

Immune Recovery Uveitis: A Comprehensive Review

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Abstract: Immune reconstitution inflammatory syndrome (IRIS) describes a hyper-inflammatory state, often manifesting as paradoxical worsening of opportunistic or latent infections, in patients with previously suppressed immune systems who undergo treatment. Ocular IRIS is known as immune recovery uveitis (IRU), a challenging complication that can occur in patients with a compromised immune system, particularly those with human immunodeficiency virus (HIV) infection who initiate highly active antiretroviral therapy (HAART). IRU primarily manifests as posterior segment inflammation with vitritis, resulting in reduced vision and floaters in the affected eye. This review article aims to provide a comprehensive overview of immune recovery uveitis, encompassing its pathophysiology, clinical manifestations, diagnostic approaches, management strategies, and future prospects. Understanding IRU is crucial for ophthalmologists, infectious disease specialists, and other health care professionals involved in the care of individuals with HIV/AIDS, as timely intervention can help prevent vision-threatening complications and improve patients' quality of life.

Key Words: immune recovery uveitis, CMV retinitis, immune reconstitution inflammatory syndrome, HIV/AIDS

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INTRODUCTION

Background

The human immunodeficiency virus (HIV) targets the immune system by reducing the population of CD4+ T lymphocytes, causing patients to be more susceptible to opportunistic infections. Acquired immunodeficiency syndrome (AIDS) is the severe manifestation of HIV, defined as a CD4+ T cell count of <200 or a specific AIDS-defining illness (one of several opportunistic infections, malignancies, or other conditions that occur in the setting of profound immunosuppression).¹ Cytomegalovirus (CMV) retinitis is commonly observed in individuals with advanced or late-stage HIV/AIDS and low CD4+ T cell counts, typically <50 cells/ μ L. CMV retinitis became increasingly prevalent in the 1980s and 1990s as the prevalence of HIV increased.^{2,3} While 50% to 90% of

adults are seropositive for CMV, the virus typically remains latent but can become active during immunosuppression, most frequently due to HIV/AIDS but also in the setting of organ/bone marrow transplantation, chemotherapy, or malignancy.³ This is typically experienced as viremia but can cause end-organ manifestations in the GI tract, lung, liver, peripheral, and central nervous systems. Retinitis is one of these end-organ manifestations, thought to be due to hematogenous spread of the virus to the retina.³ Because it occurs in the setting of suppressed immunity, CMV retinitis is associated with very minimal or no anterior chamber and vitreous inflammation.

The introduction of protease inhibitors in 1995 marked a significant breakthrough in HIV treatment. These drugs, which were later approved by the US FDA in 1996, became the cornerstone for highly active antiretroviral therapy (HAART). HAART involves the use of a combination of 3 or more antiretroviral drugs of different classes, typically protease inhibitors and non-nucleoside reverse transcriptase inhibitors. This treatment regimen leads to a substantial reduction in HIV replication and allows the recovery of CD4+ T cells.

The implementation of HAART brought about significant improvements in health outcomes in patients with HIV. HAART enables the recovery of CD4+ T lymphocytes and, as such, leads to the recovery of the normal immune response against pathogens. The recovery of CD4+ T cell counts is typically most rapid in the first 3 months, followed by more gradual increases over the following months to years.⁴ As HAART became more widely used, there was a concurrent decline in mortality rates and a decrease in opportunistic infections in patients with HIV. In particular, the incidence of CMV retinitis was substantially reduced, with a 55% to 95% reduction in incidence,⁵ and the prognosis of those affected was improved.⁶ This progress in HIV therapy has played a crucial role in managing the disease and improving the quality of life for individuals living with HIV.

Systemically, HAART therapy may precipitate immune reconstitution inflammatory syndrome (IRIS), a hyper-inflammatory, dysregulated immune reaction often against opportunistic infections or other antigens. This syndrome typically arises within the initial 6 months of HAART treatment for HIV/AIDS, but can also occur in other scenarios when a previously suppressed immune system regains function. IRIS can manifest in various ways, including the exacerbation of infectious and non-infectious diseases.^{7,8} It is thought that IRIS occurs after the reversal of immunosuppression by HAART due to the

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recovery of immune responses against specific antigens.⁷ This then can cause paradoxical worsening of treated opportunistic infections or the unmasking of previously subclinical, untreated infections in patients with previously suppressed immune systems.

Ocular IRIS is referred to as immune recovery uveitis (IRU) and can cause significant morbidity.^{9,10} IRU was first described in the late 1990s by 2 groups—Karavellas et al¹¹ and Zegans et al¹²—when patients with AIDS and CMV retinitis were noted to develop transient intraocular inflammation associated with the initiation of HAART.^{11,12}

Karavellas and colleagues observed 130 patients with AIDS and CMV retinitis over 15 months and found that 5 developed symptomatic vitritis and optic nerve edema with cystoid macular edema (CME) or epiretinal membrane (ERM) formation. All affected patients were found to have inactive CMV retinitis, which was asymptomatic before the onset of inflammation and had had a recovery in CD4+ T cell counts with HAART. The patients were treated with systemic corticosteroids with improvement in the intraocular inflammation and without reactivation of the retinitis. When 509 patients from the 11 years before the use of protease inhibitors were evaluated retrospectively, there were no comparable cases of intraocular inflammation. As such, Karavellas et al¹¹ concluded that this syndrome of posterior segment inflammation (now known as IRU) was related to increased immunocompetence due to combined antiretroviral treatment in patients with a history of CMV retinitis.

