Acute retinal necrosis secondary to cytomegalovirus

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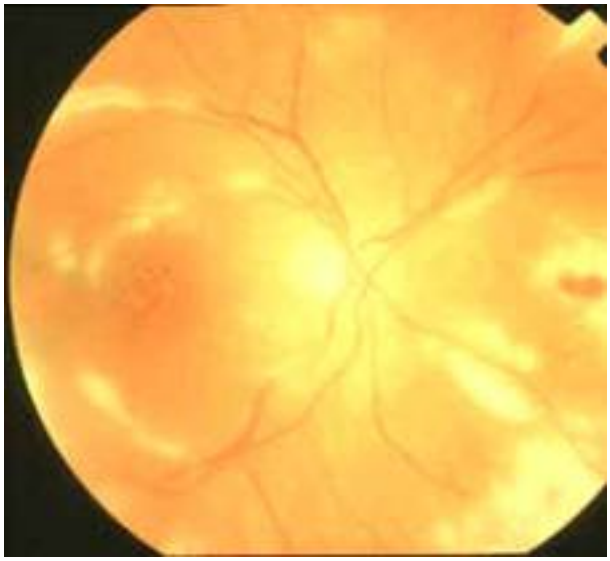
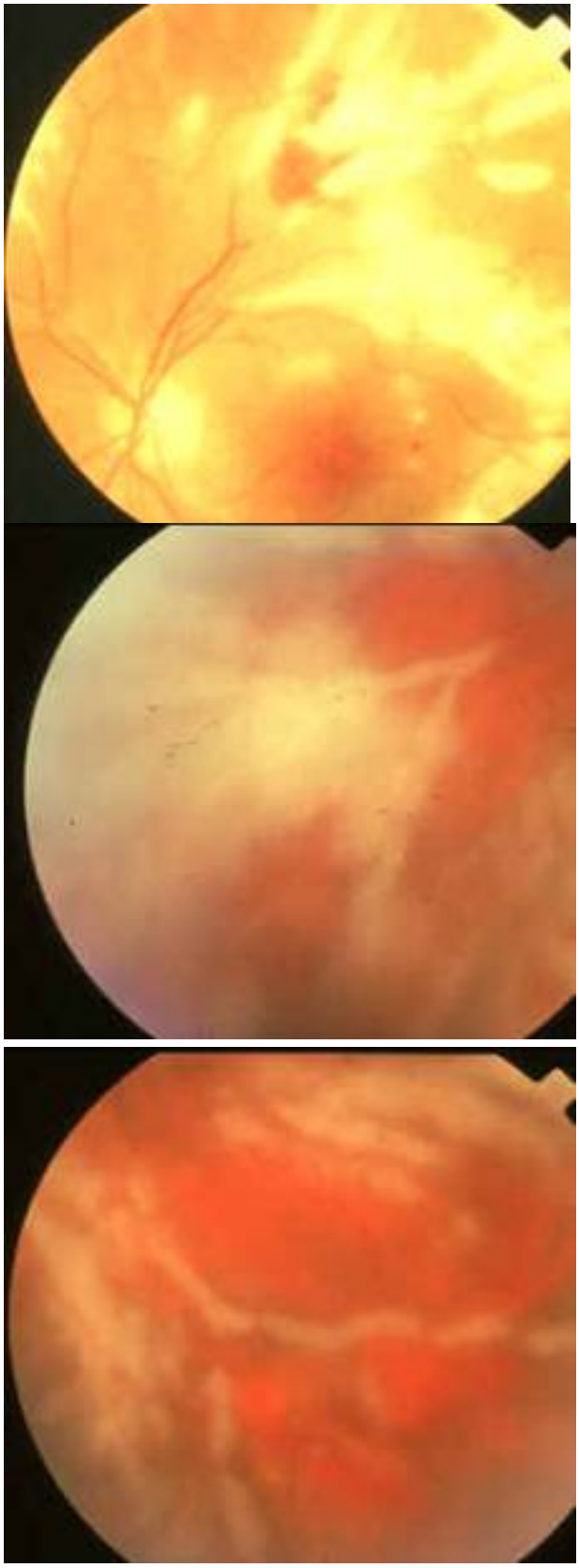
Abstract
Acute retinal necrosis (ARN) is a clinical syndrome characterized by vitritis, severe occlusive vasculitis which produces a full thickness, necrotizing retinitis. The disease is caused by an acute infection with a member of the herpes virus family,usually VZV or HSV. ARN usually occurs in healthy adults; however immunocompromised patients may also be affected. The prognosis is poor, with significant visual loss. Clinical course most often leads to detachment of the atrophic retina, regardless antiviral treatment. We present an unusual case of ARN caused by cytomegalovirus in an immunocompromised patient. Clinical manifestations, diagnosis, and management are discussed.

