Lessons in Neuroimmunology/ophthalmology

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Case 1 History – 2006

58 year-old AA man w/ 11 months of progressive imbalance, confusion and fatigue.

Past Medical History: Gout, DM2, HTN

Meds: Enalapril, Amlodipine, Atenolol, losartan, allopurinol, colchicine, novolog insulin

More History

• No smoking, alcohol, drugs; Family history unremarkable

• Exam: Slow processing speed and poor attention; mild LUE weakness and tremor; gait imbalance

MRI Brain – 2006
Cerebrospinal Fluid Examination

(2006) – Initial presentation

Opening Pressure: 350 mm H20 (very high)

75 WBC (lymphocytic, no eosinophils) (abnormal)
0 RBC
Glucose 47 (serum 224, CSF/Serum ratio 0.2) (very low)
Total protein 41
>5 oligoclonal bands and IgG index of 0.7 (abnormal)

Routine / AFB / Fungal cultures and stains negative
Viral encephalitis panel negative
Cytology benign

MULTIPLE CHOICE QUESTION #1

A low cerebrospinal fluid glucose (<0.3 CSF/serum) is consistent with all of the following causes of meningitis EXCEPT:

A. Mycobacterium Tuberculosis (TB Meningitis)
B. Carcinomatous Meningitis
C. Sarcoidosis
D. Vogt-Koyanagi-Harada Syndrome (VKH)
E. Coccidioidomycosis (“Valley Fever”)

Image Source: http://library.med.utah.edu/kw/ms/mml/normal.jpg

CXR (2006)
Hilar Lymph Node Biopsy from this patient -- 2006

Case History -- 2006-2009

Diagnosis:
1) Pulmonary Sarcoidosis
2) Probable Sarcoid Meningitis causing hydrocephalus*

Initial Treatment: VP shunt. IV pulse steroids

Maintenance Therapy: High-dose oral steroids followed by mycophenolate, hydroxychloroquine and low dose oral steroids.

Course: Severe cutaneous sarcoidosis. Insidious worsening of chronic kidney disease (bland sediment, though to be due to hypertension/DM).

*Hydrocephalus as a complication of sarcoid meningitis is well-described in the literature (e.g., Salm, R, et. al, Postgrad Med J, 1969).

Case History -- 2010

4 years after the initial presentation, he developed new visual blurring in the left eye.

Exam:
VA: 20/25 OD 20/200 OS
Question raised of possible 0.3 log RAPD OS
Cornea: Fine keratitic precipitates with pigmentation OS
AC: 1+ cell, 4+ flare OS
Vitreous: 2+ vitritis OS
Retina: dot-blot hemorrhage OD (attributed to DM)

PPD negative; RPR/FTA-AB neg; Toxoplasma antibodies neg

Working Diagnosis:
Anterior/Intermediate Uveitis, most likely due to sarcoidosis
Case History – 2010

RX: pred-forte followed by subtenon Kenalog OS.

3 wks later uveitis improved, but acuity still 20/200 OS.

IOP – 8 mmHg
Dilated exam - mild cystoid macular edema OS.

However, the relative afferent pupillary defect (RAPD) in the left eye was more prominent (0.9 log)

Full-Field Pattern Reversal VEP: Latency delay OS
(160 ms)

Case History 4 – Fall 2010

Treatment for presumed sarcoid optic neuropathy:
IV solumedrol x 3 days. Then IV infliximab 5 mg/kg.

1 wk later, NLP OS.
Dilated exam was unremarkable OU.

Two weeks later, he reported new visual blurring in the right eye and worsening gait instability. There was no headache or eye pain.

MULTIPLE CHOICE QUESTION #2

What is your leading diagnostic impression at this point?

A. The initial diagnosis of systemic sarcoidosis was incorrect -- there must be another unifying diagnosis to explain the meningitis, uveitis and now retrobulbar optic neuropathy
B. Sarcoid retrobulbar optic neuropathy, which can be hard to treat
C. Multiple Sclerosis
D. Lymphoma (B or T cell)
E. Infection
F. Medication-induced optic neuropathy
G. Progressive Multifocal Leukoencephalopathy (PML)
MULTIPLE CHOICE QUESTION #3
What treatment, if any, would you offer this patient?

A. No additional treatment at this point, stop current meds
B. High-dose IV steroids
C. Increase the dose of oral steroids to 1-1.5 mg/kg
D. Infliximab (Remicade) – a TNF-alpha inhibitor
E. Empiric Antibiotics, antivirals or anti-fungals
F. Radiation

MRI Brain (axial 3D Xeta FLAIR) performed 26 days later (9/28/2010) reveals hyperintensity of the left optic nerve now extending into the chiasm and beginning to involve the left optic tract.
**Case History**

Anterior chamber paracentesis revealed Positive VZV PCR in the aqueous humor.

Cerebrospinal fluid examination: 130 WBC (47% N, 28%L, 25%M), glucose 100 and total protein 264. VZV PCR positive. CMV and HSV negative.

