1 Uveitis Masquerades

2  • 67 year old Caucasian woman
    • Referred for second opinion for uveitis OD
    • PF 6/day OD

3 THOUGHTS
    • 50 pack year smoker
    • Chronic cough
    • CXR normal
    • FTA NR
    • PPD negative

    • What is your differential diagnosis?
    • What would you like to do?

4 WORK-UP

    • AC tap – malignant cells consistent with small cell lung CA
    • CT chest – lung mass, biopsied, small cell lung cancer

5 ENTITIES TO KEEP IN MIND

   Non-Malignant

   • Foreign Body
   • Ocular Ischemia
   • UGH
   • Retinal Detachments
   • Pigment Dispersion
   • Retinal Degeneration
   • GVHD
   • Drug Reactions
Malignant

- Primary CNS lymphoma
- PIOL
- MAR/CAR/BDUMP/paraneoplastic
- Metastatic lesions
- Leukemia

**HOW NOT TO BE FOOLLED**

- When you evaluate a uveitis case – ALWAYS look for the atypical features

- Looking at what does not fit your diagnosis will help you direct your differential

**FOREIGN BODY**

- Can present as any type of uveitis – anterior or posterior

- Must be on high alert in UNILATERAL disease, especially in young patient

- Must perform gonioscopy and depressed fundus exam

- Watch for old extruding scleral buckles

**OCULAR ISCHEMIA**

- FLARE and the PUPILS are the key on exam
- Will have flare out of proportion to cell
- Poor dilation and poorly reactive pupil
- Later stages – NVI, NVE, retinal heme

**OCULAR ISCHEMIA**

- Chronic ischemia from ophthalmic artery hypoperfusion
- See at higher rates when carotid is stenosed > 90%
• But does not have to originate from carotid

• Systemic associations:
  • Diabetes Mellitus (56%)
  • Hypertension (50-73%)
  • Ischemic heart disease/CVAs (27-48%)
  • Giant Cell Arteritis

11 PIGMENT DISPERSION
• NOT the typical myopic patient

• Will present with acute, redness and pain

• Instead may see as acute, bilateral entity (BAIT) or unilateral

• Can be medication or possibly infection induced

12 PIGMENT DISPERSION
• On exam will see mainly flare and pigment and less cell
• Must watch and treat IOP rises aggressively
• Treat with cycloplegia and very low doses of steroids
• Typically resolves around 3 months

13 CHRONIC RETINAL DETACHMENTS
• Will present with insidious symptoms of blur and floaters
• Typically will have shallow peripheral RD’s – may have folds or pigmentation denoting chronicity
• These patients typically have increased flare and can have lenticular membranes
• They typically also present with hypotony or lower eye pressures

14 UGH SYNDROMES
Keep high on differential for older patients presenting with uveitis for first time in their life
• Typically related to surgery

Look for misplaced haptics, single-piece IOLs in the sulcus, and dislocated IOLs

Can typically control with atropine and prednisolone once per day if patient prefers to avoid surgery

**RETINAL DEGENERATIONS**

- Retinal degeneration, especially retinitis pigmentosa, can present with vitritis
- Must exam the vitreous cell closely – as will see larger more pigmented cell in RP
- But can still have mild inflammation that can be treated
- It is more difficult, however, to separate autoimmune retinopathy from certain retinal degenerations
  • And just as hard to treat!

**ALWAYS RULE OUT SYPHILIS!!!**

**RETINAL DEGENERATION**

1. Retina degeneration
2. Autoimmune retinopathy

- 24 year old Caucasian female
- 3 week history redness, decreased vision OS – told iritis
- Non-responsive to hourly topical steroids and two sub-tenon steroid injections
- VA 20/20 OU
- Slit lamp exam: normal OD, IOP, Fundus normal OU
• Past medical history
  • ALL 3 years ago; chemotherapy and radiation
  • Immediate anterior chamber tap

• Diagnosis: ALL recurrence

MALIGNANT MASQUERADES
• Can present in a variety of ways, typically insidious
  • Vision loss
  • Floaters
  • Headaches

• TIP: If you see a case of uveitis that presents with visual field loss that is out of proportion to the clinical exam, you should consider neoplastic and paraneoplastic disease processes

CASE M.G.
• 51 yo Caucasian M referred with blurred vision and floaters for 4 years

• Presented in 2007 to retina specialist who saw “dots” in both eyes. Improved with PO steroids

