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Cytomegalovirus Retinal Necrosis With Occlusive Vasculopathy Secondary to Steroid Immunosuppression for Giant Cell Arteritis

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Abstract

Purpose: This case report discusses an atypical case of cytomegalovirus (CMV) retinal necrosis with panretinal occlusive vasculopathy in a 77-year-old man who was immunosuppressed following treatment for giant cell arteritis (GCA). **Methods:** A case report is presented. **Results:** Clinical examination demonstrated a central retinal artery occlusion and pale disc suspicious for arteritic ischemic optic neuropathy in the right eye. Biopsy-proven GCA prompted treatment with oral prednisone. While on glucocorticoid immunosuppression, the patient suffered vision loss in the left eye from CMV-necrotizing retinitis with occlusive vasculopathy. Treatment controlled the CMV infection but tapering of his steroids resulted in worsening GCA, requiring a steroid-sparing treatment, tocilizumab. **Conclusions:** Corticosteroid immunosuppression for GCA may lead to immune dysfunction allowing for an atypical occlusive vasculitis with retinal necrosis from CMV. Early identification and treatment are essential to adjust the level of immunosuppression and consider alternate therapies to control the GCA and prevent worsening of this opportunistic infection.

Keywords

central retinal artery occlusion, CMV chronic retinal necrosis, cytomegalovirus, giant cell arteritis, immunosuppression, necrotizing retinitis, neovascular glaucoma, prednisone, tocilizumab, valganciclovir

Introduction

Giant cell arteritis (GCA) is the most common form of systemic vasculitis among white individuals aged 50 years or older.[1,2] GCA affects medium to large arteries including the aorta and its primary and secondary branches, with granulomatous inflammation within the arterial walls leading to luminal occlusion due to concentric intimal thickening and subsequent tissue ischemia.[1-3] The most common symptoms include weight loss, fever, new onset or type of headache (particularly along the temple), jaw claudication, neck pain, and loss of vision that can lead to permanent blindness.[1-3] The incidence of ocular involvement ranges from 14% to 70%, with the most common ocular manifestation being arteritic anterior ischemic optic neuropathy[1] and a frequency of central retinal artery occlusion (CRAO) in approximately 1.6% of cases.[4]

A prolonged corticosteroid taper, often exceeding 1 year, is the mainstay of treatment for GCA: this treatment is associated with adverse effects, such as an increased risk of opportunistic infections. Other adverse effects associated with corticosteriod treatment include worsening control of diabetes and hypertension, osteoporosis, progression of cataracts, and mood disorders.[2] Tocilizumab, a humanized monoclonal antibody against the interleukin-6 receptor,[5,6] is now US Federal Drug Administration approved for the treatment of GCA,[7] but corticosteroids are often still used as first-line treatment.[2,3]

Cytomegalovirus (CMV) retinitis typically presents with minimal intraocular inflammation, focal vasculitis, and granular retinal necrosis seen in severely immunocompromised

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patients.[8] Although seroprevalence of CMV antibodies is found in the majority of the adult population, CMV infections are uncommon in immunocompetent individuals.[9] As such, CMV retinitis is most commonly seen in patients with either secondary immunodeficiencies such as HIV/AIDS, primary immunodeficiencies, malignant tumors, or in patients who are immunocompromised because of immunosuppressant-based therapies used to prevent organ transplant rejection.[9] Recently, reports have identified atypical CMV acute retinal necrosis (ARN) infections in non-HIV patients with lesser degrees of immune dysfunction manifesting with severe occlusive arteritis.[8,10] Such a presentation may occasionally be seen in patients who have a relatively decreased cell-mediated immunity, including those with diabetes mellitus, advanced age, and noncytotoxic immunosuppressive medications. Herein, we report the first case of CMV with progressive granular retinitis associated with occlusive panretinal vasculitis following glucocorticoid immunosuppression for GCA.

