

Cytomegalovirus retinitis following corticosteroid overdose for Vogt-Koyanagi-Harada disease

Sana Khochtali, Ahmed Mahjoub¹, Tarek Dridi, Imen Ksaa, Nesrine Abroug, Moncef Khairallah

A 33-year-old patient was diagnosed with acute Vogt-Koyanagi-Harada (VKH) disease and was prescribed prednisolone (1 mg/kg/day) and azathioprine (2.5 mg/kg/day). She mistakenly took an excessively high dose (4 mg/kg/day) of prednisolone for 14 days. The erroneous dose of corticosteroids was progressively corrected. Several weeks after initial presentation, the patient developed a polymerase chain reaction-proven bilateral cytomegalovirus retinitis, with extensive occlusive arteritis in the right eye. Systemic immunosuppressive therapy was temporarily discontinued and viral retinitis was successfully managed with systemic and intravitreal ganciclovir. Corticosteroids were reintroduced to control recurrent VKH disease. Final visual acuity was 20/1000 in the right eye and 20/50 in the left eye.

Key words: Corticosteroids, cytomegalovirus retinitis, immunosuppressive agents, retinal vasculitis, Vogt-Koyanagi-Harada disease

Cytomegalovirus (CMV) retinitis is a sight-threatening ocular infection, typically affecting immunocompromised individuals. It may present as fulminant hemorrhagic retinitis characterized by full thickness necrotizing retinitis and prominent retinal haemorrhages, as indolent granular retinitis, or as frosted branch angiitis.^[1,2] It is commonly seen in patients with human immunodeficiency virus (HIV) infection and a low CD4 count (<50 cells/mm³). It can also occur as an opportunistic condition in patients with systemic non-HIV-related immunosuppression mainly including hematologic malignancies, immunosuppressive therapy, and organ transplantation.^[1,2] It has also been reported following intraocular or periocular steroid administration.^[3]

We herein report the case of a patient with acute Vogt-Koyanagi-Harada (VKH) disease who developed bilateral

CMV retinitis after accidentally using an excessive dose of corticosteroids in association with an immunosuppressant agent.

Case Report

A 33-year-old woman with unremarkable medical history was referred to our department with a one-month history of bilateral blurring of vision. At presentation, best-corrected visual acuity (BCVA) was 20/500 in both eyes. The anterior chamber was quiet and there were 2+ vitreous cells in both eyes. Fundus examination showed bilateral multifocal exudative retinal detachment (ERD) [Fig. 1a and b]. Fluorescein angiography revealed early delayed choroidal perfusion and late multilobular subretinal dye pooling OU [Fig. 1c-f]. Swept-source optical coherence tomography (SS-OCT) showed bilateral extensive ERD with subretinal septa, retinal pigment epithelium (RPE) undulations, and a marked choroidal thickening [Fig. 1g and h].

A diagnosis of acute VKH disease was made. Results of pre-treatment investigations including complete blood count (CBC), erythrocyte sedimentation rate (ESR), liver and renal functions tests, syphilis serology, and chest X-ray was normal or negative. The patient was prescribed oral prednisolone 1 mg/kg/day and azathioprine 2.5 mg/kg/day. Three weeks after presentation, BCVA was 20/100 in both eyes and there was a significant improvement of ERD, OU. However, the patient reported having mistakenly received four times the prescribed dose (4 mg/kg/day) of prednisolone for 14 days. CBC showed elevated leukocyte count at 15100 cells/mL with high neutrophil count at 13000 cells/mL. Haemoglobin was 13 g/dL and platelet count was 400000 cells/mL. The erroneous dose of corticosteroids was progressively corrected with the help of endocrinologists.

Six weeks later, the patient complained of decrease in vision in the right eye (RE). BCVA was 20/1000 in the RE and 20/80 in the left eye (LE). Slit-lamp examination showed granulomatous keratic precipitates, 1+ cells in the anterior chamber, and 2+ cells in the vitreous in the RE. The anterior chamber was quiet and there were 2+ cells in the vitreous in the LE. Fundus examination revealed sunset-glow fundus OU, a diffuse vascular sheathing and narrowing with multiple retinal haemorrhages in the RE. It also showed areas of small granular punctate yellowish retinal lesions predominantly in the inferonasal periphery of the LE [Fig. 2a and b]. Fluorescein angiography revealed marked retinal arterial occlusions in the RE, and optic disc hyperfluorescence in the LE [Fig. 2c and d]. SS-OCT angiography showed a diffuse loss of microvasculature in the superficial and deep retinal capillary plexuses in the RE [Fig. 2e and f]. SS-OCT demonstrated hyperreflectivity and thickening of the inner retinal layers, with a few intraretinal cysts and some shallow