Case Presentation
A 62 year old white female was referred with a history of progressive deterioration of her peripheral vision in both eyes for 2 weeks, getting dramatically worse with loss of central acuity over the last 3 days. Her past ocular history was unremarkable. Her past medical history was significant for Non-Hodgkin's lymphoma for 3 years. She had active herpes zoster dermatitis at the time of presentation. She was on systemic prednisone 50 mg daily which she had taken for the past year. Ophthalmic examination demonstrated visual acuity of 20/200 in both eyes. There was no afferent pupillary defect. Ocular motility and intraocular pressures were normal. Anterior segment examination revealed 3+ cells and keratic precipitates bilaterally. Dilated funduscopic exam showed moderate vitritis, vasculitis, and extensive perivascular retinitis with areas of retinal hemorrhage and whitening OU (fig.1 A, B, C, D). Our main differential diagnosis included acute retinal necrosis, and CMV retinitis. Other possibilities were lymphomatous retinitis, syphilis, diffuse toxoplasmosis, and acute multifocal hemorrhagic retinal vasculitis. With these possibilities in mind she was started on 500 mg three times a day, and we performed an initial laboratory evaluation including CBC, liver functions, BUN/creatinine, HSV 1 and 2, CMV, and FTA-ABS. The results were significant only for a macrocytic anemia and a positive CMV antibody titer. Because of the rapid progression of her disease and the non diagnostic non invasive evaluation we decided to proceed to diagnostic and therapeutic vitrectomy. Pars plana vitrectomy was performed in the left eye and specimens were obtained for PCR, cytopathology, and microbiology. Because we suspected a member of the herpes virus family based on the clinical picture we injected 400 mg of ganciclovir into the vitreous cavity.





Figures 1 A-D. Acute Retinal Necrosis

Our diagnostic studies revealed no growth of microorganisms, and the cytopathology was

negative for malignant cells. PCR testing was positive for cytomegalovirus. Based on these results the therapy was changed from acyclovir to ganciclovir 225mg IV twice a day and her prednisone was tapered to 40 mg daily.
Within one week the patient's visual acuity had dropped to CF 3ft OS and 20/400 OD. The anterior segments were unchanged, but dilated funduscopic examination of the left eye revealed a retinal detachment. The patient underwent pars plana vitrectomy, retinal detachment repair, retinal biopsy and silicone oil placement in the left eye. The retina was successfully attached (fig.2 A, B).

