Herpesviruses

35

Herpes Simplex Virus (HSV) and Varicella Zoster Virus (VZV)

Anterior Uveitis

- Epidemiology
  - Average age of onset
    40–50 years for HSV
    60–70 years for VZV
  - M = F
  - Immunocompetent
- Symptoms
  - Redness
  - Photophobia
  - Pain
  - Blurry vision
- Laterality
  - Almost always unilateral
  - Can be bilateral in patients with atopy and other immune dysfunctions
- Course
  - Acute, but can become chronic if not treated promptly
    Chronic intraocular inflammation may be due to persistent viral replication or immune response against inactivated viral antigens or damaged self-tissue
- Diagnosis
  - Typically made by characteristic findings and history
  - AC tap for viral PCR can confirm and speciate
- Exam
  - Increased IOP, often as high as 50–60 mmHg (trabeculitis)
  - Corneal edema (endotheliitis)

C. S. Foster et al. (eds.), *Uveitis*, https://doi.org/10.1007/978-3-030-52974-1_35

  - Decreased corneal sensation
  - Mild to severe AC inflammation (hypopyon possible)
  - Diffuse stellate keratic precipitates (KPs) (also seen in toxoplasmosis and FHI), but can also have mutton-fat KPs
  - Diffuse or sectoral iris atrophy (also seen in CMV anterior uveitis)
  - Iris hyperemia
  - Complications: hyphema, glaucoma, posterior synechiae, cataract, hypotony, and, rarely, phthisis bulbi
- HSV: Key points
  - Uveitis and trabeculitis can appear with or without corneal lesions (dendritic epithelial keratitis or disciform stromal keratitis)
  - Check for decreased corneal sensation
  - Iris FA shows intact circulation in atrophic area (vs. no circulation in VZV)
  - Given near-universal exposure and seroconversion by middle age, anti-HSV IgG is only helpful if negative, that is, rule out disease; IgM indicates acute infection
  - Can be complicated by encephalitis in immunocompromised
- VZV: Key points
  - Up to 40% of patients with VZV ophthalmicus may develop anterior uveitis; usually within the first week but may be delayed by weeks to months
  - Uveitis can occur without previous zoster dermatitis (*zoster sine herpete*)
  - Hutchinson's sign: cutaneous vesicles at the side of the tip of the nose; greater likelihood of ocular involvement
- Treatment
  - As it is not always possible distinguish HSV from VZV unless PCR is done on an AC tap, we recommend treating all herpetic anterior uveitis with VZV-specific dose for at least 4 weeks
    Acyclovir 800 mg 5×/day
    Valacyclovir 1 g TID
    Famciclovir 500 mg TID
  - Maintenance therapy
    Acyclovir 800 mg QD-BID
    Valacyclovir 500 mg^{-1} g QD
    Famciclovir 250 mg BID or 500 mg QD
  - Topical steroids are used aggressively once antiviral therapy is on board, as long as there is no concurrent epithelial keratitis (in the case of HSV); often tapered very slowly, and some patients may need low-dose therapy to remain quiescent even with antiviral prophylaxis, for example, 1 gtt QD-QoD
  - Topical cycloplegic for symptomatic relief and prevention of posterior synechiae
  - Caution with prostaglandin in HSV uveitis as it may lead to reactive keratitisAcute Retinal Necrosis (ARN)

