CASE REPORT

Unusual Presentation of Cytomegalovirus Infection and Retinitis in An Immunocompetent Patient: A Case Report and Review of Literature

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Abstract

Cytomegalovirus retinitis most commonly presents in immunosuppressed patients or the immunologically immature neonatal group. Yet evidence from several studies suggest that occurrence of Cytomegalovirus retinitis may appear even with no systemic immune dysfunction. Due to the lack of literature published on the immunocompetent population, we wish to present a case report with a review of the present research. A middle-aged, otherwise healthy and immunocompetent female presented with femoral thrombus, fever, blurring of vision, and documented cytomegalovirus infection. Core DNA positivity for active CMV infection was obtained, and with antiviral treatment, the patient ultimately regained full vision. CMV retinitis triggered from an isolated systemic condition such as hypertension is not common and suggests that other factors should be considered. We wish to highlight the importance of considering CMV diagnosis even in those who are immunocompetent.

Keywords: CMV; Thrombosis; Immunosenescence

Abbreviations: M: Male; F: Female; CMV: Cytomegalovirus; IgM: Immunoglobulin M; IgG: Immunoglobulin G; PCR: Polymerase Chain Reaction; DM: Diabetes; HTN: Hypertension; MS: Multiple Sclerosis; CVA: Cerebrovascular Accident; POAG: Primary open angle Glaucoma; CLL: Chronic Lymphocytic Leukemia; CHF: Congestive Heart Failure; AA: Aortic Aneurysm; CAD: Coronary Artery Disease; VZV: Varicella-zoster virus; AR: Aortic Regurgitation; MV: Mitral Valve; HSV: Herpes Simplex Virus; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; PDR: Proliferative Diabetic Retinopathy

Introduction

Cytomegalovirus (CMV) comprises one of nine herpesviruses. CMV infection is very common and mostly asymptomatic in healthy patients with proper immune function. The virus can be spread through the saliva, bodily excretions, infected blood transfusions, or through placental transfer. Once infected, the virus becomes latent by avoiding detection and immune elimination until an opportunistic event occurs. Symptomatic illness in the host indicates either reactivation of the dormant virus or reinfection with a different strain. Complications of this disease can affect many organ systems with consequential morbidity and mortality. Ocular involvement may cause devastating vision loss.

It was originally thought that patients only manifested with symptoms during a compromised state. Prior reports of systemic CMV infection in the immunocompetent have focused on organ systems other than the eye, such as the gastrointestinal and central nervous systems [1]. We report an otherwise healthy patient who presented with a femoral thrombosis and was subsequently noted to develop CMV retinitis. Thombosis is a well corrected complication in patients with CMV infection [2].

We wish to detail this case and focus on the factor of immunosenescence and its relation to CMV infection and reactivation.

Case Report

A 54-year-old Caucasian female with a history of hypertension and cervical degenerative joint disease was admitted to the hospital for left lower extremity pain localized to the medial aspect of the thigh. Review of symptoms was significant for diarrhea for 3 weeks duration, intermittent coughs, nasal congestion, fever for 2 days duration, generalized weakness for 5 days, and weight loss.

Initial work-up upon admission consisted of complete blood count, basic metabolic panel, and liver function test, which were normal except slightly elevated alanine aminotransferase (67 units/liter), and aspartate aminotransferase (71 unit/liter). HIV/

Ab screen was non-reactive. A CD4 count of 1063 cells/mL was obtained. CMV DNA using quantitative real time-polymerase chain reaction (QNT-PCR) was detected. CMV immunoglobulin G and immunoglobulin M were 3.79 U/mL and 19.3 AU/mL respectively. Inflammatory markers of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were elevated at 6.08 milligram/liter and 60 millimeters/hour respectively. Immunologic and infectious etiology were suspected, and the following labs were ordered (Table 1): rheumatoid factor, antinuclear antibody, complement component 3 and 4, anti-centromere, anti-chromatin, anti-dsDNA, Hepatitis B and C, tuberculosis, Epstein-Barr virus (EBV), CMV, Coxiella burnetii, Brucella, Toxoplasma, Borellia burgdorferi, Bartonella henselae, and fluorescent treponemal antibody absorption serology. Rheumatoid factor and antinuclear antibody were elevated, and CMV by QNT-PCR was 16278 copies/mL.