Around the same time, Zegans and colleagues reported 8 patients with AIDS and CMV retinitis who developed vitreous inflammation after CD4+ T-lymphocyte recovery from combination antiretroviral therapy. In this cohort, 6 of these patients had unilateral CMV retinitis before HAART, and the inflammatory reaction after starting combination antiretroviral therapy was isolated to the eye with CMV retinitis. Treatment included periocular and topical steroids, as well as systemic antivirals. The authors felt that the intraocular inflammation was reflective of an improved immune response against CMV.¹²

Over the subsequent years, more reports have been published regarding the clinical features, epidemiology, pathogenesis, diagnosis, and complications of IRU. We seek to summarize these in this review.

Objective

IRU has the potential for vision-threatening complications and is caused by unique pathophysiologic mechanisms. Despite remarkable advances in HIV management, IRU remains a pertinent concern for these patients. The aim of this review is to provide a summary of the biology, pathogenesis, prevalence, clinical manifestations, diagnostic criteria, prognosis, and management options for IRU. Our hope is to provide context and guidance for ophthalmologists when they encounter this rare entity.

BIOLOGY AND PATHOGENESIS

The pathogenesis of IRU is multifactorial. It primarily occurs due to the restoration of CD4+ T cells in previously immunocompromised individuals, usually those with HIV/AIDS commencing HAART.^{9,13} HAART causes polyclonal expansion of T-lymphocytes and improvement in CD4+ T cell function.¹⁴ As the CD4+ T cell counts rise, there is a robust response to various opportunistic infections or antigens that the patient was previously unable to mount a sufficient immune response against. This excessive immune response can lead to ocular inflammation and the development of IRU.¹⁵ While IRU is almost always found in the setting of increased CD4+ T cells, there are rare reports in which this is not the case.^{16,17} In addition, aside from HIV/AIDS, IRU has also been reported in the setting of immunosuppression in other conditions, including rheumatoid arthritis, systemic lupus erythematosus, leukemia, and after stem cell transplant for lymphoma.^{16,18–20}

Several mechanisms contribute to the development of IRU. One such mechanism is antigenic persistence, which refers to the persistence of microbial antigens within the eye even after the primary infection has been treated. The persistence of CMV antigens within the eye then triggers an immune response when the immune system becomes reconstituted.¹⁰ CMV antigens, in particular, are thought to play a role in the pathogenesis of IRU. First, IRU does not occur in eyes that do not have a pre-existing history of CMV retinitis. It has also been proposed that in the development of IRU, CMV retinitis causes a breakdown in the blood-ocular barrier; thus, after immune recovery, CMV antigens that enter the systemic circulation trigger a robust immune response to attack the antigens in the eye, which is normally an immune-privileged site.²¹ Immunohistochemical studies of epiretinal membranes in IRU reveals evidence of a chronic inflammatory process and a T lymphocyte population, suggesting a possible T cell mediated immune reaction to latent CMV antigens in the setting of inactive CMV retinitis.²² IRU as a CMV antigen-mediated disease is further supported by evidence that increased CMV retinitis lesion size is associated with greater risk for developing IRU.²¹ In addition, delaying HAART initiation until completion of CMV retinitis treatment decreases the rate of IRU.²³ This may minimize exposure to CMV antigens during the critical phase of immune recovery in the eye.²⁴ Finally, more aggressive anti-CMV therapy with the ganciclovir implant may reduce the risk of IRU.⁹ Of note, studies have generally found no evidence of CMV DNA in the peripheral blood nor in the eye in patients with IRU, indicating no active replication of the infectious virus; this does not contradict the possibility of antigenic persistence, which can occur in the absence of viral replication.^{21,25}

However, not all patients who have CMV retinitis and immune recovery will ultimately develop IRU. This indicates there may be genetic, environmental, and other factors involved. In fact, even in patients with 2 affected

eyes with CMV retinitis, the development of IRU may be unilateral or asymmetric.²¹ Non-CD4+ related immune dysfunction may contribute to IRU development. Hartigan et al²⁶ found that patients with prior CMV retinitis who developed IRU had significantly lower levels of Th17 cells compared with those who did not develop IRU. This study also showed that patients with IRU had poor systemic CMV-specific T cell responses, which play a role in controlling the primary infection, while CD8+ T cell responses were similar. These findings suggest that the depletion of Th17 cells and poor systemic CMV-specific T-cell responses are associated with the development of IRU in patients with CMV retinitis. Thus, IRU may be most likely to develop in patients with greater immune dysfunction before HAART initiation.²⁶

Furthermore, there is evidence to suggest that IRU may have an autoimmune component. Cross-reactivity between CMV antigens and host antigens could potentially trigger an autoimmune response within the eye, leading to inflammation. In support of this, Schrier and colleagues found that IRU eyes contain elevated IL-12, but reduced IL-6, and interferon gamma—seen in antigen-specific T-cell responses. Self-antigens do not cause an interferon gamma response, so the antigen stimulus in IRU may be a self-antigen. Alternatively, it is possible that there are CMV proteins eliciting less interferon gamma than intact virions.²⁵

