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Case Report

Cytomegalovirus retinitis followed by immune recovery uveitis in an elderly patient with rheumatoid arthritis undergoing administration of methotrexate and tofacitinib combination therapy

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ABSTRACT

Cytomegalovirus (CMV) retinitis is an opportunistic ocular infection most commonly observed in patients infected with human immunodeficiency virus (HIV). We present a rare case of CMV retinitis that developed in a non-HIV patient with rheumatoid arthritis (RA). Over the preceding 5 months, a family doctor had been treating the 78-year-old male patient with a combination therapy of methotrexate (MTX) and tofacitinib (TOF). CMV retinitis occurred when the patient's CD4+ T cells were low (196 cells/μl), and preceded the onset of *Pneumocystis* pneumonia. MTX and TOF were stopped after the diagnosis of CMV retinitis. While intravenous and intravitreal ganciclovir administration significantly improved the CMV retinitis, uveitis developed 3 months later during the maintenance therapy with oral valganciclovir, concomitantly with the recovery of the CD4+ T cell counts. As we believed this uveitis was caused by the immune reconstitution mechanism, we treated the patient with a retrobulbar injection of corticosteroids. During the 6 months following the cessation of MTX and TOF, there was no flare-up of the RA. Cases of CMV retinitis and immune recovery uveitis in RA patients have been rarely reported in the literature. In the current case, the intensive immunosuppressive therapy in this elderly patient might have been the cause of this unusual opportunistic complication of RA.

1. Introduction

Cytomegalovirus (CMV) retinitis is an opportunistic ocular infection that is most commonly observed in patients infected with human immunodeficiency virus (HIV) [1]. Following a latent period after the primary exposure, reactivation of CMV occurs within the body of immunocompromised hosts, especially when the CD4+ T cell counts in these patients fall below 50 cells/μL. Prior to the introduction and common use of highly-active antiretroviral therapy, CMV retinitis was seen in 20–40% of all HIV patients [2]. Non-HIV immunocompromised patients are also susceptible to CMV retinitis, albeit less frequently. In most cases, these patients are under intensive cytotoxic or immunosuppressive therapies for hematologic malignancies, organ transplantation, and autoimmune diseases.

Even though the recent progress in molecular-targeted therapy has led to remarkable improvements in the outcomes of patients with rheumatoid arthritis (RA), adverse effects including the reactivation of latent microorganisms such as *Mycobacterium tuberculosis* or hepatitis B virus are a major concern when using these new agents. However, CMV retinitis in RA patients has been rarely reported in the past literature, even after these new agents became available.

Our current report presents a case of CMV retinitis that developed in an elderly RA patient during the administration of methotrexate (MTX) and tofacitinib (TOF) combination therapy. At the time of the CMV retinitis onset, the level of the CD4+ T cells was relatively low. CMV retinitis symptoms improved after the

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cessation of the MTX and TOF therapy and the subsequent initiation of systemic and local administration of ganciclovir. However, thereafter the patient developed *Pneumocystis* pneumonia (PCP) and immune recovery uveitis. The clinical course of this patient resembled that seen for severely immunocompromised HIV patients. Thus, intensive immunosuppressive therapy in this elderly RA patient might have been the cause of the unusual opportunistic complication observed in this case.

2. Case report

A 78-year-old man visited his family doctor with complaints of morning stiffness and polyarthralgia lasting for more than 3 months. The physical examination revealed bilateral swelling and tenderness of wrists, metacarpophalangeal (MP) and proximal interphalangeal (PIP) joints. Elevated levels of C-reactive protein (5.3 mg/dl) and matrix-metalloproteinase-3 (362.2 ng/ml) were found. The patient fulfilled the 1987 American College of Rheumatology criteria for classification of RA, and was started on 8 mg/week of MTX, which was then increased to 12 mg/week. After 4 weeks of treatment, the family doctor added 10 mg/day of TOF due to the poor response to MTX alone. After initiation of the combination therapy with MTX and TOF, the patient subsequently achieved a low disease activity.