Methods

Case Report

A 77-year-old Iranian man with well-controlled type 2 diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, cerebrovascular disease, benign prostatic hyperplasia, and a past history of smoking presented with a sudden loss of vision in his right eye, which occurred the day after he underwent uncomplicated cataract surgery with topical anesthesia. On our review of systems, he also reported that for approximately one month prior, he noticed worsening vision initially attributed to worsening cataracts, neck pain, and jaw claudication. On examination, his visual acuity (VA) was no light perception (NLP) in the right eye and 20/50 OS. Anterior examination revealed a well-centered posterior chamber intraocular lens in the right eye and a cataract in the left eye. No signs of anterior chamber inflammation were noted in both eyes. The right eye showed central retinal whitening with a cherry-red spot and a pale optic nerve (Figure 1A). The left eye had slight temporal pallor and cotton wool spot in the superior macula but otherwise normal-appearing macula (Figure 1B).

Spectral-domain optical coherence tomography (SD-OCT) of the right eye showed loss of the normal retinal architecture consistent with CRAO, including increased reflectivity and thickness of the inner retinal layers and decreased reflectivity of the outer retinal layers of the right eye and areas of inner retinal thinning of the ganglion cell layer temporally in the left eye. SD-OCT 3 × 3 mm angiography showed significant loss of the superficial capillary plexus (SCP) and deep capillary plexus (DCP) of the right eye (Figure 1C) and appeared normal in the left eye (Figure 1D). Ultra-widefield fluorescein angiography (FA) demonstrated significant choroidal and retinal ischemia and delayed arterial-venous perfusion in the right eye, late peripheral vessel leakage in the left eye, and late optic nerve head staining in both eyes (Figure 1, E and F). The active vasculitis in the left eye and NLP vision with a CRAO in the right eye were clinically presumed to be due to ophthalmic artery occlusion from GCA.

Serologic laboratory workup noted an elevated erythrocyte sedimentation rate of 80 mm/h (normal range, < 30 mm/h) and C-reactive protein of 37.8 mg/dL (normal range, 0-9.0 mg/dL). Given the clinical presentation and elevated inflammatory markers, treatment with 60 mg of oral prednisone (1 mg/kg/d) was initiated. The patient underwent right temporal artery biopsy 5 days later. The pathology was consistent with GCA, with florid features of arteritis with complete or near-complete obliteration of the arterial lumen by marked intimal fibroplasia; intimal proliferation composed of fibroblasts, histiocytes, lymphocytes and occasional eosinophils; variable lymphohistiocytic infiltrate of the media with occasional dystrophic calcifications; and rare giant cells.

The patient was continued on high-dose prednisone and referred to a rheumatologist. Attempts to taper prednisone were unsuccessful because of ongoing elevation in inflammatory markers, refractory headache and jaw pain, and the patient's concern about the possibility of further visual impairment. Treatment with tocilizumab was recommended but delayed, first due to the patient's positive purified protein derivative (tuberculin) and concern for latent tuberculosis infection (LTBI), and later, due to complications from LTBI treatment. He was started on isoniazid, but then switched to rifampin because of isoniazid-induced hepatitis.

Five months after the initial diagnosis of GCA, the patient was still on high-dose glucocorticoid immunosuppression and returned complaining of gradual left vision loss. VA remained NLP in the right eye and was 20/200 OS. The anterior chamber remained quiet in both eyes. Posterior examination demonstrated trace vitritis, arteriolar attenuation and nonperfusion in all 4 quadrants, and a new patch of focal retinal whitening in the supratemporal periphery of the left eye (Figure 2A). SD-OCT of the right eye was unchanged, but the left eye showed further inner retinal thinning, especially temporally. SD-OCT 6 × 6 mm angiography of the left eye demonstrated significant loss of the SCP and DCP involving the central and temporal macula (Figure 2B). Ultra-widefield FA of the left eye demonstrated patchy choroidal perfusion loss, severe retinal nonperfusion, focal late leakage from the area of retinal whitening, optic nerve staining, and late vessel leakage (Figure 2, C and D).