Genetic predisposition may also play a role in susceptibility to IRU. One small study of 4 patients with IRU in Italy were positive for the human leukocyte antigen (HLA) allele HLA B18-8. While this study was limited, the fact that a specific HLA allele has been associated with an increased risk of IRU highlights a potential interplay between genetics and IRU.²⁷

Of note, not all cases are associated with a significant increase in CD4 counts. Although most studies have required evidence of immune recovery as indicated by an increased CD4+ T cell count to diagnose IRU, there have been reported cases of IRU that occurred in the absence of CD4+ T cell increases.^{15–17} This indicates that a large rise in CD4+ T cell counts may not be necessary, and this measure alone likely does not specifically capture the recovery of anti-CMV immunity. Specific assays for immune activity against CMV may be a more precise predictor of the risk of IRU, but these assays are not widely available.^{27,28}

To summarize, the pathophysiology of IRU is characterized by the restoration of immune function, typically in the setting of increased CD4+ T cell counts, resulting in an excessive immune response in an eye with previously treated CMV retinitis. It is largely thought to be a CMV antigen-related inflammatory disorder, but dysregulation of cytokines and potential autoimmune responses also contribute to its development. Moreover, genetic predisposition may further influence susceptibility to IRU. This complex interplay between prior CMV retinitis, CD4+ T cell counts, innate immune responses, and the immunocompetence achieved through antiretroviral therapy underlies the pathogenesis of IRU.

Risk Factors

In addition to the previously stated necessary precipitating factors of prior CMV retinitis and immune recovery, are other risk factors are associated with an increased risk of IRU. One risk factor is a low CD4+ T count (≤ 50 cells/ μ L) at the time of initiation of HAART.²¹ IRU complications are also more likely with a greater increase in CD4+ T cell count from the nadir to the time of IRU diagnosis, possibly due to a greater inflammatory response in these patients.²⁹

Larger areas of affected retina in CMV retinitis has also been associated with increased risk for IRU. Specifically, $>25\%$ retinal area involvement had an odds ratio of 2.72 of developing IRU in one study,²¹ and in another study, $>30\%$ retinal area involvement had a 4.5-times higher risk of developing IRU compared with an area smaller than 18% .²² The effects of lesion size may be explained by a larger extent of blood-retinal barrier breakdown but may also indicate a higher antigen load in larger lesions.²² Of note, Arevalo et al³⁰ found that eyes with IRU had an average CMV surface area of 31.7% and eyes without IRU had an average CMV surface area of 35% , showing no significance in CMV retinitis surface area in terms of developing IRU in that study. Yeo et al²⁹ similarly found no association between the area affected by CMV retinitis and IRU risk, though their cohort was primarily composed of patients with $<25\%$ retinal area affected by CMV retinitis.

The use of the antiviral medication cidofovir, both intravenous and intravitreal, for the treatment of CMV is a notable modifiable risk factor for IRU. Song et al³¹ found that the use of cidofovir increased the risk of subsequent development of IRU in patients who had recovered from CMV retinitis. Specifically, patients who were continued to be treated with any anti-CMV antiviral had a 3.8-fold increase in the odds of developing IRU with anti-CMV therapy compared with no treatment after immune recovery. Subgroup analyses revealed that this effect was due to cidofovir. The odds of eyes treated with cidofovir developing immune recovery uveitis were 3.3 greater than if treated with an alternative regimen, 4.1 greater if treated intravenously rather than intravitreally, and 5.2 greater than if not treated at all after immune recovery.³¹ This inflammatory effect of cidofovir was also noted by Kempen et al,²¹ who found that intravitreal cidofovir was associated with a 19-fold higher risk of IRU. Cidofovir itself can cause anterior uveitis possibly due to toxicity to the ciliary body.^{32,33} The increased risk of IRU in cidofovir-treated patients may be related to these toxic and inflammatory effects.

In terms of factors that are negatively associated with IRU development, posterior pole involvement of CMV retinitis was found to be protective against IRU.²¹ In addition, male sex was found to be negatively associated with IRU.²¹

EPIDEMIOLOGY

Prevalence

The prevalence of IRU after HAART initiation in patients with a history of CMV retinitis is estimated

around 20%.³⁴ However, the exact prevalence is challenging to determine due to variations in patient populations and definitions, with reported prevalence ranging from 1.5% to 63%. In US-based studies, the prevalence has been noted to be 9.6%,³⁵ 18.2%,⁶ and 63.3%,²¹ in different case series. In international studies, the prevalence has been noted to be 37.5% in a Venezuelan study,³⁰ 53.5% in a Mexican study,²³ 17.4% in an Indian study,³⁶ and 1.5% in a Japanese study.³⁷ One reason for the difference in prevalence may be differences in the timing of initiation of HAART relative to the treatment of CMV retinitis. Ortega et al²³ found a lower prevalence and severity of IRU when HIV-infected patients started HAART after completing CMV retinitis treatment than when treatments were concomitant.