• One year later, symptoms recurred, but eye exam “normal”
• Vision slowly decreasing OD, then developed similar symptoms OS, so referred to another specialist

22 M.G.
• 2nd specialist diagnosed intermediate uveitis
• RF, ACE, Lysozyme, ANA, RPR, FTA-ABS neg,
• CBC wnl, CXR wnl,
• MRI brain periventricular white matter changes

• 2 episodes of vision loss OD with a blacked out visual field, recovered with PO steroids

• Referred for second opinion

23 FIRST VISIT 7/2011
• PMH: HTN, asthma, seasonal allergies
• PSH: appendectomy, herniated disc repair

• Medications: Prednisone 40mg daily, atenolol 50 bid

• SH: born in the US, former truck driver, married, 2 children, no pets, no TB contacts, no smoking, social ETOH, no drug use, camps often, no tick bites, 10 lifetime partners, denied STIs
• FH: DM, brain tumor (mother), lymphoma (sister)

• ROS: no fever, no chills, no weight loss, occasionally short of breath on exertion, no parasthesias, no weakness

24 PRESENTING EXAM
• BCVA: OD:20/25-, OS: 20/20
• Pupils: +APD OD
• Motility: full OU
• CVF: generally constricted OD, full OS
• SLE: rare cell OU, no KP, 1+ AV cell OD, 2+ AV cell OS
• DFE:
  • OD – no haze, diffuse chorioretinal atrophy with hypopigmented areas and pigment migration, macula with stippled appearance. 1 elevated subretinal lesion
  • OS – 1+ haze, snowballs and granulomatous periphlebitis

**ASSESSMENT**
• Impression: unusual picture - inactive uveitis OD with pseudo RP appearance and RPE pigment migration, with active granulomatous intermediate and posterior uveitis with retinal and likely choroidal granulomas OS
• Rule out sarcoidosis, TB, syphilis, MS
• Recheck: FTA-ABS, QuantiFERON, ACE, lysozyme, HLA-DR15, CT-chest, and obtain ERG
  • Lysozyme elevated to 18,
  • HLA-DR15+
  • ERG: non-detectable rod function OD, not done OS

**FOLLOW-UP**
• 8/11: vision OD decreased to HM - ?MS
• Neurology consult: MRI reviewed, no significant findings
• Increased prednisone, VA returned to 20/40
• Started on Cellcept, given PST Kenalog injection
• 9/1/11: 20/25 OU increased vit cell OU, rapidly enlarging subretinal lesions OD.
• Prednisone and cellcept tapered, vitrectomy with subretinal biopsy, rule out lymphoma. Sent NEI
31 DIAGNOSIS: PIOL (PVRL)
• Significant delay in therapy. Extensive discussion with oncologists re diagnosis.
  • LP negative, MRI no lymphoma
  • Oncology doubted diagnosis
  • Ultimate treatment: high dose systemic MTX, vincristine, decadron and intrathecal MTX
  • Lesions OD resolving, OS unchanged
  • Patient passed away s/p dose#3 from massive PE

32 PIOL (PVRL) BASICS
• PVRL = diffuse large B-cell lymphoma
  • A rare subset of PCNSL
  • 15% of patients with PCNSL will develop IOL
  • Conversely, 65%–90% of PIOL patients develop CNS lymphoma
  • A T-cell rich and a T-cell form have been described

• PIOL/PVRL – most common intraocular lymphoma
• Uveal lymphomas - second most common
  • Primary choroidal = low-grade, indolent B-cell lymphoma (extranodal marginal zone B-cell) I
    • Similar to those seen in ocular adnexa and conjunctiva
  • Primary iris lymphoma – very very rare
  • Secondary choroidal lymphoma from metastasis
    • Typically confined to the choroid
    • Most common systemic lymphoma involving the choroid is DLBCL.

