CYTOMEGALOVIRUS UVEITIS AND RETINITIS

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Cytomegalovirus

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Introduction

- Cytomegalovirus is a double-stranded DNA virus in the Herpesviridae family.
- It is the most common cause of congenital viral infection and causes clinically relevant disease in neonates
- It also causes illness in immunocompromised patients with leukemia, lymphoma, or HIV/AIDS; transplant recipients; and those with conditions requiring systemic immunomodulation.
- CMV retinitis is the most common ophthalmic manifestation of both congenital CMV infection and of CMV as an opportunistic coinfection in patients with HIV/AIDS.

Types

- The clinical appearance is similar regardless of clinical context, with 3 distinct variants:

1. **A classic or fulminant retinitis** with large areas of retinal hemorrhage against a background of whitened, edematous, or necrotic retina; the retinitis typically appears in the posterior pole, from the disc to the vascular arcades, in the distribution of the nerve fiber layer, and associated with blood vessels
2. **A granular or indolent form** found more often in the retinal periphery, characterized by little or no retinal edema, hemorrhage, or vascular sheathing, and with active retinitis progressing from the borders of the lesion
3. **A perivascular form** often described as a variant of **"frosted-branch" angiitis**, an idiopathic retinal perivasculitis initially described in immunocompetent children

Presentation and association

- Early CMV retinitis may present as a small, white retinal infiltrate masquerading as a cotton-wool spot;
- It is commonly associated with an HIV-related microvasculopathy, from which it may be distinguished by its inevitable progression without treatment.

Pathophysiology and histology

1. CMV reaches the eye hematogenously, with passage of the virus across the blood–ocular barrier, infection of retinal vascular endothelial cells, and cell-to-cell transmission of the virus within the retina.
2. The histologic features of both congenital and acquired disease include a primary, full-thickness; coagulative necrotizing retinitis and secondary diffuse choroiditis.
3. Infected retinal cells show pathognomonic cytomegalic changes consisting of large eosinophilic intranuclear inclusions and small, multiple, basophilic cytoplasmic inclusions.
4. Viral inclusions may also be present in the retinal pigment epithelium (RPE) and vascular endothelium.

Congenital CMV

1. Congenital CMV retinitis is usually associated with other systemic manifestations of disseminated infection, including fever, thrombocytopenia, anemia, pneumonitis, and hepatosplenomegaly.
2. The reported prevalence in children with congenital CMV infection is between 11% and 22%.
3. CMV retinitis has been reported to occur later in life among children with no discernible lesion ophthalmoscopically and no evidence of systemic disease reactivation.
4. This pattern suggests that even asymptomatic children with evidence of congenital CMV infection should be monitored at regular intervals for potential ocular involvement later into childhood.
5. Resolution of the retinitis leaves both pigmented and atrophic lesions, with retinal detachment occurring in 1/3rd of children.
6. Optic atrophy and cataract formation are not uncommon sequelae.

Diagnosis

1. The diagnosis of congenital disease is suggested by
    i. Clinical appearance of the lesions
    ii. Coupled with evidence of viral inclusion bodies
    iii. Or positive results of PCR testing in urine, saliva, and subretinal fluid,
    iv. Associated systemic disease findings.
2. **Congenital CMV-** complement-fixation test for cytomegalic inclusion disease is of value 5–24 months after the loss of the maternal antibodies transferred during pregnancy.
3. **The diagnosis of CMV retinitis in patients with HIV/AIDS or undergoing IMT** is essentially clinical, according to the features just described.

4. In immunocompromised patients with atypical lesions or whose disease is not responding to anti-CMV therapy, PCR-based analysis of the aqueous or vitreous samples may provide crucial diagnostic information of high sensitivity and specificity that allows the clinician to differentiate CMV from other herpetic causes of necrotizing retinitis and from toxoplasmic retinochoroiditis.

Treatment

A. **HAART**

1. The availability of combination antiretroviral regimens resulted not only in a significant decline in HIV/AIDS–associated mortality, but also in an 80% decline in new cases per year of CMV retinitis and its associated complications, including retinal detachment, which is itself associated with CMV lesion size.
2. New cases of CMV retinitis continue to occur among patients
   - In whom combination antiretroviral treatment fails as
   - Those who abandon treatment
   - Experience immune reconstitution but do not develop CMV-specific immunity.

B. Anti CMV

1. Successful management of CMV retinitis requires not only antiretroviral regimens but also appropriate anti-CMV therapy.
2. Resistant CMV infection is further associated with increased mortality among patients with HIV/AIDS being treated for CMV retinitis.
3. Aggressive anti-CMV therapy initiated at the same time as antiretroviral treatment may decrease the incidence of immune recovery uveitis.
4. Options for systemic coverage include
   - high-dose induction with either intravenous ganciclovir (5 mg/kg twice daily) or foscarnet (90 mg/kg twice daily) for 2 weeks followed by low-dose daily maintenance therapy.
   - Or oral valganciclovir (900 mg twice daily) for 3 weeks followed by maintenance therapy (900 mg/day).
   - SE- neutropenia Rx- Filgrastim (GCSF).

C. Intravitreal injection of ganciclovir or foscarnet

1. It is highly effective in treating intraocular disease and may be a useful alternative in patients who cannot tolerate intravenous systemic therapy because of myelotoxicity.
2. Duration of action 8 months
3. It leaves extraocular systemic CMV and the fellow eye untreated.
4. Combination treatment with oral valganciclovir may obviate this limitation and be particularly effective for patients with vision-threatening, posteriorly located retinitis.
5. Cidofovir, Fomivirsen IVI

D. When to stop anti-CMV

1. In patients with CMV retinitis who are on antiretroviral regimens and experience sustained immune recovery (CD4+ T lymphocytes ≥100 cells/μL for 3–6 months), systemic anti-CMV maintenance therapy may be safely discontinued.
2. Antiretroviral therapy–naive patients may require only 6 months of anti-CMV therapy with good immune reconstitution,
3. Antiretroviral therapy– experienced patients may require long-term maintenance therapy.

E. **Follow –up and relapse**

1. Despite immune recovery, patients with a history of CMV retinitis who discontinue maintenance anti-CMV therapy remain at risk for recurrence and should be monitored at 3-month intervals.
2. CMV anterior uveitis requires specific, prolonged, systemic anti-CMV treatment with valganciclovir, as relapses are common after discontinuation of therapy.

Complications

- Among immunocompetent adults, CMV infection may produce a chronic or recurrent unilateral anterior uveitis associated with
  - Ocular hypertension,
  - Corneal edema,
  - Variable degrees of sectoral iris atrophy.