PEER REVIEWED

Acute Retinal Necrosis and Saving Vision in Aggressive Disease

Carol Chang OD, FAAO

Abstract

Acute retinal necrosis (ARN) is a rapidly progressing viral infection of the retina that can be visually devastating unless a prompt and accurate diagnosis is made and treatment is initiated. This case report covers the diagnosis, treatment and management of unilateral ARN with subsequent retinal detachment in an otherwise healthy 35-year-old Hispanic male. Because ARN is relatively rare and typically occurs in young, healthy individuals, it is important for third- and fourth-year optometry students, optometry residents and practicing clinicians to learn how to recognize the disease, understand treatment options, and initiate the referrals necessary for efficiently diagnosing and treating ARN to prevent a potentially poor visual outcome.

Key Words: *acute retinal necrosis, herpes simplex virus, viral retinitis, uveitis, vitritis*

Background

This teaching case report covers the clinical manifestations of acute posterior segment infection from the herpes virus family with a focus on acute retinal necrosis (ARN). ARN is a rapidly progressive and potentially devastating viral infection of the retina that primarily presents in young, healthy individuals in the second to sixth decade with no predilection for race or sex.[1,2] The etiology of this rare viral infection is associated with varicella zoster virus (VZV), herpes simplex virus type 1 (HSV-1), and herpes simplex virus type 2 (HSV-2).[3] This report involves a 35-year-old healthy Hispanic male with sudden onset of ARN and a subsequent retinal detachment. The intention is to discuss how to recognize the disease, initiate treatment and co-manage these cases in an interdisciplinary setting. Acute retinal infections put patients at risk for further complications and vision loss if not treated early and aggressively with topical, oral and intravenous therapies. Thus, prompt and accurate diagnosis and treatment with interdisciplinary co-management are warranted. This case report is intended for third- and fourth-year optometry students, optometry residents and practicing doctors in a primary-care or urgent-care setting.

Case Description

A 35-year-old Hispanic male presented to the emergency room late at night and reported hazy vision that he described as a “plastic curtain” over his right eye. He also reported a red, painful (6 out of 10) right eye, and an associated headache on the right side. The patient had no significant medical or ocular history and was not taking any systemic or topical medications. He had no significant family medical or ocular history.

His entering unaided visual acuities were 20/20 OD and OS. His intraocular pressures (IOPs) were 37 mmHg OD and 12 mmHg OS with Goldmann tonometry. In the right eye, the cornea had fine keratic precipitates, and the anterior chamber had a reaction of 2+ cells. Ishihara color test was normal OD and OS. The anterior segment of the left eye was unremarkable. Dilated fundus exam revealed a trace vitritis

and normal posterior pole and peripheral findings in the right eye. The posterior pole and periphery of the left eye were unremarkable.

The elevated IOP in the right eye was lowered in-office with instillation of one drop of each of the following mediations: brimonidine tartrate 0.2% ophthalmic solution, dorzolamide hydrochloride 2% ophthalmic solution, timolol maleate 0.5% ophthalmic solution, and bimatoprost 0.03% ophthalmic solution. The drops lowered the pressure to 25 mmHg OD.

The patient was diagnosed with unilateral acute severe anterior uveitis OD with suspicion of a viral etiology with a secondary elevated IOP. The recommended treatment at this visit included three medications for the right eye: one drop of prednisolone acetate 1% ophthalmic suspension four times a day (QID), one drop of cyclopentolate hydrochloride 1% ophthalmic solution twice a day (BID), and one drop of timolol maleate 0.5% ophthalmic solution BID. To determine the etiology, the patient was encouraged to have blood tests. At this visit, the following tests were administered: human immunodeficiency virus (HIV), HSV-1, HSV-2, VZV, cytomegalovirus (CMV), rapid plasma reagin/venereal disease research laboratory (RPR/VDRL), antinuclear antibodies (ANA), purified protein derivative (PPD), angiotensin converting enzyme (ACE) and Lyme disease. The patient was instructed to return in the morning for follow-up during normal clinic hours.