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Department of Ophthalmology, Fattouma Bourguiba University Hospital, Faculty of Medicine, University of Monastir, Monastir, ¹Department of Ophthalmology, Farhat Hached University Hospital, Faculty of Medicine, University of Sousse, Sousse, Tunisia

Correspondence to: Dr. Moncef Khairallah, Department of Ophthalmology, Fattouma Bourguiba University Hospital, 5019 Monastir, Tunisia. E-mail: moncef.khairallah@rns.tn

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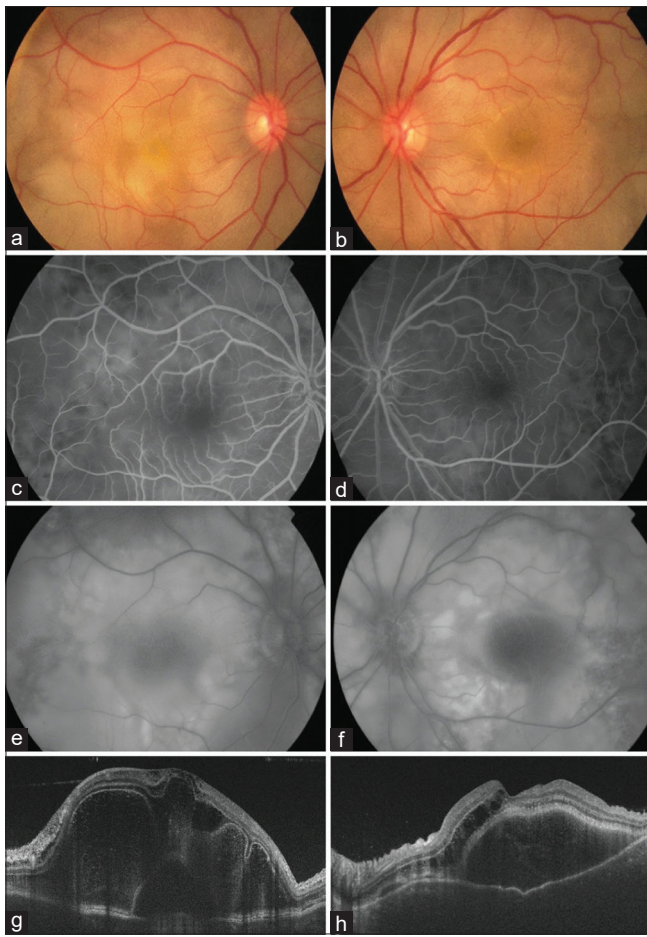


Figure 1: (a and b). Colour fundus photographs at presentation show bilateral multifocal exudative retinal detachments (ERD), OU. (c and d). Early-phase fluorescein angiograms reveal focal areas of delayed choroidal perfusion. (e and f). Late-phase fluorescein angiograms show multilobular subretinal dye pooling. (g and h). Initial structural swept-source OCT shows bilateral extensive ERD with subretinal septa, retinal pigment epithelium undulations, and a marked choroidal thickening