| Serological Test | Patient's results |
|-----------------------------------|-------------------|
| CMV | positive |
| Hepatitis B virus | negative |
| Hepatitis C virus | negative |
| HIV antigen/antibody | negative |
| HSV type 1 (IgM and IgG) | negative |
| HSV type 2 (IgM and IgG) | negative |
| Tuberculosis | negative |
| EBV | negative |
| Coxiella burnetii | negative |
| Brucella | negative |
| Toxoplasma (IgG and IgM) | negative |
| Borrelia burgdorferi | negative |
| Bartonella henselae (IgG and IgM) | negative |
| Syphilis | negative |

Table 1: Potential etiologies for fever of unknown origin that were tested

Acute leg pain and swelling pointed to possibility of thrombus. A coagulation panel was completed and found that partial thromboplastin time (PTT) and D-Dimer was elevated, PTT ratio and antithrombin III function were reduced over the course of the week. Factor V leiden and prothrombin mutation test were normal. Chest radiograph was unremarkable, while abdominal ultrasound revealed splenomegaly and hepatomegaly with diffuse fatty infiltration. Duplex imaging of the left lower extremity arteries showed near occlusion at the junction of the common and proximal superficial femoral arteries with minimal flow within the proximal and mid superficial femoral artery. No detectable flow was seen within the distal superficial femoral, popliteal, posterior tibial, or peroneal arteries. There was distal reconstitution of the left anterior tibial artery with weak monophasic flow. Computed

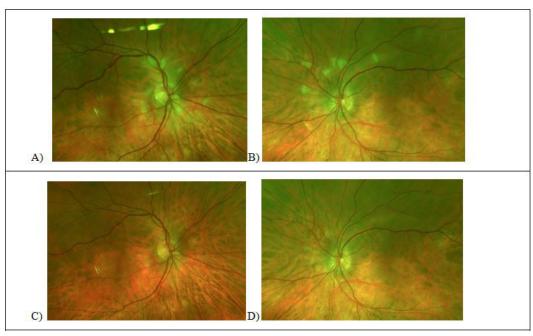


Figure 1: Fundoscopic imaging of the right (A) and left (B) eye, taken during the first outpatient visit, 1 week after appearance of ocular symptoms. Cotton wools spots were seen in both eyes, concerning of choroidal lesions and retinal ischemia. There is significant venous engorgement noted in the right eye Fundoscopic imaging of the right (C) and left (D) eye, taken post-treatment, two and a half weeks after first outpatient encounter for comparison. Nerves and vessels were within normal limits, edges were sharp without swelling OU. There was complete resolution and disappearance of cotton wool spots.

tomography angiography (CTA) revealed evidence of thrombus in the left common femoral, profunda femoris, superficial femoral, and popliteal arteries. An immediate left iliofemoral thrombectomy was performed.

Post thrombectomy, her temperatures spiked to 39.1C. This prompted a second chest radiograph which demonstrated mild left basilar atelectasis and suggestions of mild left pleural effusion. Consult with an infectious disease specialist placed the patient on valgancyclovir 900 mg oral. Within a week of these high fevers, the patient complained of blurred vision with floaters in both eyes. Ophthalmology was consulted and the examination showed an uncorrected visual acuity of 20/40 in both eyes (OU) at nearby. External examination was unremarkable, and the cornea, lens, and anterior chamber were clear OU. Patient was on valgancyclovir for a total of 3 weeks duration. Funduscopic examination showed deep areas of what appeared to be choroidal lesions and retinal ischemia OU.