Same-day follow-up

The patient returned that same day in the morning for follow-up. He reported good compliance with the prescribed topical medication treatment, but no improvement in symptoms since the night before. His entering unaided visual acuities were 20/20 OD and OS. His IOPs were 12 mmHg OD and 15 mmHg OS with Goldmann tonometry. In the right eye, there was a noted worsening of the vitritis; however, the posterior segment was normal with no significant findings. In the left eye, the anterior and posterior assessment remained unchanged with no significant findings. The patient was instructed to return in two days for an evaluation with the retina specialist.

Subsequent visits

At the two-day follow-up visit, the patient was seen in conjunction with a retina specialist. The patient reported good compliance with all prescribed topical medications but no improvement in symptoms in the right eye. The exam showed a slight reduction in visual acuity from 20/20 to 20/25-2 in the right eye. White, necrotic lesions with multiple foci in the temporal periphery of the right eye, not noted in previous exams, were present. All exam findings remained normal in the left eye. Fundus photography **(Figure 1)** and fluorescein angiography **(Figure 2)** of the right eye were performed at this visit.

Figure 1. An ultra-widefield fundus photograph of the right eye on the third day after onset of symptoms shows temporal retinal necrosis. Click to enlarge

Figure 2. Fluorescein angiography of the right eye on the third day after onset of symptoms. Click to enlarge

Also during this follow-up visit, the patient's laboratory test results were obtained. They were positive for HSV-2 and CMV, and negative for HIV and all other potential etiologies. The nature of the disease was determined to be viral, and the patient was diagnosed with ARN in the right eye. He was prescribed

valaciclovir 1g PO three times a day (TID) for 10 days. He also was instructed to continue all topical medications as prescribed at his previous visit.

The patient was closely monitored in the retina clinic and scheduled to return for follow-up every other day until completion of the antiviral therapy. Co-management with infectious disease specialists was initiated as the necrosis continued to progress and peripheral vascular occlusion and sclerosis developed in the right eye.

One week after onset of symptoms (Day 7), there was noted necrotic progression in the retina in the right eye and further worsening of visual acuity in the right eye to 20/100. Thus, based on a collaborative consult between the retina and infectious disease specialists, the oral antiviral therapy was deemed insufficient and the patient was admitted for treatment with intravenous (IV) ganciclovir and instructed to return for daily monitoring in the retina clinic as an in-patient. Five days after admission (Day 12), while the patient was receiving IV ganciclovir, the peripheral necrosis in the right eye developed into a temporal serous retinal detachment. Due to the noted progression of the retinal detachment towards the posterior pole **(Figure 3)**, the patient was treated with an intravitreal injection of ganciclovir (Day 13).

Despite IV and intravitreal intervention, the retinal detachment continued to progress (Day 15). Thus, the next day (Day 16) the patient underwent an urgent pars plana vitrectomy (PPV) with silicone oil fill to prevent further detachment. After the surgery, the patient was under close daily monitoring by the retina specialist. Once the vision stabilized and the necrosis receded **(Figure 4)**, the patient was discharged from the hospital.

Figure 3. An ultra-widefield fundus photograph of the right eye on the 13th day after onset of symptoms shows a temporal serous retinal detachment. Click to enlarge

Figure 4. Ultra-widefield fundus photograph of the right eye captured one month after pars plana vitrectomy and silicone oil fill. (The imaging artifact at the macula is likely a reflection from the silicone oil.) Click to enlarge

The patient was advised to continue follow-up visits with the retina specialist as topical prednisolone acetate 1% ophthalmic suspension in the right eye was tapered (from QID, TID, BID, then QD – with each taper period lasting two weeks). He was also instructed to follow-up with the infectious disease specialists to complete an oral maintenance dose of valganciclovir. As of his last visit, the patient's visual acuity in the right eye had recovered to 20/25 with a -6.00D lens.

