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Acute Retinal Necrosis: Diagnosis, Management, Complications and Outcomes of an 8 Year Retrospective Case Series

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Abstract

Title: Acute Retinal Necrosis: Diagnosis, Management, Complications and Outcomes of an 8 Year Retrospective Case Series.

Background: The purpose of the study was to describe demographics, characteristics and management of eyes with acute retinal necrosis (ARN).

Methods: Retrospective chart review of patients with ARN that presented to University Hospital (UH), New Jersey Medical School between January 2005 and December 2012.

Findings: Fourteen patients presented with a clinical diagnosis of acute retinal necrosis. Seven of 14 patients (50%) had bilateral involvement on presentation. Vision on presentation in the affected eye ranged from 20/40 to no light perception; the majority of patients had 20/400 vision or worse. All patients were admitted for intravenous antiviral treatment. All eyes received intravitreal ganciclovir injection (2.0 mg/0.1 cc) +/- foscarnet injection (2.4 mg/0.1 cc). Some eyes underwent multiple intravitreal treatments or ganciclovir implant placement. Thirteen eyes (62%) required rhegmatogenous retinal detachment repair.

Conclusion: We reviewed 21 eyes of 14 patients with acute retinal necrosis. Only 29% of eyes had final BCVA better than 20/200, in concert with previous reports on the high degree of ocular morbidity associated with acute retinal necrosis. Review of the literature regarding immune status and acute retinal necrosis lends insight into the evolving concepts on this clinical entity.

Keywords: Acute retinal necrosis; Infectious uveitis; Immunocompromise; Herpes uveitis; Cytomegalovirus

Abbreviations: AIDS: Acquired Immunodeficiency Syndrome; ARN: Acute Retinal Necrosis; BCVA: Best Corrected Visual Acuity; CAD: Coronary Artery Disease; CF: Counting Fingers; CMV: Cytomegalovirus; DM: Diabetes Mellitus; EBV: Epstein-Barr Virus; HLA: Human Leukocyte Antigen; HIV: Human Immunodeficiency Virus; HM: Hand Motions; HSV: Herpes Simplex Virus; HTN: Hypertension; IV: Intravenous; LP: Light Perception; NLP: No Light Perception; PO: Per os (by mouth); PORN: Progressive Outer Retinal Necrosis; PPD: Purified Protein Derivative; PPV: Pars Plana Vitrectomy; RRD: Rhegmatogenous Retinal Detachment; SB: Scleral Buckle; SO: Silicone Oil; VZV: Varicella Zoster Virus

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Introduction

Acute retinal necrosis (ARN) is a rare but potentially blinding ocular inflammatory condition consisting of areas of peripheral retinal necrosis in the presence of an occlusive obliterative angiopathy with prominent anterior and posterior segment inflammation. ARN is typically a clinical diagnosis based on criteria delineated by the American Uveitis Society [1]. There is characteristic rapid progression of retinal necrosis and secondary rhegmatogenous retinal detachment in half to three-quarters of eyes [2]. Fellow

eye involvement occurs in approximately one-third of patients, typically within six weeks of onset [3] though cases of fellow eye involvement have been noted up to 46 years after presentation [4]. While rare, with an annual incidence estimated to be one case per two million people [5], ARN frequently leads to significant ocular morbidity and poor visual outcomes. Though there has been extensive research on ARN since its initial description, this low incidence limits our understanding of the risk factors predisposing to disease onset.

Methods

A retrospective chart review of patients with the International Classification of Diseases (ICD) 9 codes of endophthalmitis and panuveitis that presented to University Hospital, New Jersey Medical School between January 2005 and October 2012 was conducted. The Rutgers Institutional Review Board approved the study, and proper ethical standards were maintained throughout the investigation. Patients were included if they had clinically diagnosed ARN. Demographic data collected included age, sex, predisposing risk factors, clinical exam information, microbiologic data, interventions, and final visual acuity.

Diagnosis was based on the fundus examination demonstrating confluent or multifocal areas of peripheral retinitis in the presence of anterior and posterior segment inflammation. Other signs and symptoms noted in support of the diagnosis of ARN included the presence of conjunctival injection, keratic precipitates, retinal hemorrhages with occlusive vasculopathy, necrotic retinal holes, papillitis and optic nerve edema.

