Diagnosis and Management of Vitreoretinal Lymphoma

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Primary Vitreoretinal Lymphoma (PVRL)

- Rare, high-grade extranodal non-Hodgkin lymphoma
- Older literature: “reticulum cell sarcoma”
- Vitreous, retina, and occasionally optic nerve
- Subset of primary CNS lymphoma

- 0.047 case/100,000 people/year
- 15% of PCNSL
- 12-19% of VR lymphoma

Mucosa-associated lymphoid tissue (MALT) lymphoma: LOW GRADE

- 95%: Diffuse large B-cell lymphoma (DLBCL): HIGH GRADE
- 5%: Unclassifiable B-cell lymphoma
- Follicular lymphoma
- T-cell lymphoma
Typical Clinical Course

• 50-60s, no strong gender or racial predilection
• Blurry vision + floaters with minimal redness or pain
• Insidious onset
• Partial response to corticosteroids
• Delay in diagnosis: 6 – 40 months
  • 35 days in PCNSL
• Bilateral involvement 80%
• MRI q3 months to monitor for CNS involvement
Clinical Findings

• None or minimal AC reaction
  • Scattered grayish KPs
  • Systemic lymphoma mets more common and intense
• Vitreous sheets/large clumps (>50%)
• Mild to dense vitritis
• Multifocal yellow sub-RPE or subretinal infiltrates (<50%)
• Optic nerve infiltration
• CME rare
• Choroid spared
  • Otherwise, primary choroidal lymphoma (MALT) or mets from systemic lymphoma
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Courtesy: Chi-chao Chan, Nida Sen
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Foster, Vitale, eds. Diagnosis & Treatment of Uveitis (2nd ed)
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intravitreal MTX x1
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Differential Dx

- Sarcoidosis
- Syphilis
- Tuberculosis
- Viral retinitis
- Amelanotic melanoma
- Leukemic infiltrates
- Metastasis from solid organ malignancy
- Benign hyperplasia of the uvea
- White dot syndrome in an elderly → THINK LYMPHOMA!!!
OCT: Sub-RPE or subretinal infiltrates

- May simulate soft drusen
- Wax and wane w/ or w/o treatment, leaving behind areas of atrophy
- Associated with recurrent or persistent ocular disease & worse VA
  - But no difference in CNS/systemic disease or death
    - Dalvin et al, Ophthalmology Retina 2019

Soussain et all, Blood 2021
OCT: Sub-RPE or subretinal infiltrates

Superior macula (fovea not involved) at presentation

s/p intravitreal MTX, CF@6’

4 weeks later...20/200

RPE/Bruch’s complex
Diagnosis: Leopard-skin pattern on FA/FAF
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Diagnosis: Vitrectomy

• Steroids held 2-3 weeks prior
• Lower vitrector cut rate (<5000)
• Fresh tissue: communication between Surgeon and Pathologist!
• Undiluted vitreous
  • Cytopathology (45-60% sensitivity)
• Diluted vitreous
  • IL-10 > 400 pg/ml (sensitivity: 80%, specificity: 99%)
  • IL10/6 > 1
  • PCR testing for monoclonality: IgH rearrangement (B) and TCR (T)
  • MYD88 and CD79B mutation
• Repeat PPV in same eye if necessary; retinochoroidal biopsy rare
Diagnosis: AC Tap

IL-10 ≥50 pg/ml

- IL-6 low
  - IL-10/IL-6 ratio > 1
    - Highly suggestive of PVRL

- IL-6 ≥50 pg/ml
  - IL-10/IL-6 ratio < 1
    - Suggestive of infectious disease

IL-10 < 50 pg/ml

- Suggestive of inflammatory uveitis

Sensitivity 89%, specificity 93%

Soussain, Malaise & Cassoux. Blood 2021
Fig. 1 Diffuse large B cell lymphoma in the vitreous of a patient (a). Cytomorphology of the vitreoretinal diffuse large B cell lymphoma cells (H&E ×400—photograph thanks to Diva Salomao, MD (b). Immunostaining for CD20 of the vitreoretinal lymphoma cells (×400) (c). Ki-67 staining of the vitreoretinal cells; note the extensive staining which is consistent of marked local replication (×200) (d).
Treatment: Local

- Goals
  - Prevent irreversible vision loss
  - ? Delay progression to CNS involvement
- External beam radiotherapy (30-36 grays)
  - Cataracts, DES, Persistent epi defect, retinopathy, optic neuropathy
  - Higher recurrence rate than intravitreal chemo
- MTX 400mcg/0.1ml
  - Various regimens (next slide)
- RTX 1mg/0.1ml
  - Given together with MTX in refractory cases
  - Systemic Tx makes NO difference in ocular recurrence
Intravitreal MTX

- Fishburne (Archives 1997): 2x/week until vitreous clears, weekly x4, monthly x12
- Frenkel (BJO 2008): 2x/week for 4 weeks, weekly x8, monthly x9
- MERSI: weekly for 8 weeks, then monthly for 6-8 months, and extend based on eye findings
- Local remission rate as high as 95-100%
- Corneal epitheliopathy common, due to MTX toxicity to limbal stem cell
  - AT + topical steroids
  - Folic acid 1mg PO QD + folinic acid 0.003% gtt TID
  - ↑ injection interval
  - Pre-injection AC tap → IL-10 (Pulido 2018)
CNS Involvement in PVRL

- 56-90% of PVRL progress to CNS involvement within 30 months
- **Memory loss, personality change, altered alertness** often come before gait imbalance, weakness, seizure due to deeper structural involvement rather than cerebral cortex
- Median progression-free survival: 18-29 months
- Overall survival: 58-75 months; 5-yr survival: 59-69%
- Mechanisms
  - Subclinical disease at time of ocular diagnosis
  - Direct dissemination from the eye
- Systemic Tx in absence of CNS disease
  - Current guideline says no, but practice differs amongst centers
CNS Lymphoma: Treatment

• High-dose MTX based therapy
  • MTX usually given IV, but intrathecally if leptomeningeal involvement
  • Cytarabine, cyclophosphamide, temozolomide, rituximab, thiotepa, etc

• Autologous stem cell transplant (ASCT)
  • Younger patients with better functional capacity and few medical co-morbidities

• Whole-brain radiotherapy (WBRT)
  • Most damaging to neurological functions
  • Reserved for patients who respond poorly to chemo and poor candidate for ASCT
CNS Lymphoma: Treatment

• Ibrutinib (IMBRUVICA®)
  • Bruton tyrosine kinase inhibitor (first-in-class)
    • BTK pathway up-regulated by MYD88 L265P mutation
  • Approved for CLL, Waldenström’s, mantle cell lymphoma, chronic GVHD
  • 560mg QD, 50% overall response rate; 840mg QD: 77%
  • Crosses BRB- in a French trial, 560mg QD monotherapy led to ORR 86% & CR 50% in 14 pts with PVRL

• Tisagenlecleucel (KYMRIAH®)
  • Anti-CD19 chimeric antigen receptor (CAR)-T cells, drawn from and re-administered back to patients
  • Approved for follicular lymphoma
  • Shown promise in CNS metastasis from systemic lymphoma