Education Guidelines

Learning objectives

1. Recognize signs and symptoms of ARN
2. Discuss differential diagnoses of anterior, posterior and hypertensive uveitis
3. Review indicated laboratory tests to confirm diagnosis
4. Review how to initiate appropriate treatment
5. Understand the role of the optometrist in an interdisciplinary setting

Key concepts

1. Differentials for anterior, posterior and hypertensive uveitis
2. Pathophysiology of acute retinal necrosis and its subsequent clinical complications
3. The importance of accurate and early treatment for best visual prognosis
4. The role of laboratory testing in determining etiology of infection and treatment plan
5. The importance of interdisciplinary co-management to address all treatment options and to optimize the visual outcome
6. The importance of close monitoring for disease progression

Discussion points and questions

1. Knowledge, concepts, facts and information for case review:

    a. Describe the signs and symptoms of ARN vs. other causes of posterior uveitis
    b. Discuss the epidemiology of ARN
    c. Discuss the laboratory work-up that aids in diagnosis of ARN
    d. Discuss the natural history and course of disease
    e. Discuss the treatments available and efficacy of antiviral agents

2. Generating questions, hypothesis and diagnosis:

    a. What diagnostic/lab tests were used to determine the final diagnosis?
    b. How were the clinical findings used to rule out other differentials?
    c. What are the official criteria that need to be met to establish a diagnosis of ARN?
    d. If a patient presents with ARN, what associated systemic conditions should the patient be tested for?

3. Management:

    a. What are the different types of antiviral medications and how are they ranked in terms of efficacy?
    b. Why are steroids needed? What precautions should be taken when using steroids, oral and topical?
    c. Why are IOP-lowering drops needed?
    d. What course of action is needed should the symptoms regress with treatment?

4. Patient management and ethics:

    a. What are the consequences of patient non-compliance with treatment?
    b. What are some important points to discuss during patient education regarding the patient's disease progression and visual prognosis?

Discussion: Literature Review of ARN

Epidemiology and pathophysiology

The American Uveitis Society[4] defines ARN by the following set of clinical manifestations:

a. one or more foci of retinal necrosis with discrete borders located in the peripheral retina
b. rapid progression in the absence of antiviral therapy
c. circumferential spread
d. evidence of occlusive vasculopathy with arterial involvement

e. a prominent inflammatory reaction in the vitreous and anterior chamber

Though specific requirements need to be met to classify ARN, it can present in a range of severity and visual prognosis.[5]

ARN is a unique and rare ocular manifestation of a viral infection that is usually seen in healthy and immune-competent individuals, though some studies have suggested expanding the diagnosis of ARN to immune-compromised patients as well.[1] The presentation is usually unilateral, but can become bilateral in 9-33% of cases.[1,2] Bilateral spread of ARN can occur from either the local (non-synaptic) transfer of the virus crossing at the optic chiasm, or from passing (trans-synaptic) through the neurons along the visual pathway.[3]

The incidence of ARN, as reported in a United Kingdom study, is one case in 1.6-2.0 million people.[6] Typically, ARN presents in patients 20-60 years old,[1] with no known sex predilection.[2] Multiple viruses can cause ARN, from most common to least common: VZV, HSV, CMV and Epstein-Barr virus.[3] There is also an age predilection in viral etiology. In older patients, infections are more likely caused by VZV or HSV-1,[7] while in younger patients, infections are more likely from HSV-2.[2]

Clinical presentation and prognosis

ARN can be classified into two phases, the acute herpetic phase and the late cicatricial phase.[8] In the acute phase, the patient presents with mild to moderate ocular pain, irritation, elevated IOP and a red eye.[1] Anterior-segment findings include episcleritis, scleritis, anterior granulomatous uveitis or, rarely, a hypopyon.[8] During the acute phase, the most common posterior-segment findings are chorioretinal vasculitis, vitritis and retinal necrosis.[1] The necrotic lesions in the posterior segment occur when the virus proliferates and causes rapidly progressive necrosis of the retina, choroid and vitreous. These distinctive retinal opacifications are thought to be caused by either an excessive immune response to the virus or a buildup of the virus infiltration itself.[2] ARN starts in the peripheral retina and typically does not affect the posterior pole in the early stages; therefore, central vision can initially remain undisturbed.[1]