Given the suspicion for acute viral retinitis, an anterior chamber paracentesis was performed for directed viral polymerase chain reaction (PCR) for herpes simplex virus (HSV), varicella zoster virus (VZV), and CMV. The patient was also started on induction antiviral treatment with valganciclovir 900 mg twice per day for 2 weeks. His anterior chamber PCR returned positive for CMV and negative for VZV and HSV. After confirmation of CMV infection, the patient received an induction course with intravitreal foscarnet (2.4 mg twice per week) for 3 weeks and was continued on oral valgancyclovir treatment. His prednisone dosage was also tapered expeditiously to 20 mg daily in an effort to reduce his immunosuppression.

Seven months after the diagnosis of GCA, the patient's CMV retinitis was improving, and he was taking a prednisone

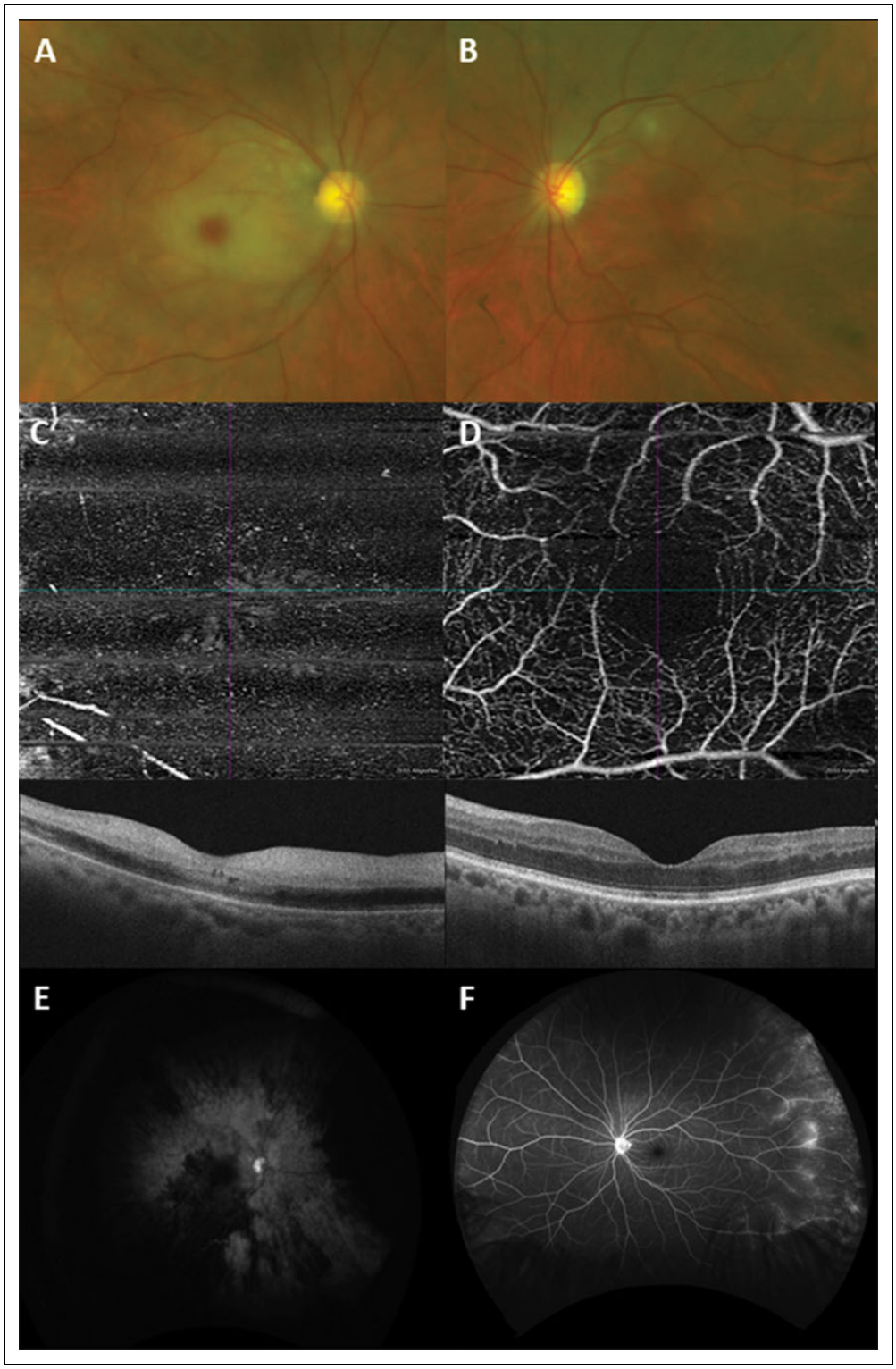

Figure 1. Multimodal imaging of a 77-year-old man with central retinal artery occlusion (CRAO), pale optic nerve in the right eye, and temporal pallor and cotton wool spot in the superior macula in the left eye due to giant cell arteritis (GCA) at initial presentation. (A) Fundus examination of the right eye (eye exhibiting no light perception) shows optic disc pallor, significant retinal whitening, and cherry-red spot due to a CRAO. (B) Imaging of the left eye demonstrates minimal temporal optic disc pallor and cotton wool spot in the superior macula. (C) Spectral-domain optical coherence tomography (SD-OCT) and 3 × 3 mm angiography (SD-OCTA) of the right eye showed loss of all superficial capillary plexus (SCP) vasculature with increased reflectivity and thickness of inner retinal layers and decreased reflectivity of outer retinal layers on the B-scan consistent with CRAO. (D) SD-OCT of the left eye demonstrates inner retinal thinning of the ganglion cell layer from prior ischemic changes and a normal-appearing SCP on 3 × 3 mm SD-OCTA. (E) Ultra-widefield fluorescein angiography (FA) of the right eye demonstrates significant choroidal and retina ischemia in the early frames and nonperfusion 360° with optic disc staining. (F) FA of the left eye shows late optic disc staining and peripheral vascular leakage clinically presumed to be due to GCA.