- Epidemiology
  - Age: bimodal with one peak at age 20 (HSV-2) and another at age 50 (HSV-1 and VZV)
  - M = F
  - Immunocompetent
- Symptoms
  - +/− Pain
  - Redness
  - Photophobia
  - Blurry vision
  - Floaters
  - Visual field defects
- Laterality
  - Starts unilaterally, but becomes bilateral in 35–40% of cases within 6 weeks
- Diagnosis
  - Usually made on clinical findings, but aqueous and vitreous samples for viral PCR and fungal/bacterial culture are appropriate in atypical presentation or if there is no response to anti-viral therapy
- Exam
  - One or more foci of necrotic retina with discrete borders in the peripheral retina; may have macular lesions as well
  - Circumferential spread of retinal necrosis
  - Rapid progression without antiviral therapy
  - Occlusive vasculopathy with arteriolar involvement
  - Prominent vitritis and AC inflammation
  - Optic neuropathy/atrophy (disc edema a common early finding)
  - Scleritis
  - RD is very common, occurring in three-fourths of untreated cases within 6–12 weeks; vitreous traction and PVR further complicate matters
- Differential diagnosis
  - Progressive outer retinal necrosis
  - CMV retinitis
  - Atypical toxoplasmosis
  - Syphilitic retinitis
  - Intraocular lymphoma
  - Leukemia
  - Metastasis
  - Autoimmune retinal vasculitis (sarcoid, Behcet's, etc.)
- Treatment
  - Intravenous (IV) acyclovir 10–15 mg/kg TID for 7–14 days, followed by prolonged oral therapy, is the classic approach
    PO valacyclovir 2 g TID may be equally effective as induction therapy
    IV foscarnet is effective in cases resistant to traditional antiviral

  - Intravitreal antiviral is repeated twice weekly until retinitis resolve
    Foscarnet 2.4 mg
    Ganciclovir 2 mg
  - Oral corticosteroids appropriate if vision loss is significant from optic nerve inflammation, but only after 24–48 h of systemic antiviral
    Topical corticosteroids safe for AC inflammation
  - Prophylactic laser retinopexy if there is clear view
  - Pars plana vitrectomy for RD

Progressive Outer Retinal Necrosis (PORN)

- Epidemiology
  - VZV most common: two-thirds of patients have previous or concurrent cutaneous zoster
  - HIV/AIDS (CD4 $\leq$ 50) and profoundly immunocompromised patients
- Symptoms
  - Painless loss of vision often out of proportion to exam findings
    May be NLP
  - Constricted visual field
  - Redness, irritation, photophobia if positive VZV ophthalmicus
- Laterality
  - 70% bilateral
- Diagnosis
  - Based on clinical history and findings, but vitreous tap can confirm organism
  - FA
    Late staining of active lesions; window defects in inactive lesions
    +/− focal vascular occlusion
  - OCT
    Outer retinal disorganization
    Inner retinal hyper-reflectivity
    CME
- Exam
  - Characterized by minimal or no AC or vitreous inflammation (clear view)
  - Multifocal patches of outer retinal whitening that coalesce quickly
    Affect both posterior pole and periphery
  - 50–70% complicated by RD (rhegmatogenous or exudative)
- Differential Diagnosis
  - Similar to ARN
- Treatment
  - HAART to increase CD4 count
  - Treatment otherwise similar to ARN, though visual prognosis often poor

Non-necrotizing Herpetic Retinopathy

- HSV/VZV can also cause panuveitis in the absence of retinal necrosis, with or without concurrent papillitis or retinal vasculitis
- More like ARN/PORN than anterior uveitis, these cases are often bilateral
- Consider this diagnosis when presumed autoimmune panuveitis or retinal vasculitis fail to respond to systemic IMT

Cytomegalovirus (CMV)

Anterior Uveitis

- Epidemiology
  - Most common ocular manifestation of CMV in the immunocompetent
  - M > F
- Symptoms
  - Redness
  - Photophobia
  - Pain
  - Blurry vision
- Laterality
  - Unilateral
- Course
  - Acute and hypertensive in younger patients (20–50 years)
    Implicated in Posner-Schlossman syndrome (along with HSV)
  - Chronic in older patients (>50 years)
- Diagnosis
  - Typically made by characteristic findings and history
    Consider CMV when what otherwise appears to be viral AU does not respond to acyclovir or valacyclovir
  - AC tap for viral PCR
- Exam
  - AC inflammation
    Little to none in acute form
    1–2+ in chronic form
  - Increased IOP
    Much higher in acute form
  - Diffuse stellate KPs
  - Diffuse or sectoral iris atrophy (not always)
  - Iris heterochromia
  - In contrast to HSV/VZV anterior uveitis