In the late cicatricial phase, the posterior segment is more heavily involved in fast-progressing retinal necrosis and vitreal structural changes.[3] Retinal necrosis is usually seen in the temporal periphery, extending towards the posterior pole. The areas of retinal necrosis develop rhegmatogenous retinal detachment in 50-75% of cases[7] due to a thinned atrophic retina, weak retinal adhesions and vitreal traction.[2] The highest probability of an associated retinal detachment occurs on average at the third week after the onset of symptoms, but can occur as late as five months after.[3] The late cicatricial stage is associated with occlusive vasculopathy including arteritis and phlebitis at the retinal and choroidal vasculature. As the disease advances into later stages, ARN can progress to affect the macula and optic nerve, which can result in poor visual outcomes of 20/200 or worse. The decrease in central vision is likely secondary to macular edema or ischemia, and optic nerve hyperemia, edema or neuropathy.[1,9] Though less commonly seen, ARN can also further progress and lead to proliferative vitreoretinopathy, sclerotic vessels and optic atrophy.[10] Other less common presentations that can lead to a reduced visual outcome are hypotony, macular pucker, or macular hole.[1]

Because ARN has a variable presentation with unpredictable levels of severity, the visual outcome is based on disease course and progression. If the diagnosis is made within the first two weeks of onset, and if treatment is initiated immediately, the probability of bilateral spread can be reduced and the patient has a better visual prognosis.[3] Early treatment is important as it takes the antiviral medications approximately one week to halt progression of the necrosis.[3] If no treatment is initiated, the infection and inflammation can self-resolve in 6-12 weeks, though the visual prognosis is likely to be worse than if the patient received treatment.[1]

Laboratory testing and differential diagnosis

Identification of the causative virus in ARN is accomplished with polymerase chain reaction (PCR) analysis of viral DNA from fluid samples taken from either the anterior chamber or the vitreous. PCR testing has high (>90%) sensitivity and specificity in detecting VZV, HSV and CMV.[8] While PCR is the standard for determining etiology, false negatives or atypical presentations of ARN can confound results and affect treatment and management.

Suggested laboratory tests in a patient presumed to have ARN (CBC, HIV, HSV-1, HSV-2, VZV, CMV, PPD, RPR/VDRL, ACE and toxoplasmosis)[1] are intended to identify viral, bacterial and parasitic etiologies. Usually, in cases that present with hypertensive uveitis (elevated IOP with intraocular inflammation), infectious etiologies are implicated.

When working up a patient for ARN, the clinician should rule out progressive outer retinal necrosis (PORN). PORN presents with a similar etiology, pathophysiology and presentation to ARN. PORN is described as a set of clinical manifestations including:

a. full-thickness necrosis in the peripheral retina
b. extremely rapid progression with propensity for bilateral involvement
c. minimal intraocular inflammation
d. poor response to treatment with high doses of IV antiviral therapy[2,11]

The main differences between PORN and ARN are the patient demographics and speed of progression of the disease. PORN is usually seen in HIV-positive, immune-compromised patients with a CD4+ lymphocyte count less than 50 cells/µL.[12] Like ARN, PORN is characterized by a quickly progressing outer retinal necrosis; however, unlike ARN, PORN does not present with prominent intraocular inflammation or vitritis.[11] It also progresses more aggressively than ARN with more retinal hemorrhages and a characteristic “cracked mud” pattern of opaque yellow-white retinal lesions.[12] In addition to PORN, other differentials to keep in mind when seeing peripheral retinal necrosis include CMV retinitis, toxoplasmosis, syphilis, endophthalmitis, Behcet’s disease, pars planitis, sarcoidosis and intraocular lymphoma.[8]

Systemic treatment

Antiviral medications are considered the standard of care for ARN. The current standard is to use IV acyclovir (1,500 mg/m^2) for 5-10 days followed by maintenance oral acyclovir (800 mg 5x/day) for 4-6 weeks.[13] IV acyclovir is the preferred drug as it is less systemically toxic than IV ganciclovir and IV foscarnet.[11] The current recommendation is to treat the disease empirically upon initial ocular manifestation, prior to diagnostic confirmation by PCR, because the average time for antiviral medications to take effect in stopping the progression of retinal necrosis is seven days.[3]

Treatment with oral antivirals alone can also be considered in less severe forms of ARN.[14] There is some ongoing debate about the efficacy of oral monotherapy in reaching therapeutic levels in the blood serum and its ability to resolve active retinal lesions and prevent contralateral involvement.[5,9,15] However, this concern focuses mainly on oral acyclovir (800mg 5x/day) failing to reach therapeutic levels, thus, acyclovir is generally not used as oral monotherapy.[14] Alternative antivirals that may be more effective, such as famciclovir, valaciclovir or valganciclovir, should be considered.