Results

Fourteen patients presented with a clinical diagnosis of acute retinal necrosis during the study time period. Seven of 14 patients (50%) had bilateral involvement on presentation for a total of 21 study eyes. Mean age was 51 years (range 26-80), 12 were males. Average time from onset of symptoms to presentation was 15 days with large variability (range 1-42 days). Patient demographic data can be found in **Table 1**. The most common presenting symptom was progressive loss of vision. Vision on presentation in the affected eye ranged from 20/40 to no light perception (NLP); 14 of 21 eyes (67%) presented with vision of 20/400 or worse. All affected eyes presented with anterior uveitis, vitritis and peripheral confluent retinitis. Of the patients with bilateral involvement (7/14), all had second eye involvement on presentation. On average, there was a three-week interval between primary and fellow eye involvement (four patients reported simultaneous onset of diminished vision in both eyes). No patient with unilateral involvement of ARN on presentation developed fellow eye involvement once anti-viral treatment was initiated.

All patients were admitted for intravenous acyclovir treatment (15 mg/kg/day every 8 h), with an average inpatient stay of 11 days. All eyes also received intraocular antiviral therapy consisting of intravitreal ganciclovir injection (2.0 mg/0.1 cc) +/- foscarnet injection (2.4 mg/0.1 cc). Intravitreal treatment was administered upon diagnosis and repeated as needed at the bedside or intraoperatively. Eyes in our study received an average of 1.75 intravitreal antiviral injections (range 1-3). Certain eyes additionally received intravitreal antibiotics (e.g. vancomycin 1.0 mg/0.1 cc, ceftazidime 2.25 mg/0.1 cc) if there was concern for bacterial co-infection **(Table 2)**. Four eyes underwent ganciclovir implant placement, seven to 18 days after presentation, due to concerns about patient follow up and compliance with outpatient systemic anti-viral treatment. Following 10-12 days of intravenous antiviral treatment, patients were prescribed oral antiviral treatment with acyclovir or valacyclovir for six weeks to five months.

All but 3 patients (79%) underwent biopsy; only one eye had a biopsy if both eyes were affected. Six patients underwent aqueous sampling; four patients had vitreous biopsy. One patient underwent both aqueous and vitreous biopsy. Samples were sent for the following polymerase chain reaction (PCR) studies: herpes simplex virus 1 and 2 (HSV 1 and 2), varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and toxoplasma. Eight of twelve (67%) samples returned positive microbiological cultures. Seven of twelve samples returned positive for herpes simplex virus (HSV); four for HSV type 1 and three for HSV type 2. One of twelve samples returned positive for VZV. Given that this a retrospective review, we cannot be certain why studies were not obtained in 3 patients; however, we may surmise that perhaps the clinical picture and response to empiric treatment were sufficient to establish a likely diagnosis.

Thirteen of 21 eyes (62%) were diagnosed with rhegmatogenous retinal detachment (RRD). All such eyes underwent pars plana vitrectomy and RRD repair, typically with silicone oil and barrier retinal photocoagulation **(Table 2)**. Mean time from presentation to surgery was 23 days (range 2-90 days). Two patients had an RRD on presentation; the majority of patients, however, developed retinal detachments later in their course. Of the seven patients with bilateral ARN, three developed bilateral retinal detachments. Two patients with bilateral ARN and bilateral retinal detachments received intravitreal ganciclovir implant in both eyes during their RRD repair surgeries. Only one eye required repeat retinal detachment repair (two years after presentation). No eye underwent silicone oil removal. See **Table 2** for a summary of intraocular and systemic treatment. Final best-corrected visual acuity (BCVA) ranged from 20/25 to NLP; only 6 of 21 eyes (29%) had a final vision of better than 20/200.

Discussion

The investigators reviewed all cases of acute retinal necrosis presenting to our institution over an eight-year period. Despite aggressive systemic and ocular treatment, there were devastating ocular complications associated with ARN in our case series. Consistent with previous literature, thirteen of 21 eyes (62%) required rhegmatogenous retinal detachment repair. Only 6 of 21 eyes (29%) had a final vision of better than 20/200; less than half of the eyes (10/21, 48%) achieved a final vision better than their vision on presentation. In our study, HSV was the most common virus noted on PCR testing in ARN eyes, though data from larger series support VZV as the most common agent responsible for ARN [6,7].