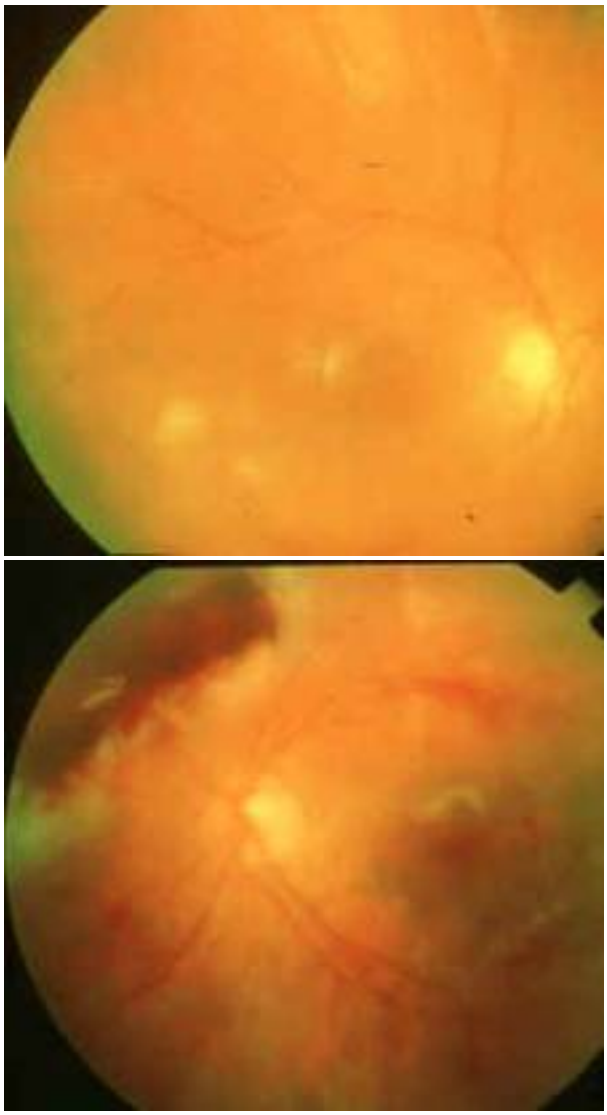


Figure 2 A & B. Post PPV, RD repair, retinal biopsy and silicone oil placement, OS

Immunohistochemical studies of the biopsied retinal tissue demonstrated enlarged cells staining positively for CMV (fig.3). Immunohistochemistry for HSV and VZV was negative. These results confirmed our diagnosis of CMV retinitis and the patient was continued on ganciclovir, while the prednisone was slowly tapered to 20 mg daily.

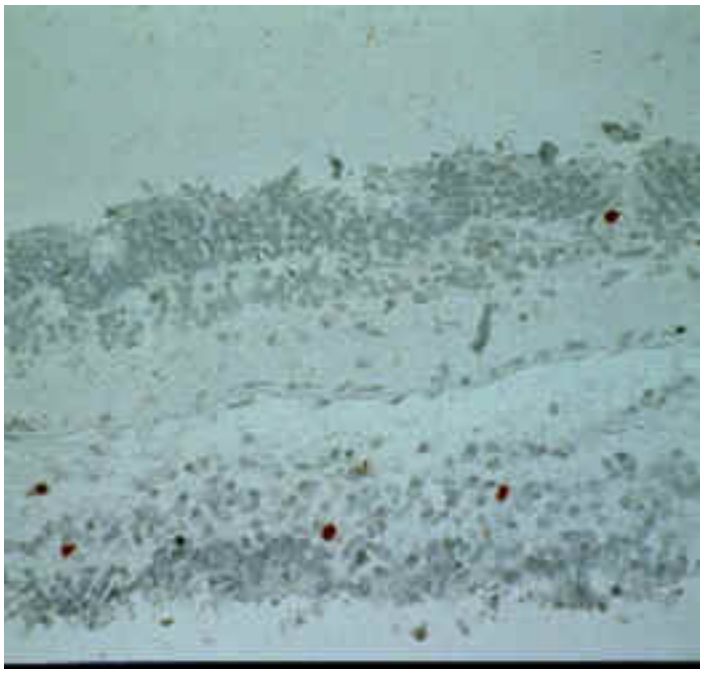


Figure 3. Immunohistochemistry

Three weeks after the initial presentation the patient returned complaining of worsening of vision in the right eye. Her visual acuity was HM OD, 20/300 OS. Anterior segments had reduced inflammation (1/2+cells) OU. Funduscopic exam showed a retinal detachment OD. Surgical repair consisted of pars plana vitrectomy, RD repair, intravitreous ganciclovir, and silicone oil instillation. The retina was successfully reattached postoperatively. Her ganciclovir was reduced to 225 mg IV daily due to leukopenia.