Funduscopic findings taken same day after hospital discharge showed diffuse cotton wool spots in the periphery OU (Figure 1A and 1B). Similarly, optical coherence tomography of the macula confirmed presence of edema and areas of infarct OU (Figure 2A-2B). OCT angiography (OCT-A) of the right macula demonstrates capillary dropout and upper plexiform and retinal nerve fiber layer edema (Figure 3A). Vision and general health improved within 2 weeks after treatment. Visual acuity improved to 20/20 in the right eye and 20/25+2 in the left. Funduscopic images taken two and a half weeks after the first set of images showed complete resolution (Figure 1C and 1D). CMV DNA QNT, CRP and ESR returned to normal limits after treatment.

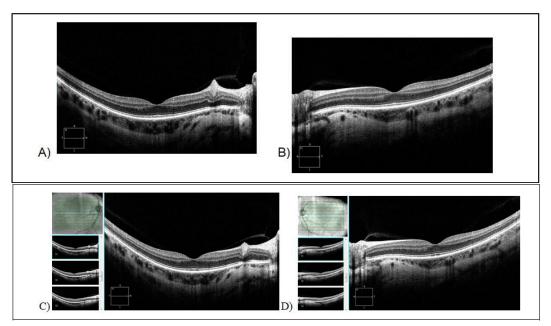
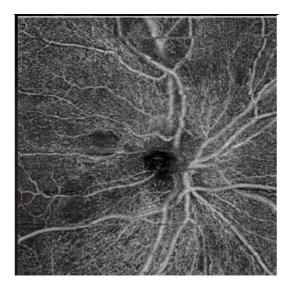


Figure 2: OCT macula of the right (A) and left (B) eye, taken during the first outpatient visit, 1 week after appearance of ocular symptoms. Image A shows elevation, edema, and cotton wool spot more in the right than the left OCT macula of the right (C) and left (D) eye, taken post-treatment, two and a half weeks after first outpatient encounter for comparison. Image C and D shows regression of the edema and cotton wool spots



Methods

A literature search of articles published between 1976 and 2017 using PubMed was performed using the keywords "CMV," "cytomegalovirus," "retinitis," and "immunocompetent." Cases that included infants, existing history of intravitreal injections or eye surgeries, eye trauma, immunodeficiency, recurrent or chronic infections, and patients who tested negative for CMV infection or that were not confirmed were not included. Titles and abstracts were reviewed to ensure patients were not in a compromised state prior to diagnosis of CMV infection. Only articles in English were incorporated into our analysis.

Results

Using the above keywords, our search yielded a total of 80 publications. A total of 11 articles describing 18 patient cases of CMVR met our search criteria. Information extracted from each report were age, gender, diagnostic confirmation of CMV infection, and co-existing medical history. The average age of immunocompetent patients selected for our review was 63 years old, with diabetes (44%) as the most common co-existing medical diagnosis and hypertension (28%) as the second (Table 1). There were more reported cases of CMVR in men (67%) than women (33%).

Discussion

Seroprevalence of CMV worldwide ranges between 60 and 100 percent of adults [3]. Prevalence is inversely correlated to the country's socioeconomic status, increases with age, and differs between race and ethnicity, with the highest incidence in Mexican Americans (4, 5, 6). Any condition that leads to a decline in immune function can lead to CMV reactivation and the potential for CMV retinitis. Reactivation was mainly observed in those who are immunocompromised, however immunocompetent patients may also be at risk. Recent studies have noted common non-immunological factors that may weaken the immune system enough for viral appearance. These factors include age over 60 years, malignancy, local immunosuppression therapy, and diabetes mellitus [1,7-9]. Literature review has found 18 cases also reporting CMV retinitis in healthy individuals (Table 2).