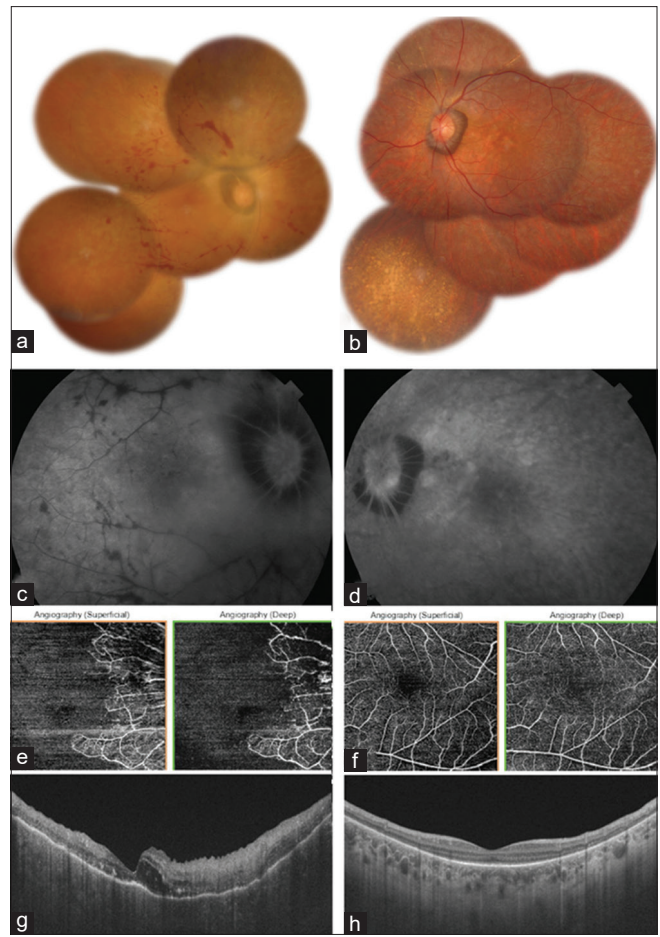


Figure 2: (a and b). Composite colour fundus photographs, nine weeks after presentation, shows bilateral sunset-glow fundus, bilateral peripapillary subretinal fibrosis associated with retinal pigment epithelium (RPE) proliferation, diffuse vascular sheathing and narrowing with multiple retinal haemorrhages in the right eye (RE), and a patch of granular retinitis in the inferonasal periphery of the left eye (LE), consistent with CMV retinitis. (c and d). Late-phase fluorescein angiograms reveal occlusion of the main retinal arterial branches in the RE, and optic disc hyperfluorescence OU. Note the presence of a peripapillary hypofluorescence due to the masking effect of peripapillary RPE proliferation. (e and f). Swept-source OCT angiography shows a diffuse loss of microvasculature in the superficial and deep retinal capillary plexuses in the RE, and projection of superficial vessels onto the deep capillary plexus in the LE. (g and h). Swept-source OCT shows hyperreflectivity and thickening of the inner retinal layers, with a few intraretinal cysts and some shallow RPE undulations in the RE, with no obvious macular abnormalities in the LE

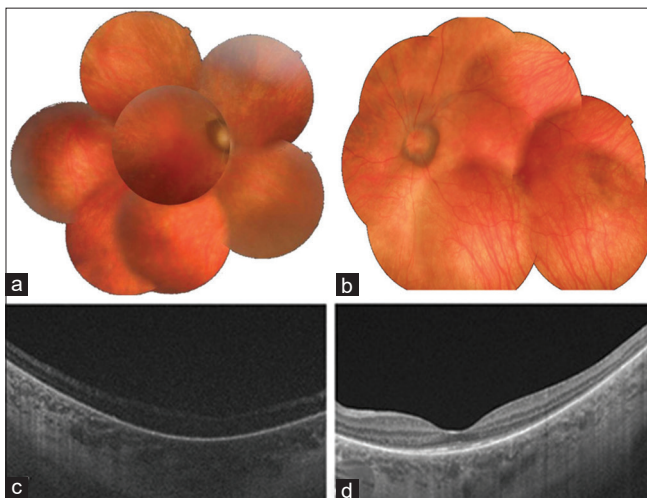


Figure 3: (a and b). Composite colour fundus photographs, one year after initial presentation, show a sunset-glow fundus with peripapillary subretinal fibrosis associated with retinal pigment epithelium proliferation OU, and residual gliotic sheathing of vessels around the optic disc in the right eye. (c and d). Swept-source OCT shows some degree of residual retinal atrophy in the macular area in the right eye, and quite normal findings in the left eye

RPE undulations in the RE. It showed no obvious macular abnormalities in the LE [Fig 2g and h].

The newly developed clinical and multimodal imaging findings, except for the sunset-glow fundus, were considered to be atypical for VKH disease. Alternative diagnoses were considered including a masquerade syndrome, infectious disease initially mimicking VKH disease, and superimposed infectious condition. Systemic corticosteroids and azathioprine were withdrawn. An extensive work-up including CBC, syphilis serology, C-reactive protein, ESR, serum protein electrophoresis, chest X-ray, Mantoux test, QuantiFERON-TB Gold, human immunodeficiency virus serology, thoraco-abdominopelvic computed tomography scan, and MRI of the brain was performed. Results were all

normal or negative. Real-time polymerase chain reaction (PCR) on aqueous sample for CMV, varicella zoster virus, herpes simplex virus 1, and herpes simplex virus 2 was performed. It was positive for CMV DNA (2000 copies/ml), confirming opportunistic CMV retinitis.