Table 1 Patient demographics.

Case	Age	Past Medical History	Time to diagnosis (days)	Ocular Microbiology	Presenting VA	Final VA
1	59	h/o TB (1970)	21	HSV II (vitreous)	20/400	20/200
2	52	Multiple myeloma s/p radiation treatment	5	HSV II (vitreous)	HM	NLP
3	50	-	14	VZV (aqueous)	20/400	HM
4*	62	DM Kidney transplant	21	Negative (vitreous)	20/60 (OD) 20/80 (OS)	20/80 OD) 20/200 (OS)
5*	80	HTN, glaucoma Recent cataract extraction	28 (OD) 3 (OS)	HSV I (aqueous)	LP (OD) NLP (OS)	LP (OD) NLP (OS)
6	29	Recent pregnancy (delivered six weeks before start of symptoms)	1	HSV II (aqueous)	20/400	CF
7	49	HTN, CAD	7	HSV I (aqueous)	HM	CF
8	72	DM, HTN Renal cancer	14	NONE DRAWN	HM	HM
9*	54	DM, HIV (CD4 12) Acute Renal Failure	42 (OD) 14 (OS)	Negative (aqueous)	CF (OD) 20/40 (OS)	20/400 (OD) 20/25 (OS)
10*	48	HIV (CD4 35)	14 (OU)	HSV 1 (aqueous)	NLP (OD) NLP (OS)	NLP (OD) NLP (OS)
11*	48	Positive PPD	30 (OD) 8 (OS)	Negative (aqueous) Negative (vitreous)	20/80 (OD) HM (OS)	20/60 (OD) 20/400 (OS)
12*	42	HIV (CD4 28)	3	NONE DRAWN	20/200 (OD) 20/400 (OS)	20/80 (OD) 20/200 (OS)
13*	37	HIV (CD4 12)	1	NONE DRAWN	20/200 (OD) 20/200 (OS)	20/100 (OD) CF (OS)
14	26	Positive PPD	21	HSV 1 (vitreous)	CF	20/80

*bilateral cases; CAD=Coronary Artery Disease, CF=Counting Fingers, DM=Diabetes Mellitus, HIV=Human Immunodeficiency Virus, HM=Hand Motion, HSV=Herpes Simplex Virus, HTN=Hypertension, LP=Light Perception, NLP=No Light Perception, PPD=Purified Protein Derivative, TB=Tuberculosis, VZV=Varicella Zoster Virus

Acute retinal necrosis and immune status

Many of the larger ARN cases series report some percentage of patients manifesting clinical or subclinical immune compromise, commonly HIV, malignancy or iatrogenic immune suppression. Study rates vary considerably, with reports of up to 55% of patients having immune dysfunction [8]. Combining the larger case series in the literature, 50 of 230 patients (22%) showed some degree of immune compromise **(Table 3)**.

Our cases series showed patients with variable immune status **(Table 1)**. Four of 14 patients had HIV with a CD4 count <50 cells/mm^3. Other immunocompromising conditions included history of malignancy in two patients, immunosuppression for renal transplant, and recent pregnancy. Other patients had mildly compromising conditions such as diabetes and hypertension; only one patient had no medical history. Of note, all four HIV positive patients in our study presented with bilateral involvement. Progressive outer retinal necrosis (PORN) was not suspected in these patients given the fundus appearance – specifically the level of vitritis, anterior location of retinitis and occlusive retinal arteritis noted on presentation.

While traditional teaching is ARN is an affliction of the immunocompetent and PORN is instead seen solely in patients with compromised immune function, the delineation between these two clinical entities may not be so simple. There is mounting evidence that these conditions lay on a spectrum of viral retinitis. A retrospective review consisting of 18 patients with ARN or PORN showed that disease severity related to the degree of immune dysfunction. Specifically, the study noted cutaneous anergy and decreased in-vitro lymphocyte proliferative response in clinically healthy patients diagnosed with ARN [9]. A study by Rochat, et al showed certain patients with ARN had a relative and absolute increase in B-lymphocytes, leading the authors to hypothesize that an imbalance in the cellular and humoral arms of the immune system may be the prevailing mechanism mediating the onset of ARN [10].