33 EPIDEMIOLOGY
• Rare. PCNSL is 0.46 per 100,000, all eye cancers 0.8 per 100,000, PIOL small subset
• Estimate: 100-400 cases per year in the US
• Slight male preponderance, no race predilection
• Most common age 50-60’s
• Median survival 58 months, unknown if therapy impacts outcomes

### 34 BIOLOGY

• 3 primary themes
  • 1. Extremely rare to manifest or recur outside the brain – CNS tropism
  • 2. Worse prognosis than other extranodal NHL isolated to one site (e.g. bone)
  • 3. Responds best to methotrexate and less so to doxorubicin based regimens
    • Opposite of other lymphomas
    • 20% achieve long progression free survival on MTX

### 35 CLINICAL DISEASE

• Most cases have little AC rxn, no posterior synechiae
• Vitreous sheets and clusters of cells, larger than inflammatory cells
  • Less haze than expected for number of cells
  • CME is rare
• Retinal/RPE involvement is helpful when present
• Focal, solid detachments of RPE or leopard spotting when more diffuse involvement

### 36 OUR ROLE IN DIAGNOSIS

• This case had a 3 month delay in time to treatment because the oncologists originally did not believe the pathology report

• Our role is not simply to send tissue, but to understand the issues surrounding the diagnosis and the tests used by our ocular pathologist, in order to advocate for our patient with other treating services
37 DIAGNOSIS

• Diagnosis requires both the identification of abnormal lymphocytes AND establishment of monoclonality

• However, this can be difficult given quality and quantity of the our specimens

• There are necrotic and mechanically altered malignant cells in vitreous samples. In such cases even the experienced cytopathologists may have difficulties identifying the PIOL cells
  • Placing undiluted vitreous directly into tissue media can help

38 DIAGNOSIS

• Cytology and histopathology provide morphological evidence: large, atypical lymphoid cells, large, irregular nuclei, prominent nucleoli, scanty basophilic cytoplasm

• Monoclonality: B-cell population with lamda or kappa restriction
  • Techniques such as immunohistochemistry & flow cytometry can demonstrate monoclonality, but require larger sample
  • Newer technique - Molecular analysis with microdissection and PCR to detect \( \text{IgH} \) gene rearrangement
  • Beware of false positive and negatives given small samples
  • Microdissection identifying the atypical lymphoid cells is critical for molecular analysis

• Adjunctive Test: elevation of IL-10 in ocular fluid, IL-10:IL-6 ratio >1 highly suggestive of, but not diagnostic of B-cell PVRL
  • Cannot serve as a sole marker of disease, need other evidence
39 **MONOCLONALITY**

- B cells are precursors of antibody-secreting cells. Antibodies consist of two heavy (H) and two light (L) polypeptide chains, with constant and variable regions

- IgH has three gene segments: V (variability), D (diversity), and J (joining)

- V(D)J recombination is critical for B-cell development and results in generation of unlimited number of antibodies

- Demonstration of IgH monoclonality is strong evidence for PIOL. DNA sequences at the junction of V, D, J segments are used as clone-specific markers

40 **GENE REARRANGEMENT**

- Variability of IgH gene linked to 3 regions of complementarity determining region (CDR1,2,3)

- Because rearrangement is always in the CDR3, the third CDR of the V_HDVJ (variability (V), diversity (D), and joining (J) gene segments) region of the IgH gene, all samples are tested using primers termed FR3A and FR2A and CDR3

- Primers set to conserved regions of variable genes

41 **GENE REARRANGEMENT**

- Nucleotides are randomly removed and inserted at the V-D and D-J junction.

- As a consequence, the distance between two points situated outside the recombination junctions, such as the primer binding sites, varies from molecule to molecule.
• Thus, the lengths of DNA fragments amplified using PCR and consensus primer will vary between different Ig molecules produced by different B lymphocytes

42 **IGH GENE MONOCLONALITY**

• Monoclonality of B lymphocytes characterized by amplified DNA showing fragment length homogeneity, i.e., discrete band of amplified DNA on electrophoresis
• Polyclonality characterized by DNA fragment length heterogeneity, i.e., broad band or smear on electrophoresis
• FR3A primer set, IgH rearrangement found in all 50 cases (100%) of PIOL. FR2A primer set: 44%, CDR3 primer set: 88%.