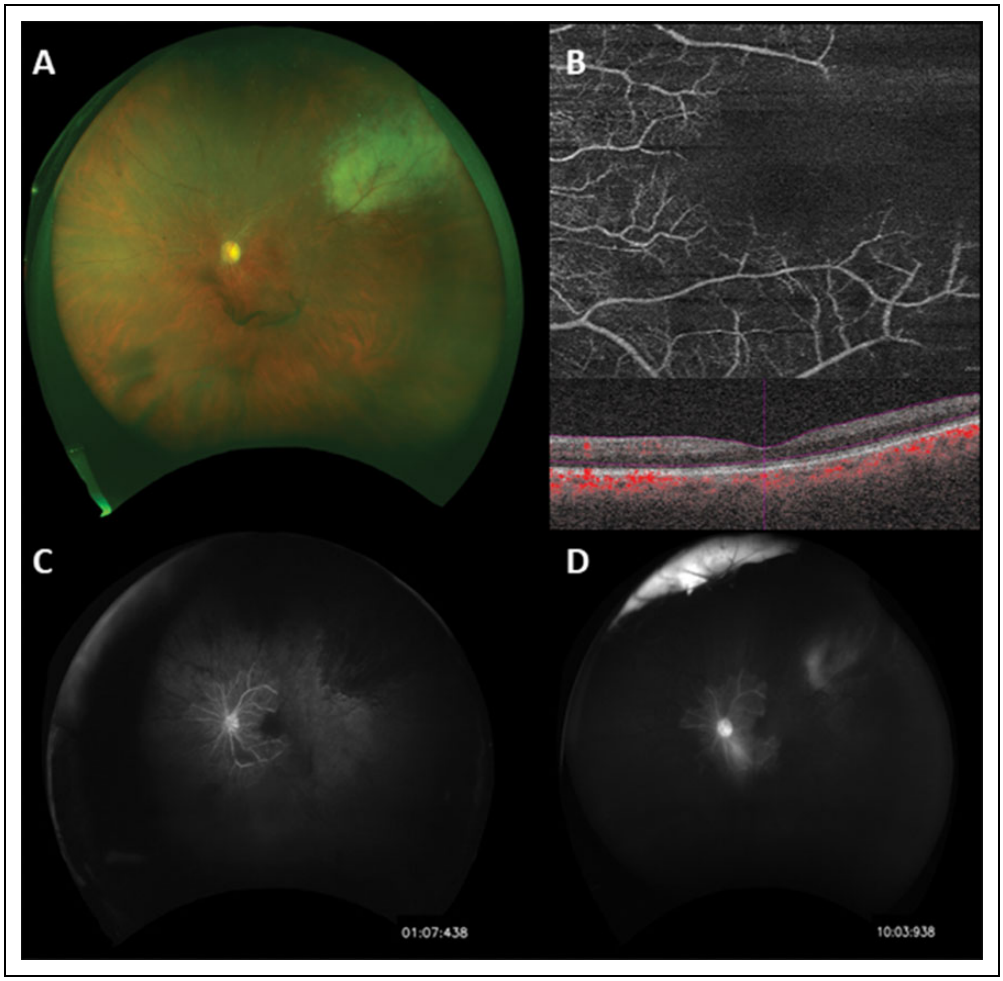

Figure 2. Multimodal imaging of the left eye 6 months after diagnosis with giant cell arteritis now presenting with gradual left vision loss and new vitritis, focal retinitis, and panretinal occlusive vasculitis. (A) Fundus examination shows an area of focal whitening in the temporal periphery. (B) Follow-up spectral-domain optical coherence tomography (SD-OCT) and 6 × 6 mm angiography (SD-OCTA) demonstrates worsening temporal inner retinal thinning on the B-scan and significant loss of the central and temporal superficial capillary plexus on SD-OCTA. Repeat ultra-widefield fluorescein angiography of the left eye shows (C) impaired filling of the choroid and retinal arteries consistent with worsening ischemia in the early frames and (D) late optic disc staining and vascular leakage.

dosage of 20 mg daily. However, he reported increasing jaw pain and headache, raising concern that his GCA may be worsening. A magnetic resonance imaging/magnetic resonance angiogram of the patient's brain and chest was ordered and showed a known right carotid stenosis (Figure 3A), focal narrowing of the bilateral superficial temporal arteries (Figure 3A), focal wall thickening in the descending aorta (Figure 3B), and subtle increased enhancement of the right brachiocephalic artery consistent with active GCA vasculitis (Figure 3, C and D). Given concerns about possible worsening systemic GCA and the need to transition him to a steroid-sparing treatment regimen, tocilizumab was initiated (162 mg subcutaneous injections every other week), and a slow taper of prednisone was also initiated.

Two months later, the patient presented with new neovascular glaucoma in his left eye with iris rubeosis from ischemia. This was treated with 3 monthly intravitreal antivascular endothelial growth factor (VEGF) injections and panretinal photocoagulation (PRP). During this period, prednisone was tapered to 7.5 mg daily; treatment for GCA continued with tocilizumab subcutaneous injections every other week. The CMV obliterative retinitis remained stable with a maintenance dose of oral valganciclovir 900 mg daily.

Results

CMV retinitis appears to present on a spectrum of disease manifestations from the classic hemorrhagic, retinal necrosis to chronic retinal necrosis with panretinal obliterative vasculitis depending on the level of immunocompetency. Most commonly, in patients with HIV/AIDS, cytotoxic immunosuppression for previous organ transplant, or malignant tumors, CMV presents with classic focal or multifocal perivascular areas of hemorrhagic, granular retinitis with varying levels of inflammation and nonocclusive venous sheathing around areas of retinitis.[8] Several reports have also shown that the classic