The patient was given intravenous ganciclovir treatment (5 mg/kg twice a day) for 6 weeks and 2 intravitreal ganciclovir injections (2 mg/0.1 ml) in the RE. CMV retinitis was controlled, but the patient developed a VKH disease recurrence with bilateral choroidal thickening, RPE folds in both eyes, and a shallow ERD in the RE on SS-OCT. Repeated PCR on aqueous sample showed a significant reduction in viral load (200 CMV DNA copies/ml). VKH disease recurrence was managed with oral prednisolone, at an initial dose of 0.5 mg/kg/day introduced while the patient was still receiving intravenous antiviral treatment. Systemic steroids were then progressively tapered.

One year after initial presentation, the patient was receiving 5 mg/day of prednisolone and dexamethasone drops twice a day, OU. BCVA was 20/1000 in the RE and 20/50 in the LE. There was a marked fundus depigmentation without associated anterior chamber or vitreous inflammatory reaction [Fig. 3]. The patient developed no CMV retinitis recurrence.

Discussion

This patient, initially diagnosed with acute VKH disease, developed bilateral CMV retinitis after using by mistake an overdose of corticosteroids in association with azathioprine. CMV retinitis was indolent in type, and was associated with moderate vitritis, and unilateral major retinal arterial occlusions. It occurred in combination with pre-existing inflammatory changes related to VKH disease, and therefore diagnosis was challenging. Such infectious sight-threatening condition could be overlooked or misinterpreted as a worsening of the primary non-infectious uveitis.^[4] However, the unusual occurrence of retinal vasculitis mainly manifesting as occlusive arteritis was highly suspicious in our patient.

Active CMV retinitis has rarely been reported in HIV-negative patients under systemic immunosuppression for chronic non-infectious uveitis including Behçet uveitis, VKH disease, and idiopathic uveitis. It developed in all these cases following intraocular or periocular corticosteroid injection in one side.^[3-6] Although our patient did not receive any local steroids, she mistakenly took excessively high doses of systemic steroids for a couple of weeks, in association with azathioprine.

CMV retinitis in HIV-patients is classically characterized by areas of retinitis typically in a perivascular distribution, associated with venous sheathing in areas of retinitis and mild anterior chamber and vitreous inflammation.^[1,2] A recent study by Ho M *et al.* showed that non-HIV patients are more likely to have prominent vitritis, retinal arteritis, and extensive vascular occlusions beyond the site of retinitis.^[7] All these distinctive features were seen in the present case. The spectrum of clinical manifestations of CMV retinitis in non-HIV patients is wide, probably due to varying degrees of immunocompromise between affected patients. Timely recognition of such manifestations is of utmost importance to avoid misdiagnosis and subsequent delay in initiating appropriate treatment.^[7]

Occurrence of CMV retinitis in HIV-negative patients under systemic immunosuppressive therapy requires adjustments to their initial corticosteroid and/or non-corticosteroid immunomodulating therapy to be adequately made.

Furthermore, antiviral therapy should be maintained at least until regression of the retinitis lesions and recovery of patients' immune status.^[3] Both oral prednisolone and azathioprine were temporarily discontinued in our patient. She was treated with intravenous and intravitreal ganciclovir. But, oral valganciclovir is not available in our country. Transient withdrawal of immunosuppressive therapy resulted in VKH disease recurrence, and this led to the reintroduction of medium-dose oral corticosteroid therapy in combination with antiviral agent to control intraocular inflammation. No recurrence of CMV retinitis or related retinal detachment occurred, but a severe visual loss persisted in the RE due to extensive arterial occlusions involving the macula.

Conclusion

In summary, CMV retinitis may occur in patients with non-infectious uveitis as a consequence of highly aggressive systemic immunosuppressive therapy. Signs of viral retinitis overlap with signs of the pre-existing non-infectious uveitis. Both diagnosis and management are challenging.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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