43 **DIAGNOSTIC TESTING YIELDS**

44 **TREATMENT IS DEBATED**

• Recommendations of PCNSL working group:
  • 1. Without CNS or systemic involvement:
    • If only one eye involved, use local therapy.
      • Local intravitreal methotrexate and/or rituximab
      • 30–35 Gy of EBRT is still under contention.
    • If both eyes involved, still preference for local therapy, though systemic treatment should not be excluded. Consider addition of intravitreal chemotherapeutic agents to systemic therapy
  
  • 2. With CNS involvement:
    • High-dose methotrexate-based therapy (possibly with systemic rituximab) in conjunction with local therapy (limited penetration of systemic agents into vitreous)
    • Whole brain radiotherapy in conjunction with ocular radiotherapy should be considered in those who have failed systemic therapy and are too debilitated or do not meet the criteria for more aggressive therapy such as
TREATMENT

• When methotrexate-based regimens are used prior to cranial radiation, the median survival is increased to at least 40 months

• Fewer patients are receiving ocular radiation as primary therapy because of the delayed toxic effects, including radiation retinopathy, optic neuropathy, dry eye, corneal epithelial defects, loss of limbal stem cells, cataract, and glaucoma

OUR ROLE IN PVRL CARE

• Does not end with a diagnosis

• Advocate for best care
  • Strongly consider local vs systemic therapy
  • Communicate and work with the oncologist

• Learn the patient’s regimen and help monitor for SE’s

Some credit Gass with the first case, but he likely described a case of a VKH-like syndrome

Most credit Berson and Lessell with the first report (1988)

Presentation: subacute vision loss, scotomas, photopsias, nyctalopia, and photoaversion

Clinical features:
  • Early: typically good Va, unremarkable fundus, mild vitritis
  • Late: vascular attenuation, retinal atrophy, disc pallor
Most cases associated with cutaneous melanoma, but cases associated with mucosal, choroidal, and ciliary body also described

Most cases described after primary melanoma was diagnosed
  - Latent period 3.6 years [2 months to 19 years]
  - Typically affects rod-mediated function
  - Commonly get shimmering photopsias and nyctalopia

Visual Fields
  - Generalized constriction > arcuate/central/paracentral scotomas

ERG
  - Is classically electronegative resembling CSNB
  - Markedly attenuated B-wave – points to bipolar cell dysfunction

**UTILITY OF AUTO-RETINAL ANTIBODIES**

- Some Auto-Abs found support ERG findings
- Abs found are directed to bipolar cell function
  - Transducin-a, transducin-b, arrestin, rhodopsin
- However, many others found
  - May explain heterogeneity of the disease

- Utility of testing is debated
  - May come at the cost of the patient

**TREATMENT**

- Many reviews state treatment is largely ineffective
- Keltner et al reviewed 62 cases (52 published, 11 of their own)
  - Only 2 had increased Va at end of follow-up
  - But 8 benefitted from various therapies
  - With cytoreduction surgery/therapy and IVIG being the cases treated with the most benefit
- Only one case treated with cytoreduction surgery and
interferon-b monthly recovered ERG function
• IVIG had field and field recovery, but ERG remained unchanged

TREATMENT

TREATMENT
• Steroids – mixed reports, many with visual recovery, but only moderate recovery in those with severe vision loss

• There are case reports of CAR successfully treated with IVIG and rituximab, as well

• The caveat to IVIG is that they have different pools of human donors so will have a wide-range of anti-idiotypic antibody specificities

• Concern that both may increase cancer mortality given protective effect of immune system in preventing tumor spread

MY TREATMENT STRATEGY
• Presumed antibody mediated disease
• As such my initial theoretic treatment strategy was as follows:
  • Rituximab – attack antibody producing B-cells

  • IVIG – attack already circulating auto-antibodies

  • High-potency local steroids – attack antibodies already present in retinal tissue
  • Subtenons kenalog + dexamethasone 0.7mg implant

INITIAL RESULTS: CASE 1: JG
• 62 yo M with 4 months prior woke up with flashing white lights described as a kaleidoscope with propellers.
• Within one week could not drive at night
• Patient was referred after a lung mass discovered and
diagnosed with Stage 4 melanoma
• Had in situ melanoma on ear excised one year prior

• Vision at presentation: 20/20 ou
• Exam: largely unremarkable, occ vitreous cells
• OCT: mild IS/OS disruption
• HVF: marked constrictions
• ERG: Scotopic rod-isolated responses were greatly attenuated, electronegative waveforms, diminished oscillatory findings
  • These findings confirm the diagnosis of melanoma-associated retinopathy

CASE 1 – HVF ON PRESENTATION

CASE 1 – ERG ON PRESENTATION

FOLLOW-UP FIELDS

CASE 1 – HVF ON LAST FOLLOW-UP

CASE 1 – SUMMARY OF FOLLOW-UP
  • Melanoma treated with surgery, radiation, chemo and then ipilimumab
  • Retreated once with ozurdex implant ou
  • 6/14 – last follow-up, 20/20 ou, full fields