Seven weeks after the initial presentation her visual acuity was 20/125 OD, 20/200 OS. Anterior segments showed trace of inflammation. Posterior subcapsular opacification had developed in both eyes. The funduscopic exam showed areas of chorioretinal scarring and no further progression of the retinitis (fig 4). In addition there was subretinal fluid inferiorly in both eyes, with round retinal breaks OD. The silicon oil was left in place and she was maintained on IV ganciclovir 225mg daily and prednisone 20 mg PO daily. Shortly later the patient died of her Non-Hodgkin's lymphoma.

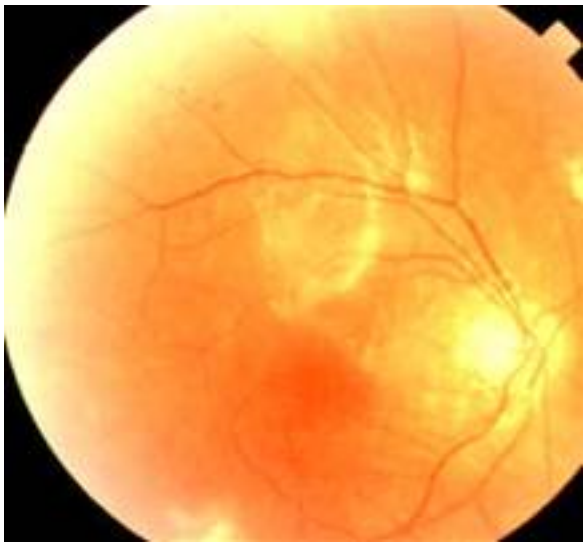


Figure 4

Based on the clinical presentation, the course of the disease, and its complications, a final

diagnosis of acute retinal necrosis caused by cytomegalovirus was made.

Acute Retinal Necrosis

Introduction
Acute retinal necrosis (ARN) is a clinical syndrome characterized by vitritis, severe occlusive vasculitis of the retina and the choroid, and a full thickness, confluent, necrotizing retinitis that affects primarily peripheral retina. Originally described in Japan in 1971 by Urayama and coworkers, ARN has only recently been documented to be caused by retinal infection with herpes virus. ARN usually occurs in healthy adults, but can also present in immunocompromised patients.

Epidemiology
ARN is slightly more common in men. It can occur at any age, but it is more common between 20 to 60 years of age. There is no racial predilection. Some authors have proposed an immunogenetic predisposition. Holland and coworkers found 55% of patients with ARN were positive for HLA-DQw7 antigen compared to the general prevalence of 19% in the general population. Additionally, there was also an excess of the Bw62, DR4 phenotype which was present in 16% of patients with ARN compared to 2.6% in the normal population.

Clinical findings
Patients with ARN frequently give a recent or remote history of herpes zoster or varicella infection. Cutaneous herpes simplex ulcers are also known to be associated with ARN. ARN usually presents with mild to moderate ocular or periorbital pain as the first symptom. Patients also frequently note floaters and conjunctival injection. However, in some cases pain and redness may be absent. Patients may notice aberrations of their peripheral vision early, but decreased central acuity is generally a late finding due to circumferential spread of the disease. The disease is multifocal and spreads quickly causing massive areas of retinal necrosis. The second eye becomes involved within 1 to 6 weeks in 2/3 of cases.
Ophthalmic examination typically reveals conjunctival injection with limbal flush, occasionally with episcleritis or scleritis. There is notable anterior chamber inflammatory reaction with keratic precipitates. Intraocular pressures are frequently elevated, and some degree of optic disc swelling is also seen in most cases. Funduscopic examination reveals the classic triad of necrotizing retinitis, vitritis, and generalized retinal vasculitis. Retinal arteritis is generally more prominent than phlebitis. Scattered small to medium sized intra-retinal hemorrhages may occur along the course of the involved vessels. Occasionally, if the phlebitis is particularly severe, widespread areas of hemorrhage may occur. Initial retinal lesions are small, patchy, white-yellow areas in the midperiphery that typically have distinct boarders. Over time lesions tend to enlarge, increase in number, and coalesce. The retinitis spreads circumferentially, and the posterior pole may become involved leading to loss of central acuity.
Untreated acute lesions tend to resolve in 6-12 weeks when the host's immune system controls the infecting virus, or when there is no more retinal tissue to infect. Antiviral therapy shortens the duration to about 4-6 weeks. Healing is gradual and patchy with RPE atrophy and hypertrophy. The retina becomes very thin and atrophic, and often develops multiple breaks. Most observers have noted that the retinal holes with ARN develop at the junction of normal and affected retina. Clarkson and coworkers, however, described retinal tears in areas of healthy retina caused by proliferative vitreo-retinopathy and traction. Rhegmatogenous retinal detachment commonly occurs weeks to months after the onset of the disease, and may even occur as soon as one week after the initial symptoms. Tractional or rhegmatogenous RD ultimately develop in 86% of patients. The prognosis is poor and the magnitude and extent of visual loss is often unpredictable.