In a similar study by Kezuka et al. conducted in the setting of acute, VZV-induced ARN, patients were found to have an absence of virus-specific delayed hypersensitivity (DH) during the acute ocular inflammatory stage. There was not global anergy as noted previously, however, as many of these patients manifested positive PPD skin tests (likely secondary to Bacillus Calmette–Guérin (BCG) vaccination). Patients with more severe ARN were found to have the lowest DH responses to VZV antigens. These DH responses were restored at 3 months in patients who recovered from ARN. This evidence points to a temporary impairment in VZV-antigen specific cellular immunity associated with onset of ARN [11].

Data collected from a case series of nine patients further supports the hypothesis of diminished cellular immunity in ARN. The study patients demonstrated reduced plasmacytoid dendritic cells (PDC) in ARN patients, which function in the production of type I interferon as part of the innate immune defenses against microbial pathogens [12]. These patients also showed impaired

Table 2 Ocular microbiology and treatment summary.

Case	Age	Symptom-to-diagnosis (days)	Ocular Microbiology	TREATMENT				RETINAL DETACHMENT SUMMARY					Presenting VA	Final VA
				Ocular	Systemic			Presentation-to-RDR (days)	Surgery	SO or Gas	Endo-laser	Intravitreal antimicrobials at time of surgery		
				Intravitreal	Medication	Route	Duration							
1	59	21	HSV II (vitreous)	Ganciclovir† Foscarnet‡	Acyclovir	IV	10 days	90	PPV	SO	(+)	Ganciclovir† Foscarnet‡	20/400	20/200
					Acyclovir	PO	3 months							
2	52	5	HSV II (vitreous)	Ganciclovir† Foscarnet‡ Vancomycin§ Ceftazidime‖	Acyclovir	IV	9 days	7	PPV	SO	(+)	Ganciclovir† Foscarnet‡	HM	NLP
					Acyclovir	PO	3 months							
3	50	14	VZV (aqueous)	Ganciclovir†	Acyclovir	IV	7 days	60	PPV/PPL SB	C3F8	(+)	(-)	20/400	HM
					Valacyclovir	PO	6 weeks							
4*	62	21	Negative (vitreous)	Ganciclovir† Foscarnet‡	Acyclovir	IV	10 days	-	NO RD	-	-	-	20/60 (OD) 20/80 (OS)	20/80 (OD) 20/200 (OS)
					Valacyclovir	PO	4 months							
5*	80	28 OD 3 OS	HSV I (aqueous)	Ganciclovir† Foscarnet‡	Acyclovir	IV	7 days	-	NO RD	-	-	-	LP (OD), NLP (OS)	LP (OD) NLP (OS)
					Valacyclovir	PO	6 weeks							
6	29	1	HSV II (aqueous)	Ganciclovir† Foscarnet‡ Vancomycin§ Ceftazidime‖	Acyclovir	IV	7 days	2	PPV	SO	(+)	Ganciclovir† Foscarnet‡	20/400	CF
					Valacyclovir	PO	5 months							
7	49	7	HSV I (aqueous)	Ganciclovir† Foscarnet‡	Acyclovir	IV	2 weeks	48	PPV	SO	(-)	Ganciclovir† Foscarnet‡	HM	CF
					Valacyclovir	PO	5 months							
8	72	14	NONE DRAWN	Ganciclovir† Foscarnet‡	Acyclovir	IV	6 days	7	PPV	SO	(+)	Ganciclovir† Foscarnet‡	HM	HM
					Valacyclovir	PO	4 months							
9*	54	42 OD 14 OS	Negative (aqueous)	Ganciclovir† Foscarnet‡ Vancomycin§ Ceftazidime‖	Acyclovir	IV	21 days	-	NO RD	-	-	-	CF (OD) 20/40 (OS)	20/400 (OD) 20/25 (OS)
					Acyclovir	PO	6 weeks							
10*	48	14 OU	HSV 1 (aqueous)	Ganciclovir† Foscarnet‡	Acyclovir	IV	8 days	7	PPV OD	SO	(+)	Ganciclovir† Foscarnet‡	NLP (OD), NLP (OS)	NLP OU
					Valacyclovir	PO	3 months	28	PPV OS	SO	(+)	Ganciclovir† Foscarnet‡		
11*	48	30 OD 8 OS	Negative (aqueous), Negative (vitreous)	Ganciclovir† Foscarnet‡	Acyclovir	IV	21 days	4	PPV OS	SO	(+)	Ganciclovir† Foscarnet‡	20/80 (OD) HM (OS)	20/60 (OD) 20/400 (OS)
					Acyclovir	PO	3 months							
12*	42	3	NONE DRAWN	Ganciclovir implant OU	Acyclovir	IV	12 days	11	PPV OS	SO	(+)	Ganciclovir Implant	20/200 (OD) 20/400 (OS)	20/80 (OD) 20/200 (OS)
					Acyclovir	PO	5 months	18	PPV OD	SO	(+)	Ganciclovir Implant		
13*	37	1	NONE DRAWN	Ganciclovir implant OU	Acyclovir	IV	14 days	6	PPV OS	SO	(+)	Ganciclovir Implant	20/200 (OD) 20/200 (OS)	20/100 (OD) CF (OS)
					Acyclovir	PO	3 months	14	PPV OD	SO	(+)	Ganciclovir Implant		
14	26	21	HSV 1 (vitreous)	Foscarnet‡	Acyclovir	IV	10 days	-	NO RD	-	-	-	CF	20/80
					Acyclovir	PO	2 months							