| Author (year) | Age | Gender | CMV testing | Notes/ Medical History |
|------------------|-----|--------|---|--|
| Assy (2007) | 36 | M | CMV IgM, IgG, protein pp65 antigenemia, PCR | Splenectomy after blunt trauma |
| Chawla (1976) | 39 | F | Serial complement fixing antibody test | None |
| Davis (2013) | 71 | M | PCR | DM, HTN |
| Davis (2013) | 81 | M | PCR | MS, CVA, DM, hyperlipidemia |
| Davis (2013) | 66 | M | PCR | POAG, CLL |
| Davis (2013) | 61 | M | PCR | CHF, HTN, DM, AA |
| Davis (2013) | 80 | F | PCR | HTN |
| Davis (2013) | 75 | M | PCR | DM, CAD |
| England (1984) | 45 | F | Complement fixing antibody | Open abdominal wound |
| Gupta (2013) | 81 | M | PCR | DM, HTN, CAD |
| Gupta (2013) | 30 | M | PCR | None |
| Nakamura (2015) | 65 | F | PCR Vitreous | VZV |
| Radwan (2013) | 55 | M | AC paracentesis, PCR, CMV, HSV, VZV IgG detected CMV, HSV, VZV IgM negative | |
| Rungger (1984) | 70 | M | Complement fixation titers | Contralateral eye enucleated |
| Schneider (2013) | 83 | F | PCR Aqueous | DM, HTN, CAD, anemia |
| Schneider (2013) | 78 | M | PCR | DM |
| Stewart | 51 | F | PCR, CMV IgG and IgM, pp65 antigen levels | CT and MRI only (2005) remarkable for leaking silicone breast implants |
| Takayama (2013) | 69 | M | PCR | DM, PDR, exudative lesion observed during vitrectomy |

 Table 2: Summary of previously reported cases of cytomegalovirus retinitis in the immunocompetent [20-28,35]

In 2008, Rafailidis and associates reported a review of severe CMV infections in immunocompetent patients. In their review, a total of 89 publications reported severe CMV infection in 209 immunocompetent patients. GI tract (colitis) and CNS abnormalities (meningitis, encephalitis, transverse myelitis) were the most frequent sites of severe CMV infections. Other areas included hematologic (anemia, thrombocytopenia, and thrombosis of the venous system), ocular involvement (uveitis) and lung disease (pneumonitis) [1]. In immunocompetent patients, primary CMV infection runs its course like an undifferentiated viral syndrome or is manifested by a mononucleosis like syndrome, "fever and myalgia". This has been thought to be benign and self-limiting; however, the medical literature shows a number of reports of severe clinical manifestation in immunocompetent patients [1]. There are a number of infectious, metabolic, inflammatory, and autoimmune conditions that can cause fever and malaise. Thus, a comprehensive evaluation of patients with fever and malaise should be undertaken, such as was done in this case report.

The most common CMV ocular presentations in decreasing frequency are: retinitis, vasculitis, retinal hemorrhages, keratic precipitates, anterior chamber cells, and vitritis [10].

Our patient's medical history and demographic information makes this a very unusual case presentation. The negative anticardiolipin antibodies ruled out antiphospholipid antibody syndrome as an etiology of her unexplained thrombosis. CMV-associated thrombosis has been linked to viral production of antiphospholipid antibodies [11] Thrombotic events independent of other predisposing factors in the setting of an acute infection needs more awareness.

The relationship between CMV infection and immunosenescence has not been thoroughly explored. Immunosenescence refers to the progressive decline in immune function secondary to age-associated changes. As T cells play a critical role in controlling infections in immunocompetent patients, changes to the cellular population explains the vulnerability to CMV. Alteration to T cell phenotype has been documented in the older population where repetitive T cell stimulation with CMV antigen is a driving force for immunosenescence [12]. The consequence of committing increased amounts of resources to manage CMV is the impaired overall function

of the immune system [13]. This deterioration is seen clinically as decreased efficacy of vaccination in the elderly (influenza, tuberculosis) due to deficient immune cell recruitment [14,15]. In 2007, Stowe and associates attempted to investigate herpesvirus reactivation in the aging population and found that overtime, there is a progressive increase in senescent CD8+ T cells without its costimulatory CD28 molecule. Presence of this molecule is necessary for its survival and clonal expansion. They compared young and elderly patients with known co-infection with CMV and EBV. Results from PCR of CMV in urine showed positivity in the elderly subjects and negativity in all of the younger subjects [5]. This suggests that the aged immune response is not effective in controlling viral reactivation.