At 5 months after starting the combination therapy, the patient noted a visual disturbance of his left eye and visited a local ophthalmologist. He was then referred and admitted to our hospital with a tentative diagnosis of acute retinal necrosis. Upon admission, fundus examination revealed yellow-white necrotizing retinitis in the periphery with soft exudate and occlusive vasculitis in his left eye, all of which suggested viral retinitis (Fig. 1a). The MTX and TOF combination therapy was stopped and the patient immediately received a retrobulbar injection of triamcinolone. A few days later, however, fundus findings worsened with expansion of the necrotizing retinitis (Fig. 1b). Table 1 shows laboratory data obtained on admission. The patient had lymphocytopenia with decreased CD4+ T cell counts (196 cells/μL) and CD4/CD8 ratio (0.36). IgG antibodies were positive against CMV, herpes simplex virus (HSV), and varicella zoster virus (VZV). Serology for HIV and human T-cell leukemia virus type-1 was negative. The CMV antigenemia assay (SRL, pp65 antigens detected in leukocytes) was negative, and plasma CMV-DNA (BML, geni-Q CMV®) was marginally positive at 200 copies/ml. Multiplex PCR (SRL, Japan) that simultaneously amplifies DNA of 6 distinct herpesviruses specifically identified CMV-DNA in aqueous humor at a titer of 2.2×10^7 copies/ml (reference: undetectable). Based on these virological data, especially on the result of Multiplex PCR, 2 expert ophthalmologists, who independently examined patient's optic fundi, reached a consensus that the patient was suffering from CMV retinitis.

The patient received a 2.5 mg/kg intravenous administration of ganciclovir (GCV) every 12 h in conjunction with intravitreal injections of 300 μg/0.075 mL GCV (a total of 4 times) after obtaining written informed consent for the off-label use of intravitreal GCV, which was approved from the Pharmaceutical Affairs Council of Gunma University Hospital. Screenings of the patient by a whole body computed tomography (CT) scan, gastroscopy and colonoscopy found no other CMV-related organ involvement. Two weeks later, the patient was switched from GCV to 900 mg/day of oral valganciclovir (VGCV) for the purpose of CMV retinitis maintenance therapy. The patient was discharged on day 26 of his hospital stay.

Two weeks later, he was admitted to a different hospital due to fever and general fatigue, and transferred to our hospital again with a diagnosis of PCP. The patient received a therapeutic dose of sulfamethoxazole-trimethoprim (ST). Table 2 shows laboratory findings obtained at the time of his 2nd admission. Lymphocytopenia (569 cells/μL) along with decreased CD4 cells (124 cells/μL)

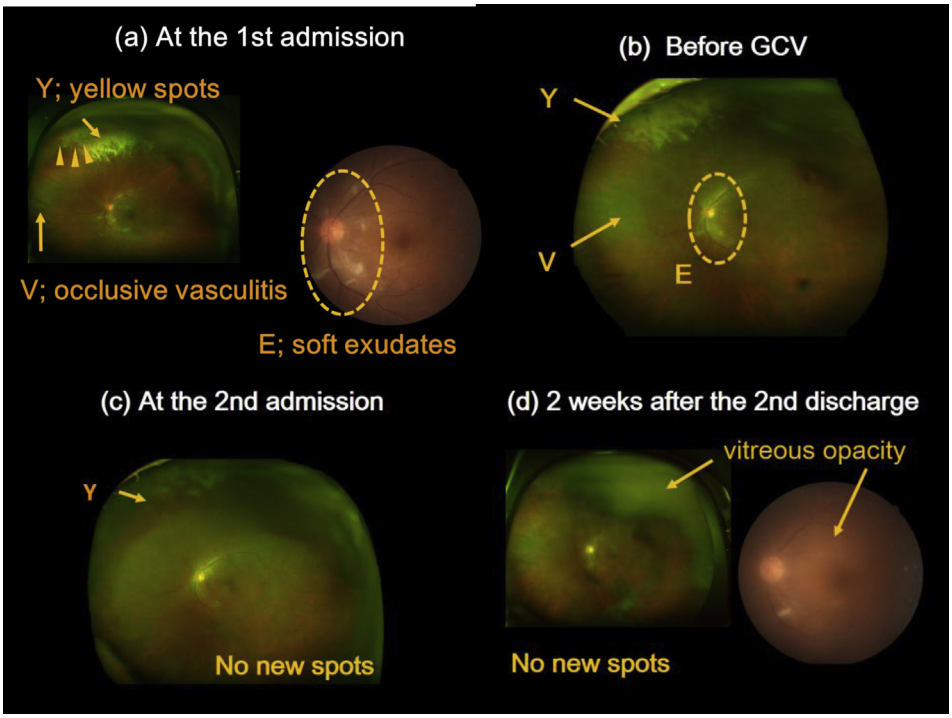

Fig. 1. Fundus findings obtained at (a) the 1st admission. Yellow spots (Y), occlusive vasculitis (V) and soft exudates were detected in the left retina. The arrow head shows retinal hemorrhage; (b) just before the administration of GCV, and which showed worsening of the retinitis; (c) the 2nd admission, and which showed improvement of the retinitis; and (d) 2 weeks after the 2nd discharge, and which showed vitreous opacity that was diagnosed as IRU.