*bilateral presentation

†Ganciclovir dosage 2.0 mg/0.1 cc, ‡Foscarnet dosage 2.4 mg/0.1 cc , §Vancomycin dosage 1 mg/0.1 cc, ‖Ceftazidime dosage 2.25 mg/0.1 cc,

C=Counting Fingers; HM=Hand Motions; HSV=Herpes Simplex Virus; IV=Intravenous; LP=Light Perception; NLP=No Light Perception; PO=per os (by mouth); PPV=Pars Plana Vitrectomy; RD=Retinal Detachment; SB=Scleral Buckle; SO=Silicon Oil; VZV=Varicella Zoster Virus

Table 3 Review of patient immune status in ARN studies

Study	Number of study patients	Immune-compromised patients No. (%)	Listed causes of immune deficiency
Muthiah et al. [5]	31	7 (23)	AIDS Malignancy Iatrogenic
Sims et al. [8]	22	12 (55)	Malignancy Iatrogenic
Cochrane et al. [24]	45	13 (29)	HIV Malignancy Iatrogenic
Wong et al. [25]	74	7 (9)	HIV (CD4>400 cells/mm^3)
Tibbetts et al. [26]	58	11 (19)	Systemic disease Iatrogenic
TOTAL	230	50 (22)	

AIDS=Acquired Immunodeficiency Syndrome; HIV=Human Immunodeficiency Virus

CD8+ T-cell activity, important in the control and maintenance of herpes virus latency [13,14].

Research into human leukocyte antigen (HLA) typing in patients with ARN suggests the possibility of genetic susceptibility to disease contraction. Major histocompatibility complex class II HLAs such as HLA-DQw7 (phenotype Bw62) and DR4 positivity have been associated with acute retinal necrosis in a subset of Caucasian patients [15]. Furthermore, the severity of ARN presentation has been linked to HLA-DR9 positivity [16].

Case reports exist in the literature of patients presenting with ARN following brief periods of iatrogenic immune compromise. Systemic [17], intracameral [18] and intravitreal [19] steroid administration have all been noted as factors preceding the development of ARN. Systemic steroids have also been linked to recurrence of ARN in quiescent eyes [20]. These reports support a connection between the immunosuppressive effects of corticosteroids and ocular herpes virus infection. Other immunomodulatory stressors such as pregnancy [21], recent surgery [22] and vaccination [23] have coincided with ARN development and recurrence.

The wealth of research on this topic suggests there very likely exist certain immune characteristics that place patients at an increased risk for the development of ARN. The inciting event may be secondary to identifiable exogenous sources or more subtle modulations in the systemic immune status. Hopefully, further research will explore the chain of events that predispose to disease development.

Conclusion

Acute retinal necrosis can be a devastating ocular infection caused by several viral entities. In this series of 21 eyes of 14 patients with ARN, only 29% of eyes had final BCVA better than 20/200, in concert with previous reports on the high degree of ocular morbidity associated with this disease. Review of the literature regarding immune status and ARN lends insight into the evolving concepts of the clinical entity.

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