Famciclovir (500 mg TID) is widely used and has shown similar visual outcomes to IV acyclovir treatment.[16] Valaciclovir (1g TID), an acyclovir prodrug, is a newer oral antiviral that is safe and well-tolerated with minimal side effects. It has been shown to reach similar plasma levels as IV acyclovir.[5,17] Valganciclovir (900 mg BID), a ganciclovir prodrug, is effective against HSV and VZV and is thus able to

treat ARN, PORN and CMV retinitis, which establishes it as a logical first-line treatment choice.[8,16] However, due to its severe systemic side effects, valganciclovir is generally reserved for CMV retinitis or acyclovir-resistant ARN.[16] Prodrugs are considered a good alternative because they are converted within the body and provide greater bioavailability of the drug.[16] Though multiple studies claim the efficacy of oral monotherapy, until further evidence is provided, IV antivirals remain the recommended standard of care.[14]

Following the resolution of ARN, maintenance treatment with oral antivirals is used in an effort to prevent ARN onset in the contralateral eye.[1]

Other medications used in ARN treatment include oral prednisone, aspirin and warfarin. Steroids are used to decrease intraocular inflammation and improve visual outcome; however, steroids are not to be added until 24-48 hours after the start of antiviral treatment to assure adequate antiviral coverage prior to the addition of an immune-suppressing steroid.[8] Intravitreal triamcinolone can be used to treat choroidal neovascularization if it develops.[18] Blood thinners are used to prevent retinal ischemia, though there is no strong evidence for the benefits of these adjunct therapies.[8]

Ocular treatment

As stated in the prior section, standard of care for ARN is IV antiviral medication with the option of corticosteroids. In addition to systemic treatments, ocular-specific treatments are used to contain the disease and prevent progression to the contralateral eye, most notably antiviral intravitreal injections.[16,19]

Intravitreal injections are considered the most direct and immediate treatment for ARN presenting with retinitis or active inflammation at the macula or optic nerve head. An intravitreal injection combined with antiviral therapy generally achieves a better visual outcome and reduces the incidence of a retinal detachment, as opposed to systemic treatment only.[8] Commonly used antivirals for intravitreal injection are ganciclovir and foscarnet.[9] Intravitreal ganciclovir and foscarnet are widely used as they are non-toxic to the retina.[20] As such, they are a prudent alternative for patients who have developed resistance or experience side effects to oral antiviral therapies.[8]

Topical treatments for ARN are dependent on the symptoms secondary to intraocular inflammation. Topical steroids are recommended to treat anterior-segment inflammation in combination with a topical cycloplegic for pain control.[1] Topical ocular hypotensive agents are also indicated should the patient have increased IOP.[21] Generally, treatment of the underlying condition will resolve elevated IOP. Topical antivirals are not proven to be clinically effective in ARN and are not reported in the literature as a method of treatment or adjunct therapy.

Retinal detachment following ARN has been reported in up to 75% of cases;[1] therefore, prophylactic laser photocoagulation or retinopexy has been common practice. Historically, the benefits of prophylactic laser have been uncertain, but multiple reports in the literature indicate laser can reduce the likelihood of retinal detachment if applied within the first two weeks of disease onset.[1,3,9] Prophylactic laser cannot stop the spread of retinitis. Instead, it is used to create a “new” ora serrata posterior to retinal holes that develop in thinning atrophic retina[1,8] and prevent progression to retinal detachment. Laser can also be used to treat neovascularization that may develop from ARN.[1]

When retinal detachment does develop with ARN, PPV is recommended with or without scleral buckle (SB) with either gas or silicone oil fill. Recent studies show PPV alone (without SB) has yielded similar or better visual outcomes than PPV with SB.[3,9] In general, cases of retinal detachment secondary to ARN have improved visual outcomes with early PPV intervention.[3]

Case Review

This case illustrates key concepts and goals in the care of a patient with acute disease with rapid progression. The clinician must be careful to complete a detailed and comprehensive examination. Early ARN can present as anterior uveitis that, if misdiagnosed and mismanaged, can lead to poor visual outcomes. Moreover, ARN can mimic other viral necroses, which requires the clinician to be cognizant of the relevant differential diagnoses. In the case reported here, had the small patch of peripheral necrosis been missed in the early stages of the disease, initiation of treatment would have been delayed.