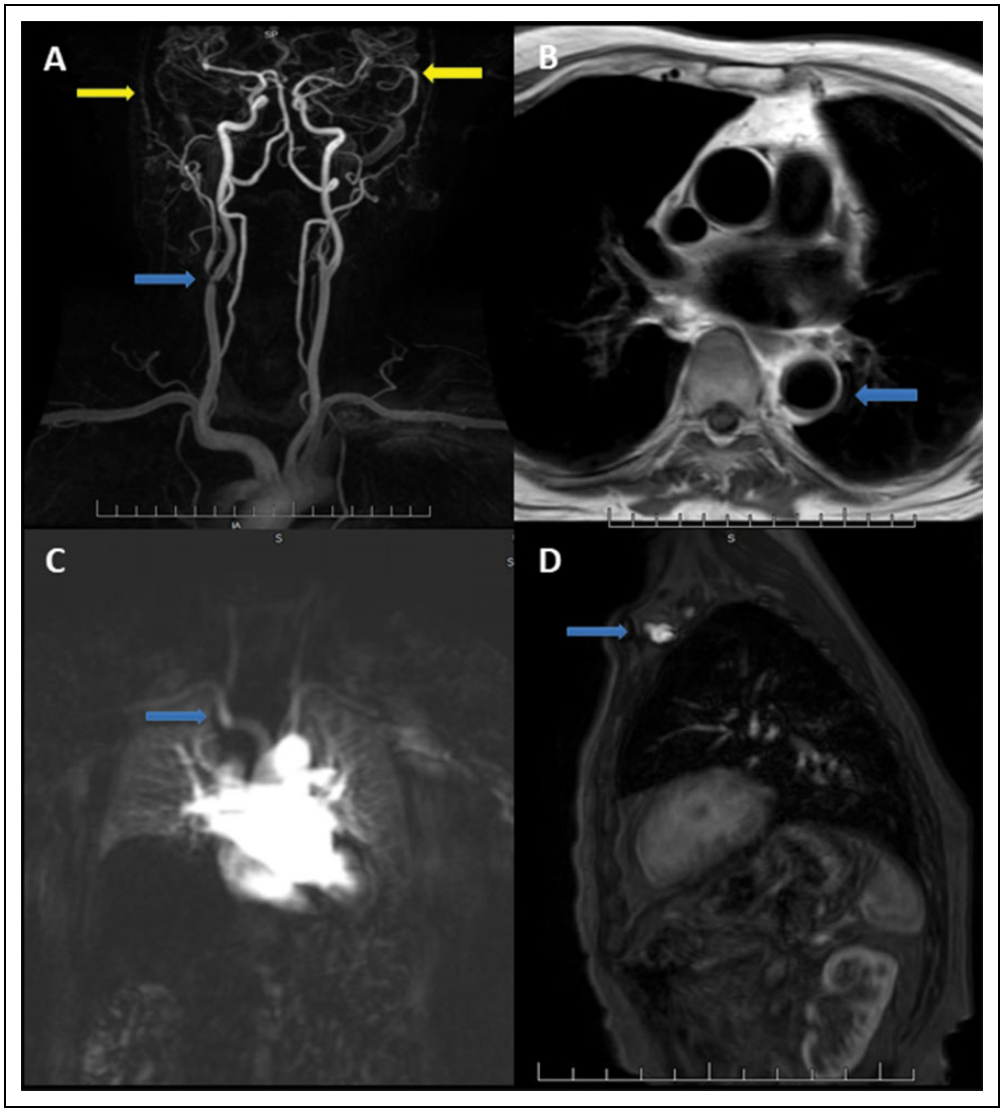

Figure 3. Systemic magnetic resonance imaging (MRI) 7 months after diagnosis with giant cell arteritis during tapering of oral prednisone to 20 mg per day because of concurrent cytomegalovirus retinitis. (A) Coronal magnetic resonance angiogram imaging of the patient's head and neck demonstrates right carotid stenosis and focal narrowing (blue arrow) and narrowing of both superficial temporal arteries (yellow arrows). (B) T1-weighted axial MRI demonstrates focal wall thickening in the descending aorta (blue arrow). (C) Coronal and (D) sagittal maximum intensity projection MRI images demonstrate subtle increased enhancement of right brachiocephalic artery (blue arrows) consistent with active giant cell arteritis vasculitis.