Although no definitive conclusion can be drawn about CMV's vascular manifestations, studies strongly support a causal relationship [16]. The result of one study states that after the virus infects endothelial cells, expression of adhesion molecules triggers the thrombotic event [17,18]. Overtime, expression of Von-Willebrand factor was also seen to increase, which is a risk factor for arterial thrombosis. Viral activity appears to promote coagulation through alteration and injury to the vasculature [17]. However, vasculopathy is a rare complication of CMV infection and is mainly reported in immunosuppressive therapy patients in preparation for organ transplant or HIV positive individuals. Our patient does not fall into these risk groups and does not demonstrate any predisposing hematologic disorders. For this reason, this case report may partially advocate for the alternative belief that inflammation rather than immune dysfunction precipitates reactivation of latent CMV (15). The CRP and sedimentation rate of the patient were correspondingly elevated during the symptomatic period and returned to normal limits during resolution. CMV establishes latency in myeloid cells until stimulation from inflammatory cytokines induce differentiation into macrophages or dendritic cells. Two important cytokines, tumor necrosis factor-alpha and interferon-gamma, are responsible for this process, which ultimately allows for viral reactivation. This stimulatory rather than inhibitory mechanism suggests that cytokines may promote viral persistence [13,15]. In fact, the aforementioned expanding CD28 null T cells that increase with age produces both of these proinflammatory molecules [19]. This further points to the possibility that the virus may be causing this expansion for the purpose of its own survival. Interestingly, immunocompetent patients with a history of inflammatory bowel disease who develop CMV colitis have frequently elevated levels of these cytokines [1].

The benefit of antiviral therapy in immunocompetent patients have been conflicting. In 2008, Yoshinaga documented two separate cases of CMVR in diabetic patients that both resolved in one month without antiviral treatment [8]. Review of the literature showed that physicians will prescribe appropriate treatment for severe cases, including cases of ocular involvement. The generally self-limiting course of this disease makes attributing successful recovery to antiviral drugs difficult. In a case like our patient, prescribing foscarnet or ganciclovir is shown to block platelet aggregation, significantly reducing thrombogenic episodes [17]. Evidently, her vision and health did improve and return to normal. More randomized controlled trials are needed before a conclusive answer can be reached. As of 2020, of the 3116 articles involving CMV retinitis on PubMed, only two reviews of literature have been made regarding CMV retinitis in immunocompetent patients which shows that this is an extraordinarily rare phenomenon [36,37]. From these reviews of literature, it has been indicated that there have only been 10-12 reported cases where people develop CMV retinitis without the patients being on immunosuppressant drugs, having HIV, or having complications from diabetes [36,37]. This review of the literature indicates that there have been at least 18 reported cases regarding this disease within immunocompetent individuals. Using data from recent studies, it is estimated that the incidence rate of immunocompetence in individuals with CMV retinitis is 1.32/100 person decades [38]. This portrays how exceedingly infrequent this condition is in immunocompetent individuals, and how more research is needed to understand the idiosyncrasies of the immune system.

Conclusion

Complications from CMV infection in those who are deemed immunocompetent may not be as rare as we thought. It is important for physicians to consider cytomegalovirus infection in their differential diagnosis in patients presenting with fever and malaise even though they are in the low-risk group. Although use of gancyclovir therapy is not conclusive in the immunocompetent host, our patient showed improvement after treatment and may serve as confirmation in future cases to avoid ocular sequelae. The patient was not HIV positive, diabetic, nor were they on any medication that alters the immune system. It still remains an enigma

how this condition occurred in an immunocompetent host and only affected their eyes, especially when considering the severity of the condition. Perhaps with more immunoanalysis, the variability of the T-cell response across the human body may be better understood.

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