Incidence

Similar to the prevalence, incidence also has varied between studies. The early cohorts of patients with IRU, observed in the years immediately after HAART was approved and became widespread, had incidences ranging from 0.109 per person-year to 0.82 per person-year.^{6,22} A few years after these initial reports, Jabs et al² then reported an incidence of IRU of 2.7 to 3.6/100 person-years. While the rates of IRU vary widely, these reports indicate that IRU is an important consideration in patients with a history of CMV retinitis who subsequently undergo immune recovery. Contributing to the variable incidences and prevalences reported in the literature is the heterogeneity in study definitions; for example, vitritis is a part of the definition in most studies, but CME and ERM are more persistent complications that are variably included in definitions.³⁸

Timing of Onset

The time from HAART initiation to the development of IRU ranges in the literature, from as short as weeks,^{11,39} to 4 to 5 months, and up to 128 months.²⁶ Median time of onset is typically around 20 to 43 weeks (5 to 9 mo).² To highlight some specific studies: Zegans et al¹² found IRU set in on average 8 months after the addition of a protease inhibitor, Karavellas et al³⁵ found a median time from HAART initiation to IRU of 43 weeks (9.9 mo), Sudharshan et al³⁶ found an average of 4 months to 2.5 years between the start of HAART and onset of IRU, and Henderson and Mitchell⁴⁰ found an average of 5.5 months (range: 1 to 14 mo) between protease inhibitor initiation and vitreous inflammation. These discrepancies may be due to some studies including only symptomatic patients with others including all patients with clinically evident intraocular inflammation regardless of symptoms. Yeo and colleagues found that age was negatively correlated with the duration of time to develop IRU after HAART initiation. Specifically, the median duration from initiation of HAART to onset of IRU was 763 days in those under 50 years old and 161 days in those over 50 years old.²⁹

CLINICAL FEATURES

IRU can affect a variety of ocular structures, though most commonly presents with vitreous inflammation. As such, patients with IRU most commonly report symptoms such as decreased vision and floaters. IRU can have a component of anterior uveitis with associated symptoms such as photophobia and eye pain. Occasionally, IRU can be asymptomatic. IRU may follow an acute and self-limiting course, or a chronic inflammatory course with long-term sequelae.¹⁰

Complications of IRU can include vitreomacular traction, retinal neovascularization, and epiretinal membrane formation, which can lead to vision loss if not managed appropriately. Retinal detachment is another potential complication, with rates varying depending on the presence of previously-diagnosed or newly-diagnosed retinitis. Proliferative vitreoretinopathy, although rare in CMV retinitis-associated retinal detachment, may be encountered in retinal detachments associated with IRU.

To further detail some of the manifestations of IRU:

1. Anterior manifestations

IRU can be associated with anterior segment inflammation. In one study, about half of the eyes had both anterior uveitis and vitritis.²⁹ Kempen et al²¹ found that 58% of IRU eyes had AC cells, while 70% had vitreous haze. This inflammation, which can sometimes be persistent, can cause posterior subcapsular cataracts, anterior subcapsular cataract, and inflammatory deposits on the lens.⁴¹ Rarely, the anterior chamber inflammation can be significant enough to cause a hypopyon, as reported in 2 case reports.^{42,43} Posterior synechiae, adhesions between the iris and lens, are common in almost all types of uveitis. However, posterior synechiae were found in 1 cohort not to differ significantly between patients with IRU when compared with those with a history of CMV retinitis but no IRU (6.0% vs. 5.7%).²¹

2. Posterior manifestations

• Vitreous

Vitritis is one of the most common findings in IRU. This finding can be either asymptomatic or symptomatic, and either transient or persistent.^{12,21,41} Henderson and Mitchell found that in 80 patients with inactive CMV retinitis who received HAART, most of these patients developed a mild transient vitritis, often not requiring treatment. Clinically evident IRU with decreased visual acuity requiring therapy developed in only 7 patients.⁴⁰ Vitritis is often associated with decreased vision. In the Henderson cohort, the eyes with significant IRU had a mean visual acuity loss of 2.8 Snellen lines.⁴⁰ Robinson et al⁴⁴ found that vitreous haze was significantly associated with lower visual acuity.

• Retina

Epiretinal membranes (ERMs) are nonvascularized, fibrocellular membranes that form on the inner surface of the retina. These can develop idiopathically or in the setting of intraocular inflammation, diabetic retinopathy, trauma, prior surgery, or retinal detachment. The pathophysiology of ERM

involves tissue damage and subsequent reparative processes, driving the proliferation of glial and retinal pigment epithelium cells on the surface of the inner limiting membrane. ERM is found frequently in IRU. Kempen et al²¹ found ERM in 48.9% of IRU eyes versus 13.3% of eyes of patients with a history of CMV retinitis but no IRU, indicating a 3.7 times increased risk. In the Karavellas cohort, 8 of 26 developed ERM. This incidence was much higher than in a cohort of patients with CMV retinitis before the age of HAART, in which only 3 of 803 eyes had ERM, and all in the setting of CMV retinitis in the macula.²² Immunohistological examination of ERMs removed from eyes with IRU shows evidence of chronic inflammation with a predominant T-lymphocyte population.²²

Cystoid macular edema (CME), characterized by intraretinal edema causing cystic retinal thickening in the macula, can occur in the setting of intraocular inflammation. IRU significantly increases the risk for CME, while CME is not commonly seen in CMV retinitis. One study showed a 12.3 times increased risk of CME in IRU—with CME found in 45.5% of IRU eyes versus 3.7% of eyes of patients with a history of CMV retinitis but no IRU.²¹ Karavellas et al²² found CME in 35% of 26 eyes with IRU. Guzak et al⁴⁵ reported a case of CME in IRU that was successfully treated with topical NSAIDs. Interestingly, in Yeo and colleagues cohort of 30 patients with IRU, there were no cases of CME. This was proposed to be related to earlier treatment of the inflammation in IRU.²⁹

