 30, visual acuity was 20/200 on the right and 20/100 on the left. Color vision was control only on the right and 3/13 Ishihara plates on the left. Stereo vision was absent. Pupils were equal with a 0.3 log unit left relative afferent pupillary defect. Visual fields were abnormal on confrontation and automated static perimetry. His right visual field had deteriorated since perimetry performed one day prior to presentation. Extraocular movements were normal. Slit lamp examination was unremarkable without anterior chamber or vitreous cells. Dilated fundus examination showed an elevated right optic nerve with an altitudinal component. There was no pallor of the nerve but there were telangietatic vessels on the disc. On the left, the nerve was diffusely pale with severe gliosis and arterial attenuation. Fluorescein angiogram showed no evidence of vasculitis. BAER was normal.

He had had several normal MRIs of the brain and orbits with contrast. Blood work showed anti-cardiolipin antibodies IgG 33 and IgM 32, ANA 1:320 (with normal profile), ESR 27 and VDRL 1:8. Lupus anticoagulant, protein S, protein C, herpes titers, rheumatoid factor, ACE, complete blood count, Lyme titers and Chlamydia titers were all normal. Lumbar puncture showed 7 WBC, 0 RBC with normal protein and glucose. Oligoclonal bands were negative, as was VDRL. Anti-cardiolipin antibodies (aCL) remained elevated. HIV 1 was negative.

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Final Diagnosis
Neurosyphilis

Summary of Case Including Pathology
Repeat ANA was negative, RPR was 1:64 and serum FT A- ABS was reactive. Beta2Glycoprotein-1 (beta2GPI) IgG and IgM were both negative. These tests confirmed a diagnosis of Neurosyphilis. He was treated with IV infusion of Penicillin G with normalization of the anticardiolipin antibodies and reduction of the RPR to 1:8. At his latest follow-up in October, his vision was a slow 20/30 OU, with 9/13 Ishihara color plates OU, and severe optic nerve pallor OU. The visual field defects persisted, but were slightly less dense. He reported a history of sexual abstinence, with the exception of a single encounter with a professional sex worker on a trip to Brazil 10 years prior, and sexual promiscuity in his youth.

Optic atrophy, papillitis, retrobulbar optic neuritis and perineuritis have all been described in syphilis. Most frequently, optic nerve edema in syphilis is accompanied by other stigmata of inflammation such as uveitis, chorioretinitis, or retinal vasculitis. Although the “primary through tertiary” staging system is widely discussed, infectious disease experts tend to use organ involvement to “stage” the illness and choose treatment. In our patient’s case, some features were suggestive of “tertiary” syphilis. However, optic atrophy is the typical ophthalmic finding of the meningo-vascular disease of late syphilis. Our patient was diagnosed with neurosyphilis. There does not appear to be an English language comprehensive review of the clinical manifestations and course of optic nerve involvement in syphilis in recent literature. The addition of immune compromise of HIV to most recent case reports of syphilis makes culling information from the literature problematic.

Neurosyphilis is not typically at the top of the differential diagnosis of bilateral sequential optic neuropathies. This patient’s course was suggestive of sequential anterior ischemic optic neuropathy, and he had no other stigmata of infection or inflammation. While his initial visual field showed a central defect, all subsequent fields showed typical arcuate and altitudinal defects. The presumed diagnosis at the time of his referral was antiphospholipid antibody syndrome with a false positive VDRL as a result of Lupus. In fact, the reverse proved to be true, with the anticardiolipin antibodies and ANA being false positive as a result of neurosyphilis.

Anticardiolipin antibodies can be found in association with both autoimmune and infectious diseases. Reactivity to beta2GPI was felt to assist in distinguishing infectious from autoimmune aCL, with high binding affinity found in autoimmune antiphospholipid syndrome, and low or no reactivity found in syphilis. Dogma held that aCL in infectious conditions were not associated with thrombosis. However, one study amongst numerous recent reports showed a prevalence of positive aCL IgG of 18%, aCL IgM of 13% and beta2GPI of 10% in syphilis, and others have reported thrombosis associated with viral hepatitis C, leprosy, HIV, CMV, VZV and EBV associated aPL.

References