Of note, oral antiviral treatment for this patient was delayed by a day because no initial clinical manifestations had suggested viral etiology and because the lab results were not yet known. Lab results play an important role in determining whether the empirical treatment initiated is adequate for the type of viral infection. However, it is not always necessary to wait for lab results before initiating treatment in cases of ARN if the diagnosis can be confirmed clinically. In addition, the etiology of the retinal necrosis can be an indicator of the severity and visual prognosis of the disease.

The most critical role for optometrists is to recognize the signs and symptoms of ARN for an accurate and prompt diagnosis. It is also in the patient's interest for the optometrist to order the indicated lab tests and make appropriate referrals to expedite diagnosis and treatment. Furthermore, the optometrist can be vital in treating signs, symptoms and pain with topical medications as was done in this case at the initial emergency room visit. Optometrists can also play an important role in educating patients about the progression and prognosis of the disease. Informing patients about ARN and available treatment options not only improves their understanding but also may allow them to feel some control over a potentially devastating disease. Because prognosis can vary, it is prudent to not promise specific visual outcomes during the course of the disease. A seemingly mild case of ARN in the acute herpetic phase can quickly deteriorate with the onset of the late cicatricial phase.

Assessment of Learning Objectives

Educators can evaluate students on the learning objectives and key points of this case report in several ways. First, the case can be presented through a PowerPoint or similar presentation accompanied by fundus and fluorescein angiography images and students can be asked to describe normal and abnormal findings. They should be able to accurately describe retinal necrosis and identify the association with an underlying condition. Through further dialogue, emphasis can be placed on correlating hypertensive uveitis with infectious etiologies and becoming familiar with the differential diagnoses and indicated lab tests for associated viral, bacterial and parasitical causes. The role of an optometrist in managing ARN, including familiarity with ocular topical treatment options and their efficacy, should also be discussed. This discussion could be extended if the educator wishes to expand the students' exposure to retinal treatments or oral and IV treatments for viral infections. Knowledge assessment can be through group case discussions or written or oral quizzes. Another suggestion is to role-play a doctor-patient interaction to teach students how to manage patient education and expectations regarding severity of the disease and how to discuss the necessary testing and convey the urgency of referral to a specialist.

Conclusion

ARN is a rapidly progressive retinal necrosis that can have poor visual outcomes if not diagnosed and treated early. Because progression typically does not stop until one week after starting treatment, it is important that optometrists are able to diagnosis the disease and initiate treatment as soon as possible in conjunction with a prompt referral to a retina specialist. The optometrist also plays an important role in patient education, including explaining the progression and prognosis of ARN and the necessity of treatments. Similarly, as the primary care provider, it is the responsibility of the clinician to encourage the patient to follow-up with specialists and, if possible, to order appropriate laboratory tests to determine etiology.

Topical treatments that can be initiated include steroids, cycloplegics and hypotensive agents to treat anterior uveitis and elevated IOP. In most states, optometrists are also able to initiate treatment with oral antiviral medications, but referrals to ophthalmology and infectious disease are highly recommended given that IV antiviral therapy is the standard of care. As primary care providers, it is vital that optometrists have the ability to precisely identify ARN. With timely diagnosis and treatment of ARN come a better visual prognosis for the affected eye and a higher likelihood of preventing involvement of the contralateral eye.

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Dr. Chang [carol.an.chang@gmail.com] graduated from the University of California – Berkeley School of Optometry in 2016. She completed her residency in Primary Care and Ocular Disease at Bronx-Lebanon Hospital Center and earned her Fellow of the American Academy of Optometry distinction in 2017. Currently, she works for New York City Health and Hospitals at Metropolitan Hospital.