Histopathology
Histopathology of ARN demonstrates sharply demarcated zones of necrotizing retinitis, retinal and choroidal vasculitis, vaso-occlusion, and a diffuse perivascular cellular infiltration involving all three ocular layers. The choroid is markedly affected with severe thickening and lymphocytic

infiltration. The cellular infiltration consists mostly of lymphocytes and plasma cells, with some polymorphonuclear leukocytes and rare eosinophils. Electron microscopy may be useful to identify viral particles within retinal cells. The typical cytomegaly observed in infected retina cells in CMV is rare in ARN.

Diagnosis
Diagnosis of ARN is made solely on clinically appearance and course. The criteria for making the diagnosis of ARN include: 1) Multiple foci of retinal necrosis in the peripheral retina, 2) Rapid progression of disease without antivirals, 3) Circumferential spread, 4) Occlusive vasculopathy that must have arteriolar involvement, 5) Prominent anterior chamber and vitreous inflammation. In addition clinical findings of optic nerve swelling, scleritis, and pain all support a diagnosis of ARN. A diagnostic pars plana vitrectomy, with PCR and /or retinal biopsy may be performed to confirm Herpes virus infection, and possibly exclude other causes. Retinal biopsy must be taken at the leading edge between healthy and affected retina during the acute phase to obtain positive results.
An experimental less invasive alternative method for confirming the diagnosis is to perform an anterior chamber paracentesis and immunofluorescence studies to asses local VZV and HSV antibody production. The specificity and sensitivity of this procedure remains to be defined.

Differential diagnosis
Syndromes that might present like ARN included syphilitic neuroretinitis, CMV, toxoplasmosis, Bechets, acute multifocal hemorrhagic retinal vasculitis, sarcoidosis and intraocular lymphoma. Before making the diagnosis of ARN these possibilities should considered.

Laboratory work up
In suspected cases of ARN baseline laboratory evaluations are indicated. Although there are no diagnostic tests for ARN some laboratory work up may be useful to rule out other diseases and monitoring medical therapy.
Suggested laboratory work up:
CBC
liver function tests
BUN/creatinine
HIV
acute and convalescent serum titers to HSV 1 and 2, VZV, CMV
chest X-ray
PPD
RPR
FTA-ABS
ACE level
toxoplasmosis titers
lumbar puncture, CT or MRI may be indicated if large cell lymphoma, CNS syphilis, or encephalitis are suspected

Treatment
Acyclovir is the standard medical treatment for ARN. The typical dosage is 500mg/M2 IV q8 for a minimum of 1 week followed by 400-800mg 5x/day PO for 6 weeks. This therapy is thought to prevent or minimize infection in the second eye, which generally occurs within 6 weeks. Although ganciclovir may be used for acyclovir failure cases, it is usually saved for cytomegalovirus cases, because it is more toxic than acyclovir. The induction dosage of ganciclovir is 5 mg/Kg IV bid for 2-3 weeks, followed by a maintenance dose of 5 mg/kg IV daily for 5 to 7 weeks. Systemic corticosteroids may be added to combat the inflammation 24-48 hours after initiating IV antiviral treatment. Antithrombotic or anticoagulant therapy such as aspirin, heparin, or Coumadin may be theoretically useful due to the vaso-occlusive nature of ARN, but these treatments have not been proven. Frequently acute retinal necrosis requires surgical treatment. Confluent laser photocoagulation may be applied posterior to the areas of active retinitis prophylactically to prevent retinal detachment, but this does not halt spread of retinitis, and may need to be repeated

if the lesions advance. Clinical therapy does not prevent retinal detachments. As the majority of patients with ARN eventually develop a retinal detachment, retinal detachment repair should be performed as indicated.