Normal corneal sensation is normal
No posterior synechiae
– Complications
Glaucomatous optic neuropathy (acute form)
Cataract (chronic form)
- Treatment
– Acute form
Valganciclovir 0.15% gel 5×/day
Topical corticosteroids or NSAIDs
Glaucoma drops for IOP control, but avoid prostaglandin
– Chronic form
PO valganciclovir 900 mg BID for 4–6 weeks, then reduce to 450 mg BID for maintenance
• Monitor for bone marrow and renal toxicities
May discontinue therapy after 1 year of disease quiescence (or if repeat AC tap is negative for CMV)

CMV Retinitis

- Epidemiology
– Often the initial presentation of systemic CMV infection in immunocompromised patients (CD4 typically <50 cells/mm^3)
– Occurred in 15–40% of AIDS patients in the pre-HAART era
– ARN-like presentation has been rarely reported in immunocompetent
- Ocular symptoms
– May be minimal or absent initially
– Vision loss
– Floaters
– Unspecific visual disturbances
- Laterality
– Unilateral or bilateral
- Course
– Slowly progressive retinal necrosis (0.2 mm/week) affecting the posterior pole, the periphery, or both; if untreated, destroy the entire fundus over 3–6 months
- Systemic association
– Fever
– Leukopenia
– Arthralgia
– Pneumonitis
– Hepatitis
– Colitis
– +CMV in blood and urine

- Diagnosis
  - Typically made by characteristic findings and history
  - Vitreous tap for unclear cases
  - DFE q3–4 months is recommended in patients with CD4 <50 cells/mm
- Exam
  - Little or no AC inflammation
  - Early retinitis may disguise as cotton-wool spots, which is common in HIV retinopathy; however, lesion enlarges with irregular borders and is surrounded by satellite infiltrates
  - Three clinical variants:
    Classic, fulminant hemorrhagic necrotizing retinitis that extends along the major vascular arcades in the posterior pole
    Granular, indolent form more often found in the periphery; little or no retinal edema, fewer hemorrhages, less vascular sheathing, and retinal atrophy
    Perivascular form often described as a variant of frosted branch angiitis, with scattered retinal hemorrhages
  - While primary involvement is rare, optic nerve infiltration can occur if retinitis spread toward the posterior pole
  - Rhegmatogenous RD in one-fourth of patients
- Treatment

  Treatment should be tailored based on the location and severity of the retinitis, as well as host's immune status. UL97 mutation confers treatment resistance in as many as one-third of patients; ensuring HAART compliance and employing combination therapy are crucial
  - Ganciclovir
    Intravenous: 5 mg/kg BID × 2–3 weeks for induction, then QD for maintenance; AE: bone marrow suppression
    Oral: 1 g TID for maintenance (not used for induction)
    Intravitreal: 2 mg twice weekly x 3 weeks for induction, then 2 mg weekly for maintenance
    4.5 mg surgical implant: replaced every 6–8 months
  - Foscarnet
    Intravenous: 60 mg/kg TID × 2–3 weeks for induction, then 90 mg/kg/day for maintenance; AE: nephrotoxicity
    Intravitreal: 2.4 mg twice weekly × 3 weeks for induction, then 2.4 mg weekly for maintenance
  - Cidofovir
    Intravenous 5 mg/kg weekly × 2 weeks for induction, then 3–5 mg/kg q2 weeks for maintenance; AE: nephropathy and hypotony uveitis (co-administering probenecid reduces risk)
    Intravitreal: 20 μg every 5–6 weeks
  - Valganciclovir
    Oral: 900 mg BID × 2–3 weeks for induction, then 900 mg QD for maintenance; AE: bone marrow suppression