Macular holes are usually the result of tractional forces on the retina, and similar to ERM, can be idiopathic or secondary to other factors such as trauma, vitreomacular traction, retinal detachment, or inflammatory processes.⁴⁶ There has been 1 reported case of a full-thickness macular hole with subretinal fluid associated with IRU.³⁰

Frosted branch angiitis is an uncommon form of severe retinal perivasculitis with prominent perivascular sheathing of arterioles and venules, which can be seen in CMV retinitis. It has rarely been described in IRU as well, in 3 case reports.^{17,39,47}

Retinal detachments can occur in IRU, with or without proliferative vitreoretinopathy (PVR). The rate of retinal detachment in IRU was 2.3/100 eye-years in 1 study.² PVR, characterized by the growth and contraction of cellular membranes within the vitreous and retina, is an abnormal healing response driven by inflammatory, retinal, and retinal pigment epithelial cells. It typically occurs in the setting of complex retinal detachments. PVR is rare in CMV retinitis-associated retinal detachment in patients with AIDS due to the lack of immune/inflammatory response. However, PVR is more commonly encountered in retinal detachments associated with IRU.⁴⁸ In 1 cohort, PVR was seen in one-third of patients.

In 1 eye, spontaneous vitreous hemorrhage from the avulsion of a blood vessel after contraction of the inflamed vitreous was seen. PVR recurred in all cases after surgery, severely compromising the visual outcome.⁴¹ In another cohort, 3 patients (16%) had retinal detachments, 2 of which were complicated by PVR.³⁰

Retinal neovascularization typically occurs in the setting of an imbalance between proangiogenic and antiangiogenic factors, often in the setting of retinal hypoxia/ischemia. However, retinal neovascularization is also sometimes associated with uveitis.⁴⁹ Wright et al⁵⁰ reported extensive peripheral retinal neovascularization as a late finding of IRU in 3 patients out of a 15-patient cohort with IRU. The neovascularization was so severe in 1 case that it required vitrectomy for recurrent vitreous hemorrhage. Neovascularization in IRU has been reported in the setting of nonperfusion, where the pathophysiology of neovascularization is clear, but also in cases without retinal ischemia. Neovascularization in this setting appears to be related to the inflammatory milieu with proinflammatory growth factors and cytokines.^{50,51}

- Optic nerve

Optic nerve edema, also known as papillitis, may occur in the setting of intraocular inflammation of all types—anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis.⁵² Papillitis is relatively frequently seen in IRU, and may be associated with the severity and duration of inflammation. In one of the original reports of IRU, papillitis was seen in all 5 patients in that cohort.¹¹

Optic nerve head neovascularization has also been reported in a few patients with IRU. Sanislo and colleagues reported a patient with IRU who developed prominent optic nerve head neovascularization without nonperfusion on fluorescein angiography. Similar to the retinal neovascularization discussed above, this optic nerve head neovascularization was thought to occur in the setting of intraocular inflammation and not nonperfusion.⁵¹ Postelmans et al⁵³ reported an atypical case of IRU-associated with bilateral peripheral occlusive vasculopathy and bilateral neovascularization of the optic disc. In addition, 1 patient in the Nguyen et al⁶ cohort was noted to have optic disc neovascularization, which resolved spontaneously.

DIAGNOSIS

IRU is a clinical diagnosis based on the proper clinical scenario and exam as described above, in the absence of other causes of intraocular inflammation. There are no formal diagnostic criteria established for IRU. The NIH-sponsored AIDS Clinical Trial Group defined IRU as a decrease in vision with at least 2 of the following signs in the absence of active CMV retinitis: (a) presence of > 2 + inflammatory cells in vitreous by slit lamp examination, (b) CME, or (c) epiretinal membrane formation in patients receiving potent antiretroviral therapy with evidence of immune reconstitution.¹ A different NIH-sponsored

group, the studies of the Ocular Complications of AIDS, defined IRU as “the occurrence of intermediate uveitis in patients with CMV retinitis who have evidence of immune reconstitution, as shown by a rise in CD4 T cell counts after initiation of HAART.” Neither of these definitions is considered to be a definitive set of criteria in current practice.¹ As such, IRU is clinically identified by a new or heightened intraocular inflammatory reaction in individuals with HIV/AIDS and a prior diagnosis of CMV retinitis, typically occurring weeks after commencing HAART with associated immune reconstitution. CD4+ T cell count recovery to more than 100 cells per microliter and at least 50 cells per microliter greater than their nadir has been used as the definition of immune recovery in several studies on IRU.^{6,21,29}

Sampling of the aqueous and vitreous of patients with IRU can also help to differentiate between IRU, active CMV retinitis, and controls. Schrier and colleagues examined cytokines IL-6, IL-12, interferon gamma using enzyme-linked immunosorbent assays, and CMV DNA by polymerase chain reaction, in the aqueous and vitreous of these groups. This study found that IRU eyes had higher levels of IL-12 compared with controls and negative CMV DNA. All of the active CMV retinitis eyes had positive CMV DNA and had higher levels of IL-6 than controls and IRU eyes. Interferon gamma did not differ significantly between CMV retinitis and IRU. As such, IRU can be differentiated from active CMV retinitis by the presence of IL-12, diminished IL-6, and absence of detectable CMV DNA.²⁵

Recent research has explored the potential of microRNA (miRNA) as biomarkers for diagnosing IRU. A study by Duraikkanu and colleagues investigated the expression of miRNA-192 and miRNA-543 in HIV-infected patients with ocular manifestations. Results indicated that miRNA-192-5p and miRNA-543 were downregulated in the peripheral blood of patients with ocular manifestations. These miRNAs showed promise in distinguishing HIV patients with IRU, as they target multiple genes involved in inflammatory pathways.⁵⁴

Differential Diagnosis

Distinguishing IRU from other forms of uveitis is crucial to initiate appropriate treatment. Conditions that may mimic IRU include infectious uveitis (eg, reactivation of CMV retinitis, syphilis, toxoplasmosis, tuberculosis, and fungal infections), noninfectious uveitis (eg, sarcoidosis, Behçet, drug-induced uveitis, and pars planitis), and masquerade syndromes (eg, intraocular lymphoma). It is particularly important to exclude infectious conditions, including syphilis and herpetic infection, as well as drug toxicity (particularly cidofovir), in these patients. A meticulous clinical evaluation and history, along with laboratory and imaging studies, can help differentiate IRU from its mimickers. Aqueous or vitreous sampling can be helpful to rule out infectious etiologies in unclear cases.

PROGNOSIS

The prognosis of IRU is not well defined in large studies. Some patients experience complete resolution of

inflammation, while others face persistent disease or vision loss from complications. Despite the improvement of inflammation, IRU patients remain at risk of complications, including cataracts, secondary glaucoma, optic neuropathy, cystoid macular edema, epiretinal membrane, and retinal detachment.

In a 5-year outcomes study, 26% lost one or more Snellen lines of visual acuity at 6 months, while most patients maintained or improved vision. Complications included cataract (66.7%), glaucoma, and ocular hypertension (33.3%). The risk of complications was associated with the absolute difference in CD4 counts between the time of IRU onset and HAART commencement ($P = 0.041$).²⁹ In a study on periocular steroids for IRU, all of the treated eyes regained vision to within 1 Snellen line of pre-IRU visual acuity.⁴⁰ Kempen et al²¹ reported that 50% of 50 eyes with IRU developed moderate vision loss at 20/50 or worse.

Even after recovery of visual acuity and resolution of inflammation, there may be persistent retinal dysfunction. In 2 patients with IRU who were followed serially with OCT and ERG, chronic retinal injury was evidenced by ellipsoid line loss in 1 case and gradual optic disc cupping despite normal IOP in the other. ERG in both cases revealed generalized retinal dysfunction, with delayed, subnormal ERGs in the eyes with IRU. In 1 patient who received serial ERGs, there was an improvement over time with treatment.⁵⁵

MANAGEMENT

The management of immune recovery uveitis (IRU) is similar to that of other noninfectious uveitis and is tailored to the severity of inflammation and clinical manifestations. The primary goals of treatment are to control intraocular inflammation, improve visual acuity, and prevent long-term complications. The management of IRU involves a combination of topical and systemic immunosuppression, typically with corticosteroids. If asymptomatic, some cases are transient and may even self-resolve. For mild to moderate cases of IRU, topical corticosteroids can be used to reduce anterior chamber inflammation. Earlier treatment of the inflammation may prevent later complications, such as CME.²⁹ Periocular corticosteroids may also be beneficial, shown to be efficacious for the intraocular inflammation.⁴⁰ In more severe cases, systemic corticosteroids may be considered. In the initial case series reported by Karavellas et al¹¹ and Zegans et al,¹² most patients were treated with systemic steroids. In cases of recurrent or refractory IRU, it may be reasonable to consider steroid-sparing immunosuppressive agents such as methotrexate or mycophenolate, though these are not commonly used in IRU.

Systemic antiviral therapy generally does not appear to improve outcomes in IRU.^{21,31,56} Cidofovir, a previously frequently used treatment for CMV, has also been identified as a primary risk factor for the subsequent development of IRU. Ongoing treatment of healed CMV retinitis after immune recovery does not appear to protect against the development of IRU. In addition, Wohl et al⁵⁷

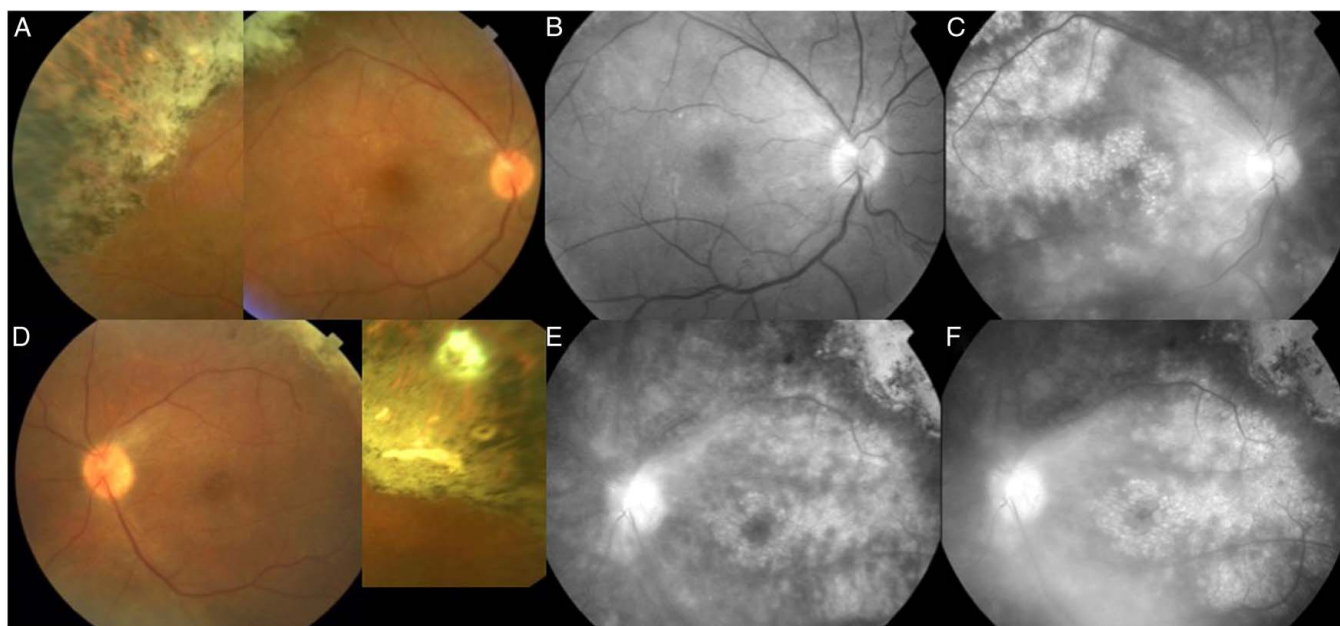


FIGURE 1. Representative case of IRU. At presentation, color photography of the right (A) and left (D) eyes and fluorescein angiography in the right (B–C) and left (E–F) eyes demonstrate optic nerve hyperemia and late leakage, areas of chorioretinal scarring/atrophy and petaloid leakage in the macula, consistent with cystoid macular edema. [full color online](#)

found no difference in occurrence of IRU in patients with CMV retinitis who continued or discontinued maintenance CMV retinitis therapy (most frequently with oral ganciclovir in their cohort). However, Kosobucki et al⁵⁸ found that valganciclovir improved visual outcomes in patients with CME in the setting of IRU. In general, additional antiviral treatment does not play a role in IRU given the overall evidence that these do not typically improve outcomes.

Management of CME

Eyes with IRU-associated CME can maintain good vision and may spontaneously improve, as such, mild cases may be amenable to observation or treated with topical therapy.^{59,60} For example, Guzak et al⁴⁵ reported a case of CME in IRU that improved with topical NSAIDs only. Subtenon injections of steroids are modestly effective for the CME seen in IRU.²² In Karavellas and colleagues cohort, corticosteroid treatment, used only in more severe cases of IRU with CME and decreased vision of 2+ lines, led to improved vision in the patients treated with steroids. In patients not treated with steroids, the macular edema persisted or worsened. Thus, local and/or systemic steroid treatment for IRU may improve visual acuity compared with observation.²² In Nguyen and colleagues cohort, 4 of 6 eyes with IRU were reported to have CME and 2 of the eyes improved with steroid treatment. In the other 2 patients, the CME persisted despite aggressive therapy with topical, periorbital, and systemic corticosteroids.⁶ Morrison and colleagues found that high-dose intravitreal triamcinolone was effective for CME in IRU. In 8 eyes with an average of 51 months of IRU before the first

triamcinolone injection, vision, and macular thickness improved significantly, with only 3 eyes requiring repeat injections.⁶¹ A fluocinolone acetonide implant has also been shown to be effective and safe in IRU-associated CME.⁶² Of note, the patients who received a fluocinolone implant also received treatment for CMV retinitis (ganciclovir implant or oral valganciclovir) in order to minimize the risk of recurrence of CMV retinitis.

Surgical Management

Surgical interventions, particularly vitrectomy, are uncommon after IRU but may be necessary to manage complications like ERM or retinal detachment. Surgical repair of retinal detachment associated with CMV retinitis has been well-described due to its complexity, and typically involves pars plana vitrectomy with silicone oil tamponade.^{3,63,64} These CMV retinitis-related detachments, often with atrophic areas and numerous breaks, may be further complicated in the inflammatory milieu of eyes with IRU; in Karavellas and colleagues cohort, 2 of 29 eyes developed rhegmatogenous retinal detachments and proliferative vitreoretinopathy, requiring vitrectomy, membrane peeling, silicone oil tamponade, and scleral buckling. The postoperative course was complicated for these patients, with epiretinal and subretinal reproliferation. One patient developed a tractional retinal detachment after silicone oil removal.²² While retinal detachments have been reported in other cohorts of IRU,^{21,30} there is a shortage of literature on the surgical management and clinical course of these detachments.

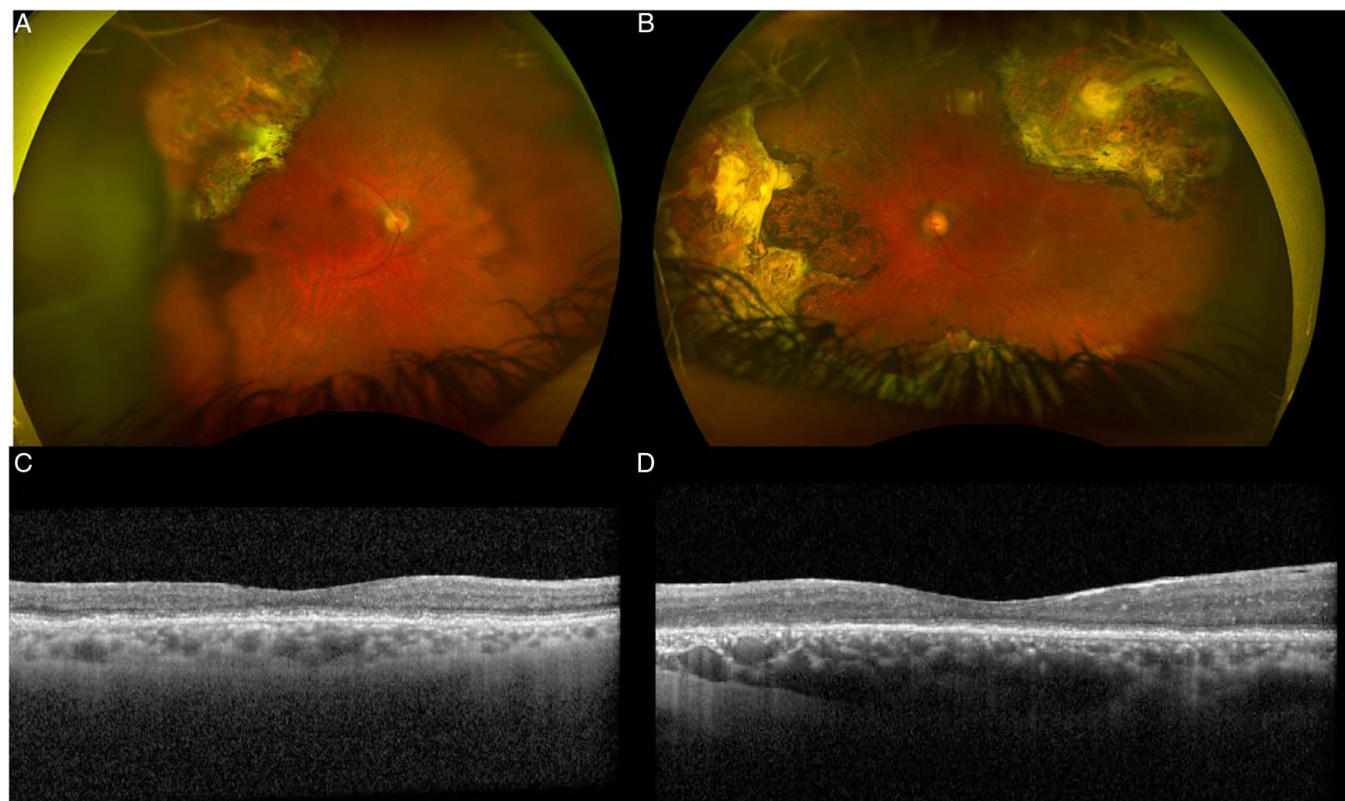


FIGURE 2. At follow-up 16 years later, ultra-widefield fundus photography shows extensive chorioretinal scarring in both eyes with a few peripheral hemorrhages (A–B). OCT (C–D) showed architectural changes with multiple areas of ellipsoid zone disruption, left more than right, consistent with prior CME. The patient did not receive treatment between the first visit and follow-up 16 years later.

ILLUSTRATIVE CASE

A 34-year-old woman with a history of HIV/AIDS and prior treatment for CMV retinitis, now on HAART, presents with gradual loss of vision in both eyes. Visual acuity was 20/200 in both eyes. Imaging from her initial presentation (Fig. 1) demonstrates optic nerve hyperemia and late leakage, areas of chorioretinal scarring/atrophy, and petaloid leakage in the macula, consistent with cystoid macular edema.

At follow-up 16 years later, the patient's exam was stable (Fig. 2). There was extensive chorioretinal scarring in both eyes with a few peripheral hemorrhages and diffuse atrophy with multiple areas of ellipsoid zone disruption on OCT. Visual acuity was 20/80 in the right eye and 20/250 in the left eye.

FUTURE DIRECTIONS

Advances in the understanding of IRU's pathophysiology and the development of targeted therapies hold promise for improving the management of this condition. Further research into biomarkers that predict risk for IRU may assist clinicians in identifying patients who may need closer monitoring.

Despite the advent of new therapies for non-infectious uveitis, there has not been significant research

into the applications of these therapies for IRU. Biologics and novel immunomodulatory agents may offer more targeted and safer alternatives to traditional corticosteroid-based therapies. In addition, further research is needed on the surgical management of IRU-associated retinal detachments, which have the potential to be complicated by PVR.

CONCLUSION

While HAART has significantly improved the prognosis and life expectancy of patients with HIV/AIDS and decreased the incidence of CMV retinitis, IRU remains a challenging and potentially vision-threatening entity. IRU typically occurs weeks to months after immune recovery, but may even occur years later, and is thought to be a CMV antigen-related inflammatory condition. It is important to rule out infectious etiologies of uveitis when managing IRU. IRU can be asymptomatic or minimally symptomatic, improving with topical or periorbital treatment only. However, there are also cases of persistent CME or severe PVR in the setting of IRU. A comprehensive understanding of the biology, clinical presentation, diagnostic criteria, and management strategies of IRU is crucial for all ophthalmologists. Further research and clinical advancements hold the potential to

improve the diagnosis and management of this complex condition.

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