form of CMV retinitis may also develop in patients with connective tissue diseases, including systemic lupus erythematosus and chronic rheumatoid arthritis in conjunction with steroid and immunosuppressant therapy.[9] Downes and colleagues reported that CMV retinitis occurred in 65.7% of patients on corticosteriods, which has been reported as the most common immunosuppressive medication associated with infection with this virus.[11] Within this disease spectrum, our current patient has similarities to the 5 patients whom Schneider and colleagues discussed, with relative limited immune dysfunction, who developed severe CMV necrotizing retinitis with panretinal obliterative vasculitis similar to the findings in ARN from HSV or VZV infections.[8] This case also has similarities to the case presented by Moussa and colleagues in which an HIV-negative patient developed a CMV infection due to other conditions (diabetes and advanced age) that resulted in a relatively compromised immune system.[10]

CMV seroprevalence is found in a majority of adults in the United States (50% to 85%). It establishes latency in mononuclear cells in the bone marrow and peripheral blood being controlled by the host's immune system, principally cell-mediated immunity.[9] However, once the immune system of the host is either relatively or completely suppressed, the virus is able to spread, infect, and replicate in other tissues in the body, including the retina. In healthy individuals, cell-mediated immunity (CMI) suppresses the disease, whereas in severely immunocompromised patients, the lack of CMI leads to direct viral organ damage and uncontrolled viral replication.[9] In these

cases of necrotizing retinitis with ischemic vasculitis, one hypothesis is that partially immunocompromised patients may have some CMV-specific CMI that limits viral spread but also causes direct specific T lymphocyte–induced tissue damage as seen in patients with HSV- or VZV-related ARN.[8]

We report the first case of CMV retinitis in a patient with GCA on prednisone monotherapy. Our patient had several risk factors for immune dysfunction, including advanced age, diabetes mellitus, and prolonged high-dose corticosteroid use for severe and refractory GCA. Aging within CD8 T-lymphocyte cells involved in CMI may occur faster and be associated with persistent viral infections such as CMV. This can lead to considerable stress on CD8 T cells and their ability to respond to infection, leading to restructuring of the immune system with progressive age, and susceptibility to GCA in parallel with age-related remodeling of the vascular wall.[12]

Previous reports included patients on multiple immunosuppressive medications for either a solid organ transplant or bone marrow transplants. Similarly, the presentation of the disease was a unilateral, focal area of patchy granular retinitis with severe panretinal occlusive vasculopathy. It developed relatively subacutely, required prolonged oral antiviral treatment, and included the development of neovascular complications. The degree of panretinal occlusive vasculitis may have been worse in our patient because of the combination of his CMV chronic retinal necrosis and ocular involvement from GCA. The combination of both these diseases in our patient may have led to the severity of his ischemia and neovascular glaucoma requiring anti-VEGF and PRP.

Conclusions

To the best of our knowledge, we present the first case of atypical CMV chronic retinal necrosis with panretinal occlusive vasculitis in a patient with relative immune dysfunction from high-dose corticosteroids for GCA. The patient has been successfully treated with tocilizumab for GCA, which has allowed for tapering of prednisone, without evidence of worsening of CMV infection. The case demonstrates that opportunistic infections of the eye may mimic ocular involvement from GCA; it therefore highlights the need to recognize infection risks and different disease patterns to avoid misdiagnosis.

Ethical Approval

This case report was conducted in accordance with the Declaration of Helsinki. The collection and evaluation of all protected patient health information was performed in a Health Insurance Portability and Accountability Act (HIPAA)-compliant manner.

Statement of Informed Consent

Informed consent was obtained before performing the procedure, including permission for publication of all photographs and images included herein.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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