MRI brain showed no new parenchymal lesions. MRI spine showed degenerative changes, but no parenchymal disease.

HIV negative

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**Final Diagnosis**

1) Progressive Outer Retinal Necrosis OU from Varicella Zoster Virus (VZV)

2) Probable VZV retrobulbar optic neuropathy, masquerading initially as sarcoid optic neuropathy

3) VZV Meningitis

4) Anterior/intermediate uveitis

5) Pulmonary Sarcoidosis; Probable Neurosarcoidosis

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**Treatment / Outcome**

**ANTIVIRALS:** IV and intravitreal ganciclovir and foscarnet and intravitreal ganciclovir implant. Also pars plana vitrectomy, silicone oil injection and laser retinopexy.

**IMMUNOSUPPRESSION:** IV solumedrol 1 gram x 1 dose was given then rapidly tapered to 20 mg prednisone per day. Mycophenolate mofetil was immediately stopped. Infliximab was not redosed.

**OUTCOME:**
3 weeks later, 20/400 OD; NLP OS.
12 weeks later: Hand motion OD, NLP OS.

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**Progressive Outer Retinal Necrosis**

A rapidly progressive, necrotizing herpetic retinitis

In the largest case series (38 AIDS patients), 67% of eyes were NLP after 4 weeks

Also observed in patients with systemic inflammatory diseases (MS, RA, SLE, ITP) being treated with immunosuppression; and post bone marrow transplant

A prior episode of VZV reactivation can often be elicited (though not necessarily in the V1 dermatome)

Upon further history, he had in fact suffered left V1 shingles in 2008
Retrobulbar Optic Neuropathy & Meningitis Can Herald the Onset of Necrotizing Herpetic Retinopathy

In AIDS

Aseptic meningitis and optic neuritis preceding varicella-zoster progressive outer retinal necrosis in a patient with AIDS

Carlos Franco-Paredes, Thomas Bellemare*, Ali Merchant*, Pramod Sanghvi, Carlos Diaz-Granados and David Rimland

AIDS 2002

In MS, RA and leukemia

Progressive outer retinal necrosis in Immunocompetent Patients Treated Initially for Optic Neuropathy With Systemic Corticosteroids
Matthew S. Bent, MD, Joel S. Glaser, MD, and Janet L. Davis, MD

American Journal of Ophthalmology 2006

Sarcoid Optic Neuropathy

Facial palsy is said to be the most frequent neurological manifestation of sarcoidosis, but in many series selected for cases of neurosarcoidosis optic neuropathy is the most common

(Frohman, et al. QJM, 2009)

Optic neuropathy may result from direct inflammation, external compression or vascular injury.

Steroids are the mainstay of treatment. Case reports of methotrexate and infliximab for refractory cases.
(Katz, Arch Neu, 2003; Salama B., Can J Ophthalm, 2006)

Sarcoidosis is Associated with Impaired Immunological Surveillance

The Association of Progressive Multifocal Leukoencephalopathy and Sarcoidosis*
Mark A. Monchiono, M.D., and Dana F. Ujekoff, M.D.

Chest 1983

Chest 2003

Sarcoidosis Following HIV Infection* Evidence for CD4+ Lymphocyte Dependence
David C. Shono, MD, Robert M. Jenson, MD, Lorraine Hung, MD, FACP; Michael P. Gentry, MD, Stephen J. Nakamura, MD, and Stephanie F. Wang, Jr., MD, FACP

Clinical Neurology and Neurosurgery 2008

LESSONS FROM THIS CASE

1) Careful dilated fundus exam is essential, as optic neuropathy can “herald” the onset of necrotizing herpetic retinopathy

2) However, retinal lesions may not be apparent on routine clinical exam at the onset of optic neuropathy. A high index of suspicion is required. A CSF exam may be helpful.

3) The use of novel immunomodulatory agents to treat diseases that themselves cause optic neuropathy (Multiple Sclerosis, Sarcoidosis, NMO, SLE) cautions us to be ever more aware of the possibility of infection in such patients
Charles Bonnet Syndrome

Visual hallucinations occur in about 11% of AMD patients with low vision.

Auditory (often musical) hallucinations occur in about 10% of patients with acquired hearing impairment.

**Diagnostic Criteria**
1) at least one complex visual hallucination within the past 4 weeks
2) a period between the first and the last hallucination exceeding 4 weeks
3) full or partial retention of insight into the unreal nature of the hallucinations
4) absence of hallucinations in other sensory modalities
5) absence of delusions

How does the “Theater of the Mind” come from the “Machinery of the Brain?”

Perception is inference.

Phantoms
45 yo man with incidental pallor found on ophtho exam

Healthy & Active

- No history of trauma, MS, brain tumor, radiation etc
- Normal general neuro exam
- No meds or toxic exposures
- 20/20 OU, "congenital" color defs
- Poor low contrast vision no RAPD
- IOP 8 OU

As a boy couldn’t fit into football helmet
Brother & dad with bilateral pallor

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