  • 7/14 died of recurrent metastatic disease to brain
  • Recurrence occurred 8 months after IVIG and rituximab
  • Oncology did not think was related to immunotherapy

CASE 2: GK
  • 79 yo F with choroidal melanoma left eye diagnosed in 1987, then with liver metastasis in 2011 s/p excision - no radiation no chemo.
  • Also has a history of breast cancer (1987) -- lumpectomy and xrt -- mammo's negative
  • January 2013 noticed new floaters,
seen in retina, diagnosed with vitreous syneresis previously,
Had increasing debris and cloudy vision so referred
Complained vision was darkening
She also reported she could not read well anymore, as well
Never had anything like this before

Vision at presentation: 20/25+2 od, NLP os
Exam: 1-2+ vit cell, minimal haze, macular drusen
OCT: drusenoid changes
HVF: dense generalized constriction
Of note had a PET scan 4 days prior – negative

HVF ON PRESENTATION AND FOLLOW-UP

CASE 2: GK

Work-up was negative
Diagnosed with MAR though no active melanoma
Treated with rituximab, IVIG and ozurdex
ERG 10/13 – post-treatment
Electronegative waveform c/w autoimmune retinopathy
But rod response was not very compromised – unsure if cancer related

PET scan with new lesion 10/13 in lung
s/p excision, again did not put on chemotherapy

MAR recurred 7/14
treated IVIG/ozurdex

Kept on maintenance ozurdex injections when vitirits recurs
Has required multiple injections
Now been >20 weeks without recurrence
GVF – SECOND FLARE AND FOLLOW-UP

CASE 3: YT

- 63 year old female presents with bilateral vision loss – states her “eye are dying.”
- She reported that everything looked "snowy and was white” since 1/15

- Previous diagnosed with melanoma of the cervix in March 2014 on routine pap smear, then found with melanoma on the back
- s/p radiation and ipilimumab followed by a resection of the tumor
- recurrence/metastasis in the lung
- Started on Pembrolizumab (Keytruda) in 1/15

- Vision at presentation: 20/20 ou
- Exam: 2+ AC and vitreous cell ou, mild disc edema and vasculitis ou
- OCT: outer retinal atrophy with IS/OS disruption
- HVF: nearly extinguished

CASE 3 – HVF ON PRESENTATION

CASE 3 – HVF AT 3 WEEKS

CASE 3 – SUMMARY OF FOLLOW-UP

- Treated with IVIG and STK and ozurdex
  - No rituximab

- Excellent response

- Has required one additional ozurdex injection
• Still stable at 8 months
  • Metastatic melanoma was successfully treated
  • But most recent PET scan with mild lung activity
  • To restart chemotherapy

68 CASE 3 – HVF ON LAST FOLLOW-UP

69 SUMMARY

• My treatment strategy for presumed antibody mediated disease → Complement cytoreduction therapy
• Initial
  • Rituximab – attack antibody producing cells
  • IVIG – attack already circulating antibodies
  • High-potency local steroids – attack antibodies already present in retinal tissue
• Follow-up
  • High-potency local steroids for relapse in cell and local inflammation
  • Add IVIG for large flares with visual field loss

70 QUESTIONS

• Cytoreduction is still the goal
  • Newest melanoma therapies are immuno-based
  • As such, we must limit our systemic therapy for the survival of the patient

• Is rituximab truly needed?
  • Will it do more harm than good?
  • While considered a previous treatment for melanoma, can it cause relapses?

• Can we control with local therapy, with bursts of IVIG for severe relapses?
71 LIMITATIONS

• The patients did not have auto-retinal antibody testing, may have disease process other than MAR
  • But clinically consistent

• Follow-up time is limited

• And may be anecdotal as only 3 cases presented

72 UNRELATED TEST QUESTION

Topical corticosteroids and cataract formation in JIA

• In a study by Thorne et al. 75 consecutive patients (132 eyes) with JIA-associated chronic uveitis were evaluated for development of cataract.
  • Significant risk factors included presence of posterior synechiae, active uveitis and topical corticosteroid use at presentation

• The incidence of new cataract was 0/EY among patients receiving ≤2 drops of topical corticosteroids per day and 0.16/EY among patients receiving >3 drops daily.

73 THANK YOU

• References: