


Vitreoretinal Lymphoma: *Simplified*

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Objectives

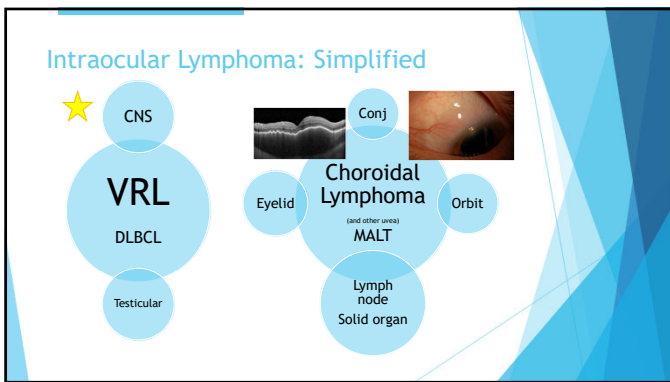
- ▶ Recognize clinical features of vitreoretinal lymphoma
- ▶ Understand how to diagnose this cancer
- ▶ Review approaches to vitreoretinal lymphoma treatment

Vitreoretinal Lymphoma

- ▶ Rare: 0.2-1 per million
- ▶ Middle age/older (range 20yo+)
- ▶ Involves retina/vitreous (vs. uveal lymphoma)
- ▶ 2/3-3/4 bilateral
- ▶ Typically aggressive DLBCL
- ▶ Strong association with CNS lymphoma
- ▶ Poor life prognosis
- ▶ Diagnostic challenge: masquerades as infectious/inflammatory uveitis



Intraocular Lymphoma: Simplified

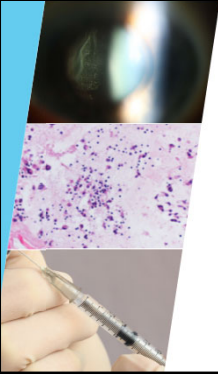


Vitreoretinal Lymphoma

- ▶ Clinical features
- ▶ Diagnosis
- ▶ Treatment



Vitreoretinal Lymphoma

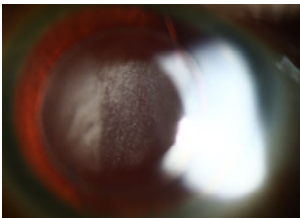


- ▶ Clinical features
- ▶ Diagnosis
- ▶ Treatment

When to think of VRL

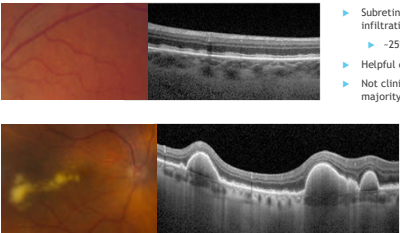
- ▶ Intraocular inflammation that does not respond to corticosteroids
 - ▶ Or transient, incomplete response
- ▶ Older patient with first time uveitis diagnosis
 - ▶ Especially if persistent signs/symptoms
- ▶ No explanation for inflammation on workup, atypical course
 - ▶ Don't rule out in young patients

Clinical features: Common



- ▶ Vitreous cellular infiltration
 - ▶ >75%
- ▶ Sheets or clumps
- ▶ Larger than inflammatory cell

Clinical features: Common



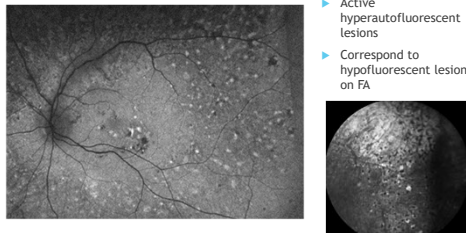
- ▶ Subretinal and sub-RPE infiltration
 - ▶ -25%
- ▶ Helpful diagnostic feature
- ▶ Not clinically evident in the majority of patients

ULTRA-WIDEFIELD MULTIMODAL IMAGING OF PRIMARY VITREORETINAL LYMPHOMA

Abstract: A LAMBERT AND CO. ARCHIVES OF OPHTHALMOLOGY, 2013, 131(10):1453-1458. DOI: 10.1093/afp/afp1453

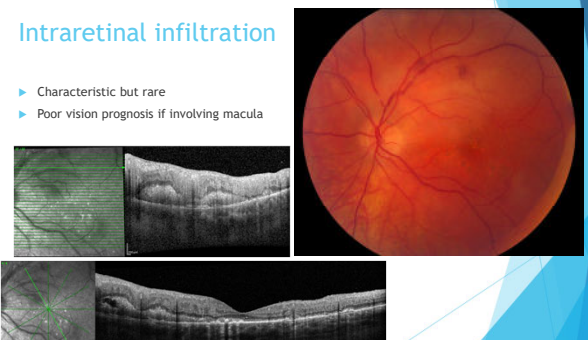
Keywords: Vitreoretinal lymphoma; Multimodal imaging; Ultra-widefield; Retinal; Lymphoma

Autofluorescence

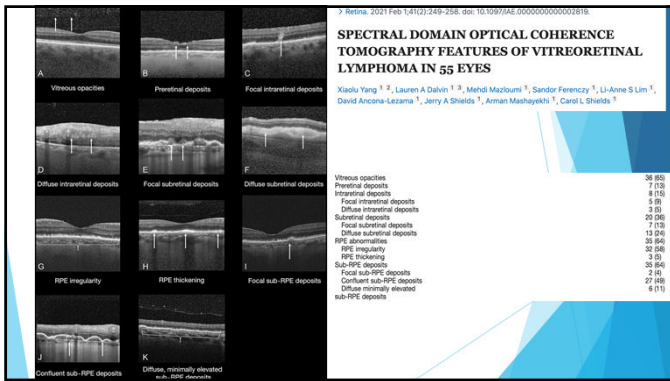


- ▶ Granular patterns
- ▶ Active hyperautofluorescent lesions
- ▶ Correspond to hypofluorescent lesions on FA

Intraretinal infiltration



- ▶ Characteristic but rare
- ▶ Poor vision prognosis if involving macula



Clinical features: Uncommon posterior segment findings

- ▶ Optic disc edema
- ▶ Disc hemorrhage
- ▶ Retinal hemorrhage

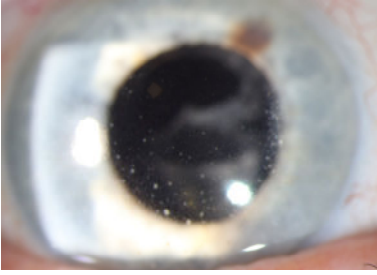
} <5%

- ▶ CME -5%
 - ▶ Treatment naïve
 - ▶ Prior surgery
 - ▶ Post-treatment inflammation

Vasculitis-like picture

- ▶ I have seen more often with T-cell lymphoma

Clinical features: Anterior segment



- ▶ AC cell
- ▶ KP (small)
- ▶ ~20%

Vitreoretinal Lymphoma



- ▶ Clinical features
- ▶ Diagnosis
- ▶ Treatment

Vitreoretinal Lymphoma



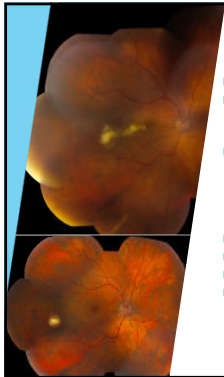
- ▶ Clinical features
- ▶ Diagnosis
- ▶ Treatment

Diagnostic biopsy

- ▶ Stop systemic corticosteroids at least 2 weeks prior to biopsy
- ▶ PPV
- ▶ Full thickness retinal or subretinal/subRPE biopsy
- ▶ Advance communication with cytopathologist
 - ▶ Notify 24-48 hours in advance
 - ▶ Ensure that sample can be processed by experienced cytopathologist
- ▶ Prioritize/plan division of specimen
 - ▶ If considering other differentials
 - ▶ Need viral PCR

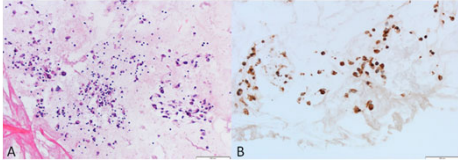
PPV

- ▶ 25g or 27g
- ▶ Infusion off for undiluted specimen
 - ▶ Assistant aspirates using 3cc syringe
 - ▶ Obtain 1-2cc
- ▶ Concentrated specimen with infusion on
 - ▶ Assistance aspirates using 10cc syringe
 - ▶ Keep vitreous cutter in most cellular area
 - ▶ Obtain 5-8cc
 - ▶ Place directly in DMEM
- ▶ Cut speed 200-400 cuts/minute to minimize cell lysis
- ▶ Increase aspiration by ~100%
- ▶ Send the vitreous cassette separately
- ▶ If subretinal/subRPE lesions, can diathermy and use vitreous cutter to biopsy
 - ▶ Endolaser around biopsy site when done
 - ▶ Can also consider soft tip aspiration for loose material

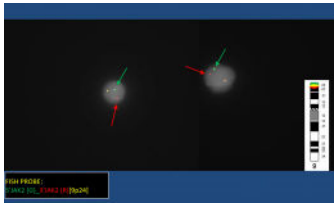


Specimen handling

- ▶ Part A: Undiluted vitreous, 1-3 mL
- ▶ Part B: Vitreous cassette, 15-30 mL
- ▶ Page pathology technician to immediately retrieve specimen
- ▶ Send on ice for immediate processing
- ▶ If processed separately, prioritize undiluted vitreous for cytology
- ▶ Our pathology team combines A and B for cell block preparation
 - ▶ H&E, CD3, CD20, CD163 for all specimens with VRL clinical suspicion
 - ▶ Other special tests as needed if enough sample
- ▶ Sensitivity of cytology likely depends on cytopathologist experience



Bland CD4+ Cells
No clear malignancy



Molecular testing: FISH for JAK2 gene rearrangement



Vitreoretinal Lymphoma

- ▶ Clinical features
- ▶ Diagnosis
- ▶ Treatment



Vitreoretinal Lymphoma

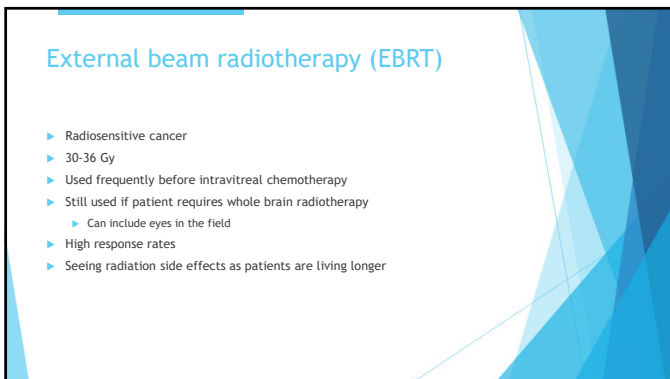
- ▶ Clinical features
- ▶ Diagnosis
- ▶ Treatment

The slide features a collage of three images on the left: a fundus photograph of an eye, a histological slide showing purple-stained cells, and a close-up of a hand holding a syringe.



Ocular treatment

- ▶ EBRT
- ▶ Intravitreal chemotherapy
- ▶ Therapeutic vitrectomy



External beam radiotherapy (EBRT)

- ▶ Radiosensitive cancer
- ▶ 30-36 Gy
- ▶ Used frequently before intravitreal chemotherapy
- ▶ Still used if patient requires whole brain radiotherapy
 - ▶ Can include eyes in the field
- ▶ High response rates
- ▶ Seeing radiation side effects as patients are living longer

Intravitreal chemotherapy

- ▶ Methotrexate
 - ▶ Antimetabolite, blocks dihydrofolate reductase
 - ▶ 1-year protocol with 25 total injections per eye
 - ▶ Twice weekly x 4 wk (induction)
 - ▶ Modified to once weekly due to travel
 - ▶ Once weekly x 8 wk
 - ▶ Modified to every other week
 - ▶ Once monthly x 9 mo (maintenance)
 - ▶ 400µg/0.05cc
 - ▶ Lower volume, less risk for reflux

bjh research paper

Efficacy and safety of intravitreal methotrexate for vitreo-retinal lymphoma - 20 years of experience

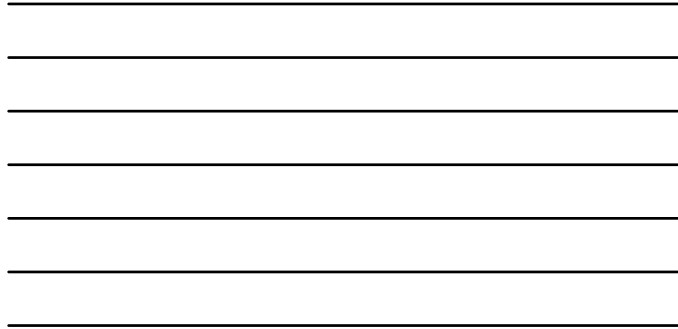
Zohar Hirschowitz^{1,2} and Sarah Ryan^{3,4*}

¹Ocular Oncology, Dana-Farber Cancer Institute, Boston, MA; ²Department of Ophthalmology, Harvard Medical School, Boston, MA; ³Department of Ophthalmology, Dana-Farber Cancer Institute, Boston, MA; ⁴Department of Ophthalmology, Harvard Medical School, Boston, MA

Summary

Vitreo-retinal lymphoma (VRL) is the most common intraocular lymphoma and is highly associated with central nervous system (CNS) lymphoma (CNL), both posing a therapeutic challenge. We investigated patient characteristics, efficacy and safety of intravitreal methotrexate (MTX) in patients with VRL and CNL. The results of 134 patients diagnosed between 1997 and 2018 were retrospectively reviewed. Lymphomas involved both the CNS and vitreo-retina (VR) with the CNS (57%) or solely the vitreo-retina (VR) by 46.4% of the patients with VRL either presented with VRL or developed it after a mean (SD) of 42.4 (24.6) months. The 41 patients with VRL (34 eyes) received a mean (SD) of 85.5 (17.5) injections between 0 and 114.6 injections were needed to reach complete remission. Local recurrence occurred in two of the 41 patients. Overall, 89.2% of eyes had an initial median vision of 20/40 and >90% of these improved. Intravitreal chemotherapy was the most prevalent side effect. A total of 48.9% developed intravitreal pressure (IVIP) after one or more intravitreal injections after 18 injections, which could be resolved with prompt intravitreal injection of bevacizumab. Intravitreal MTX injections are a safe and effective treatment for VRL. Frequent injections (15) may offer similar results with fewer side effects.

Keywords: intravitreal methotrexate injection, primary CNS lymphoma, vitreo-retinal lymphoma.



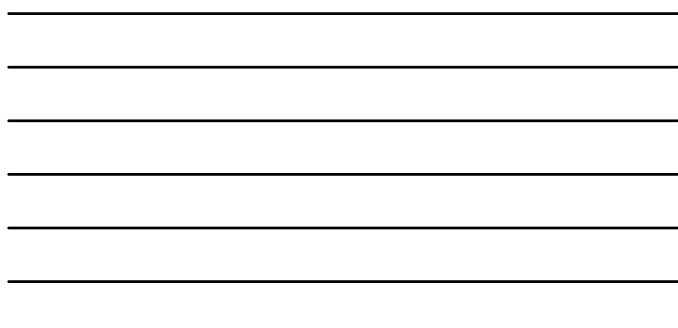
Intravitreal chemotherapy

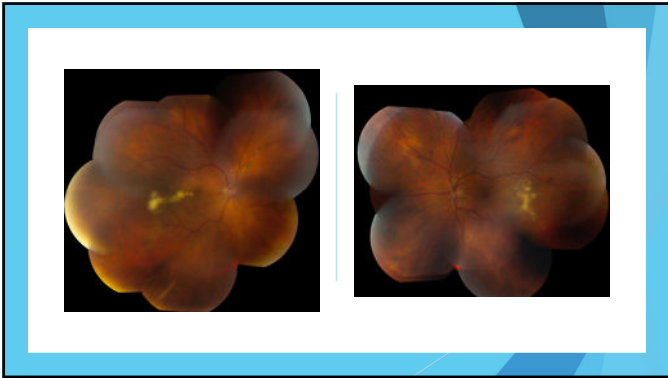
- ▶ Rituximab
 - ▶ Monoclonal antibody against CD20
 - ▶ Only for CD20+ VRL
 - ▶ Single agent or combination with methotrexate
 - ▶ May have less ocular surface toxicity
 - ▶ 1mg/0.1cc
- ▶ Melphalan
 - ▶ Nitrogen mustard alkylating agent
 - ▶ May be less effective for subretinal or subRPE disease
 - ▶ 10µg/0.05cc dosed once monthly

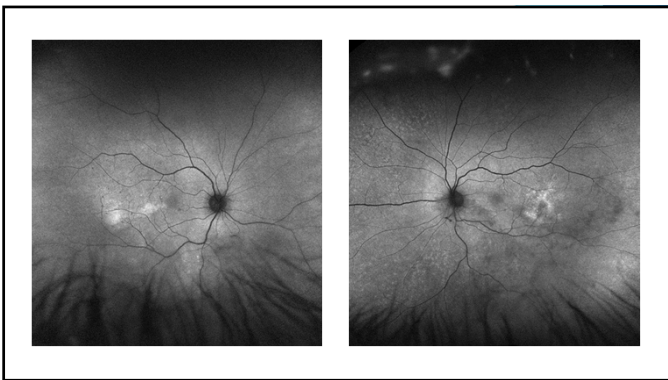


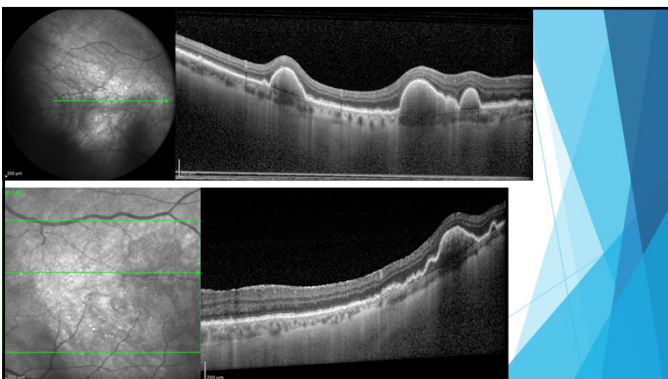
VRL managed with 1-year intravitreal MTX protocol

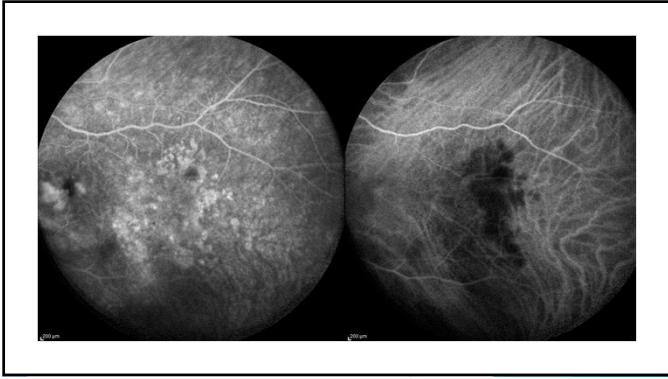
Complete response

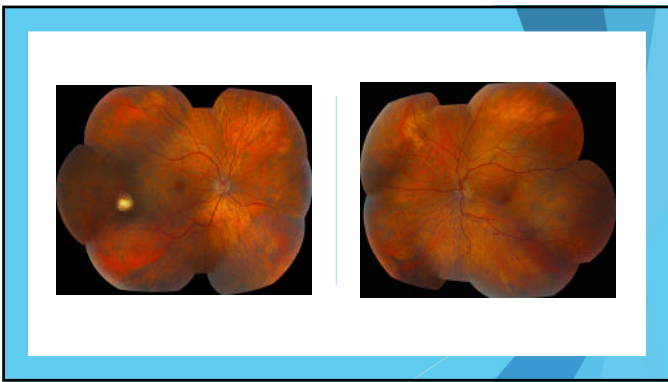


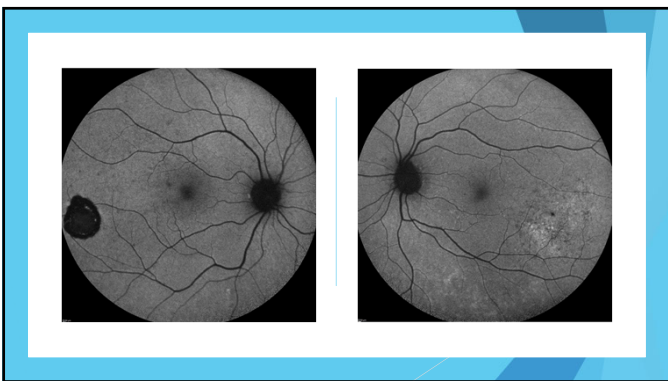


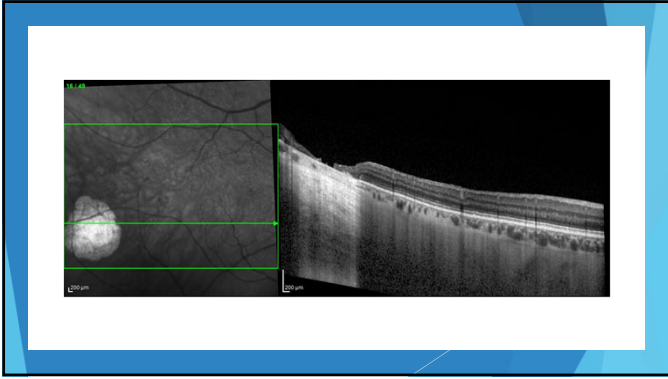




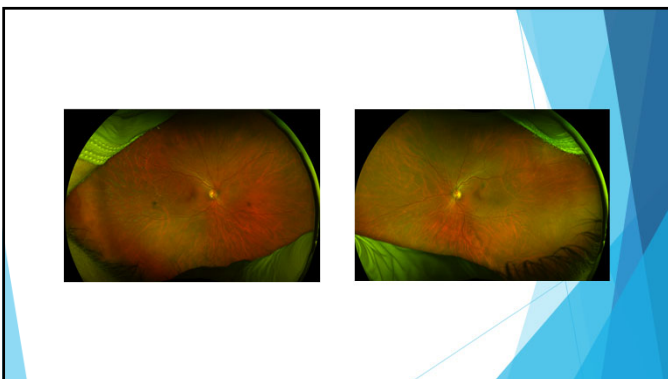


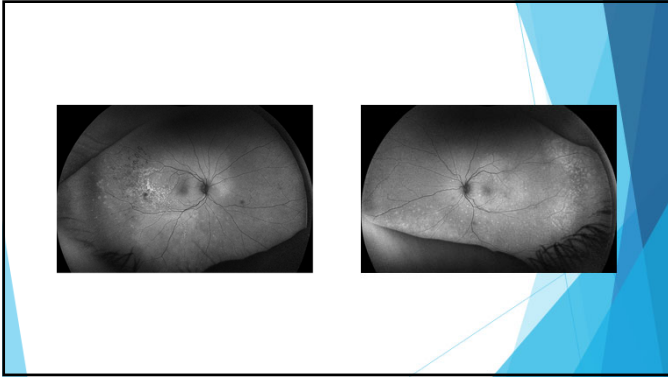


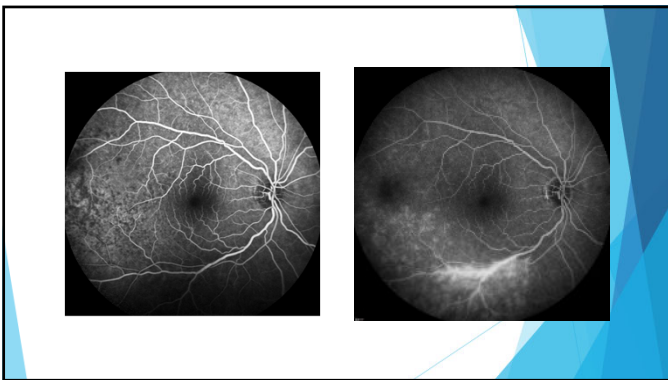


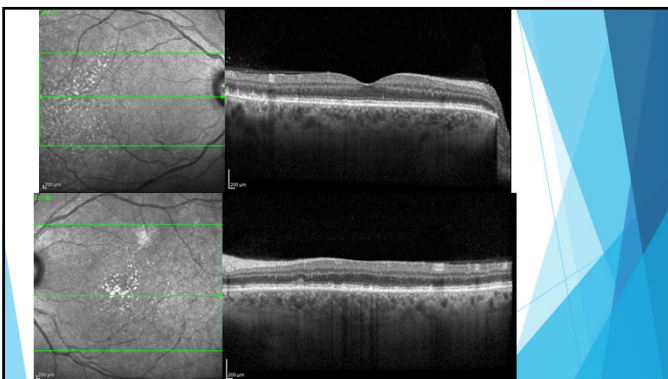


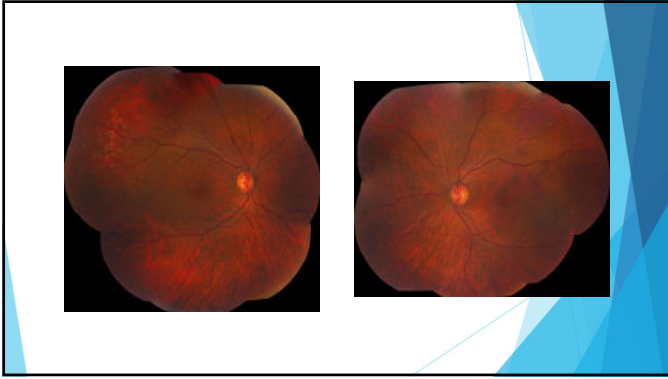


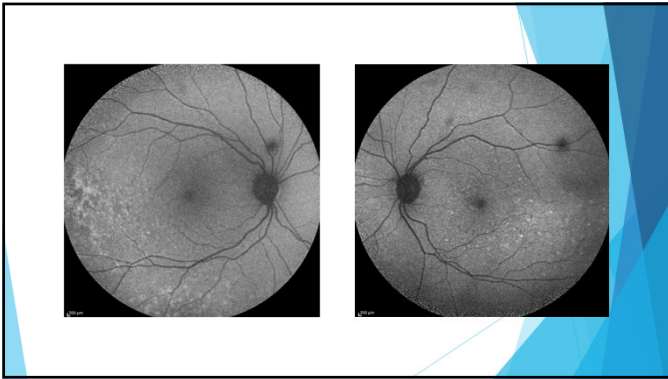


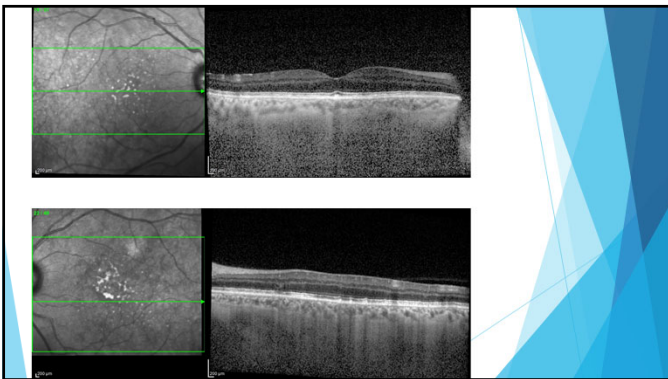


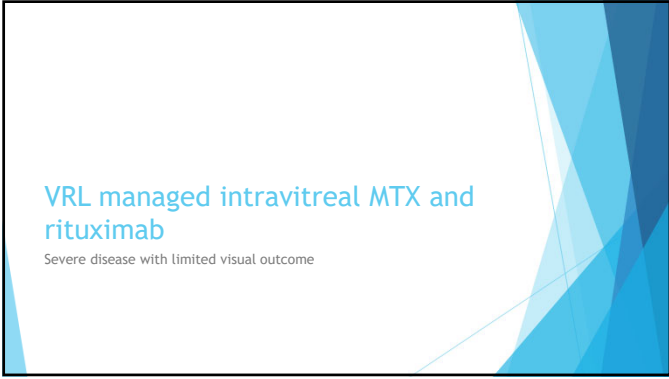


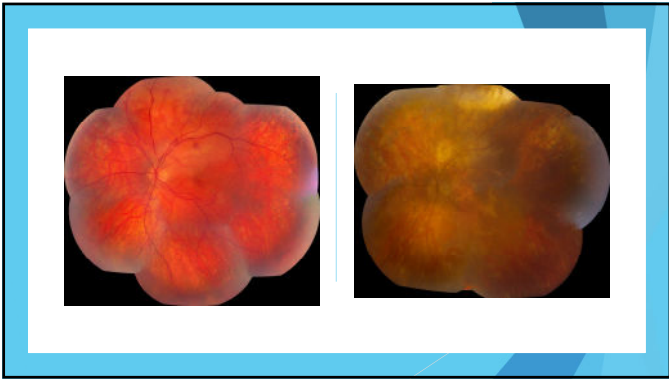


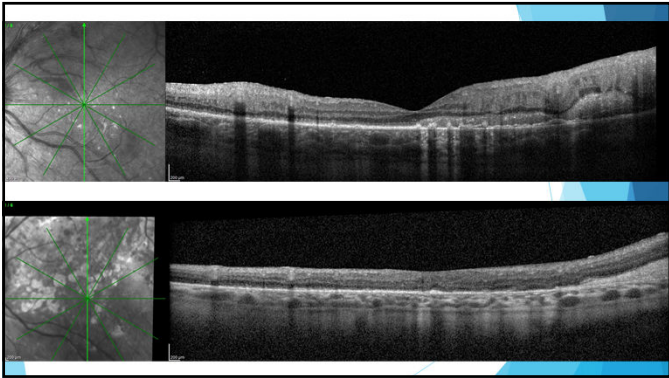












Systemic treatment

- ▶ For treatment of concomitant CNS lymphoma
- ▶ For VRL alone - recurrence rates high
- ▶ For prevention of CNS lymphoma
 - ▶ Controversial, limited evidence
- ▶ All patients require systemic workup and monitoring for CNS lymphoma
 - ▶ Work with hematology or neuro-oncology

NCCN guidelines for primary CNS lymphoma: Induction

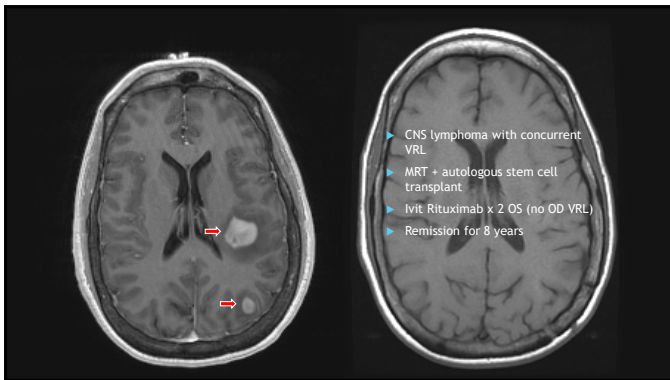
- ▶ High-dose methotrexate-based regimen
- ▶ Other systemic therapy if intolerant to methotrexate
- ▶ WBRT if not a candidate for systemic chemotherapy
- ▶ Consider clinical trials

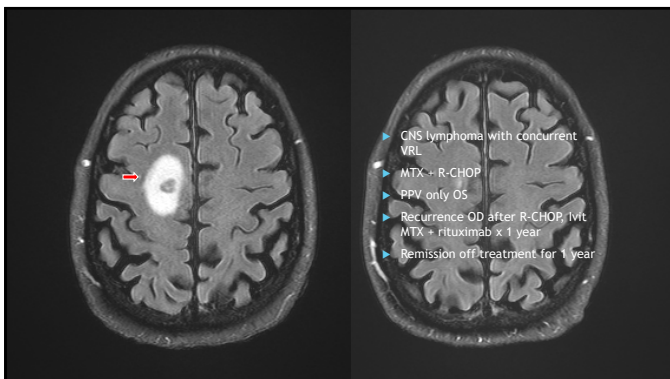
NCCN guidelines for primary CNS lymphoma: Consolidation

- ▶ If complete response consider
 - ▶ High-dose chemotherapy with stem cell rescue
 - ▶ High-dose cytarabine ± etoposide
 - ▶ Low-dose WBRT
 - ▶ Continue high-dose methotrexate-based regimen for up to 1 year
- ▶ If residual disease present consider
 - ▶ WBRT
 - ▶ High-dose cytarabine ± etoposide
 - ▶ Best supportive care

European Association for Neuro-Oncology Guidelines

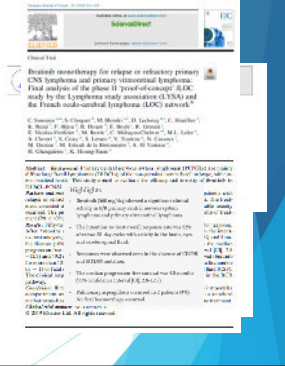
- ▶ High-dose MTX in combination with other agents that cross BBB
- ▶ WBRT after methotrexate is controversial
 - ▶ Use total doses of 40-45 Gy
 - ▶ Avoid in patients >60 years due to risks of neurotoxicity
- ▶ High-dose chemotherapy + autologous stem-cell transplant for relapsed/refractory disease if age <60

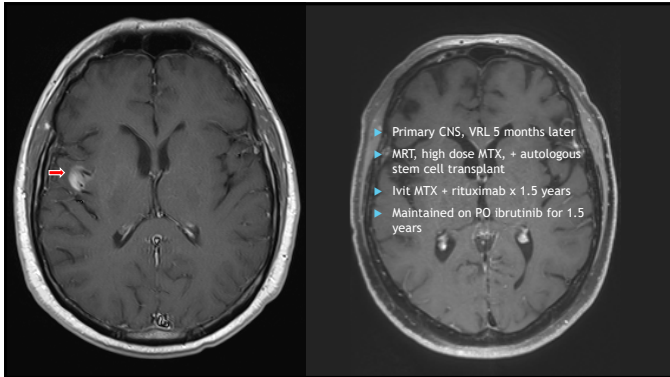




Ibrutinib

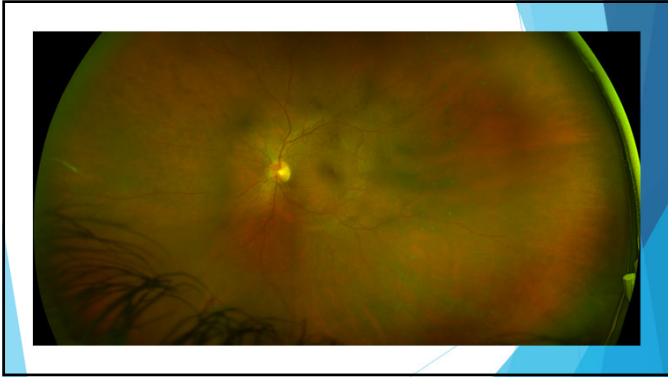
- ▶ Aberrant B cell receptor (BCR) signaling role in lymphoma pathogenesis
- ▶ Bruton's tyrosine kinase (BTK) is downstream in BCR pathway
 - ▶ Constitutive activation leads to uncontrolled cell proliferation
- ▶ Ibrutinib inhibits BTK
- ▶ Role of MYD88+ requires investigation

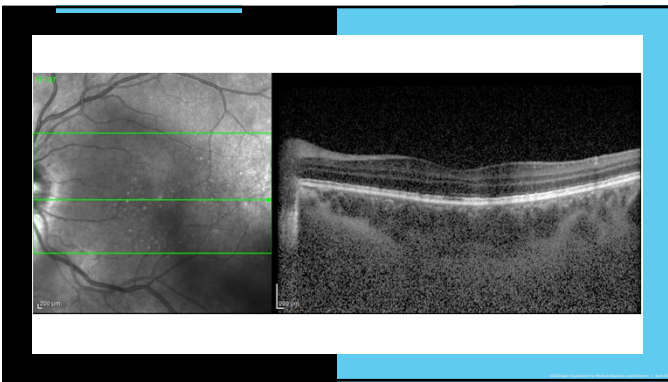


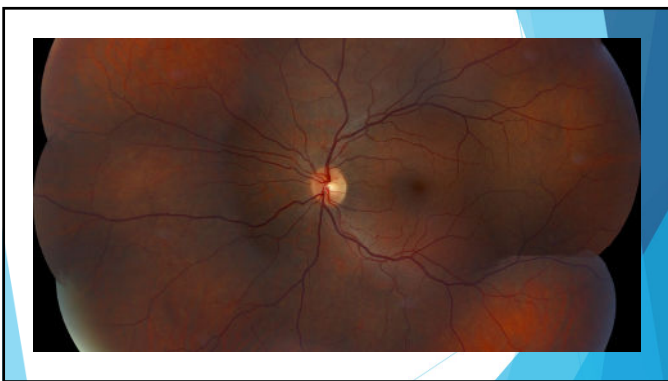


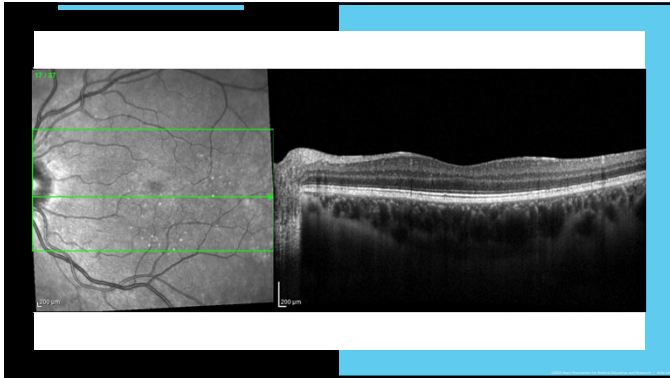
VRL managed intravitreal MTX and stem cell transplant

Complete response with good visual outcome









Conclusions

- ▶ Vitreoretinal lymphoma can be challenging to diagnose and manage
- ▶ Key clinical features: vitreous cellular infiltration and subretinal/subRPE infiltration
- ▶ Multimodal imaging and patient history can guide clinical suspicion
- ▶ Diagnosis by PPV: cytology, MYD88, IgH, IL10/6
 - ▶ Stop systemic corticosteroids
 - ▶ Refer if experienced cytopathologist not available
- ▶ Treatment predominantly with intravitreal chemotherapy
- ▶ Hematology/neuro-oncology for CNS lymphoma monitoring and treatment

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