Cytomegalovirus Retinitis

CMV is a herpes class virus that affects almost exclusively in immunocompromised hosts or systemically infected neonates. The disease is believed to be hematogenously spread, and retinal disease is by far the most common clinical manifestation. The most common presenting complaint is floaters, followed by decreased vision, or paracentral scotoma and metamorphopsia. Ophthalmic examination typically reveals little or no AC reaction in most patients, and vitritis if any is minimal. The clinical course is usually protracted, chronic with slow spreading of the disease. Generally the disease starts with one initial focus that spreads across the retina. Lesions initially tend to be posteriorly located, commonly in the distribution of the arcade vessels or involving optic disc. More than three separate areas of retinitis in one eye is unusual for CMV. There are three different clinical appearances; 1) hemorrhagic, 2) brush fire, and 3) granular. CMV infection leaves the retina atrophic and retinal detachment develops in 5 to 29% of patients.

Discussion

Obviously this patient presented a diagnostic challenge. We were faced with a clinical picture of anterior chamber inflammation, rapidly progressive extensive necrotizing retinitis, retinal vasculitis, and vitritis. These features were suggestive of ARN. We believed that in this rapidly progressive case there was no time to waste and we proceeded quickly to diagnostic vitrectomy. The PCR was positive for cytomegalovirus. We treated this fulminant retinal necrosis aggressively with antiviral therapy in an effort to preserve as much vision as possible. Shortly after the initial vitrectomy the patient's atrophic retina developed a rhegmatogenous retinal detachment. At the time of the retinal detachment repair a retinal biopsy was performed which confirmed the PCR findings. Thus we were dealing with an unusual case: a clinical picture consistent with ARN and caused by cytomegalovirus. Though CMV is a member of the herpes family there are only 2 previous reports in the literature of ARN associated with CMV. This represents the third case of ARN associated with cytomegalovirus.

Review Questions for Acute Retinal Necrosis (ARN)

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1. Acute retinal necrosis is a clinical syndrome characterized by all of the following

EXCEPT:

a. moderate to severe vitreous cellular reaction

b. necrotizing retinitis

c. rubeosis iridis

d. severe occlusive chorioretinal vasculitis

2. Acute retinal necrosis:

a. is bilateral and symmetric in 1/3 of the cases

b. is more common in Caucasians

c. is more common in the first and second decades of life

d. is caused by herpes virus family infection

3. Which of the following is not related to the diagnosis of ARN:

a. a diagnostic pars plana vitrectomy, with PCR and /or retinal biopsy may be helpful to confirm Herpes virus infection, and rule out other causes.

b. is made on clinical findings and course

c. fluorescein angiography is pathognomonic

d. there are no specific diagnostic tests

4. All of the following diseases may be considered in the differential diagnosis of ARN EXCEPT:

a. sarcoidosis

b. serpiginous choroiditis

c. toxoplasmosis

d. syphilitic neuroretinitis

e. CMV retinitis

5. The clinical course of acute retinal necrosis:

a. leads to retinal detachment in up to 86% of the cases, regardless of antiviral therapy

b. is protracted, with slow progression of the disease

c. is characterized by acute lesions that tend to resolve in 4-6 weeks in untreated patients

d. is benign, with no permanent scarring

6. All of the following are true EXCEPT:

a. Acyclovir is the standard medical treatment for ARN

b. Ganciclovir may be used for acyclovir failures or CMV cases

c. Confluent laser photocoagulation may be applied posterior to the areas of active retinitis prophylactically to prevent retinal detachment

d. aggressive immunosuppressive therapy is advised in complicated cases

Answers:

1.c 4 b

2 d 5 a

3 c 6 d