Cytomegalovirus ocular infection: A series of atypical presentations

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Cytomegalovirus (CMV) is an enveloped, double stranded DNA virus and like other viruses in herpesviridae family to which it belongs, stays latent for long periods following infection. It is transmitted systemically by way of infected blood products, secretions, or via trans placental route[1,4]. CMV is a common causative agent of viral infection with sero-prevalance rates which can be varying from 30-100% in different study populations[5,7]. Incidence of CMV seropositivity also increases with age[5,8]. Ocular CMV infections are proven to be the causative agent in presumed CMV retinitis in 1964. But ocular CMV infection was a disease so extraordinarily rare that few ophthalmologists ever observed a case before the start of the acquired immunodeficiency syndrome (AIDS) pandemic[1,2]. CMV retinitis has now emerged as a common cause of infectious retinitis worldwide. In immunocompetent persons, CMV infection rarely produces clinical disease. However, CMV is an important cause of morbidity and mortality in immunocompromised individuals. Due to the advances in antiviral therapy, visual prospects following active CMV infection has improved greatly.

Although serological tests are now widely available, due to high and variable seropositiviy among different populations diagnosis of CMV ocular infection is dependent upon high level of clinical suspicion. The hallmark lesion of CMV retinitis is a necrotizing, full-thickness retinitis with areas of active retinitis having a granular, dirty-white appearance that results due to retinal cell destruction. As the virus attacks the endothelial cells of blood vessels commonly leading to focal haemorrhage. CMV often initially affects retinal tissue adjacent to major retinal blood vessels or the optic disc. Juxtaposition of retinal haemorrhages with large zones of white, granular necrosis has led appearance of CMV retinitis to be described as either "pizza-pie" or "cottage cheese and ketchup". The retinal arteries and veins, in the areas of necrosis commonly appear sheathed, secondary to vasculitis. A second pattern of CMV retinitis has been labelled "granular" or "brushfire border". In this appearance, the focal granular infiltrates enlarge slowly across a line, leaving ever-increasing areas of destroyed retina and atrophic retinal pigment epithelium behind. The brushfire border is commonly seen in CMV retinitis lesions anterior to the equator and haemorrhages, vitreous cells are being less prominent features with this pattern.

However typical CMV retinitis features occur at a very low CD count levels and may have different presentations[2,8]. Awareness of the typical as well as the atypical presentations of ocular CMV infection provide a distinct advantage to the clinician and present an opportunity for early identification, prompt and proper management. Failure to identify these early and essential features would lead to devastating visual outcome. Authors here aim to shed light upon atypical presentations of serologically confirmed CMV ocular infection to raise awareness among clinicians.

Case series

We present four serologically confirmed CMV infections with atypical ocular manifestations, presented to the National Eye Hospital of Sri Lanka, during the period of 2012 to 2014.

Case 1

Ms. PC, 19 year old patient was diagnosed with Acute Lymphoblastic Leukaemia (ALL) was on treatment. She had completed one cycle of chemotherapy which contained prednisolone, vincristine, and anthracycline. She was referred to us by the oncology team due to a development of unilateral blurring of vision over 2-3 weeks which was later accompanied by photophobia. She had no other co-morbidities apart from clinical features of depression for which she was already receiving counselling and treatment. On examination best corrected visual acuity was 6/6 on right and 6/60 on left with normal intra ocular pressures. She had corneal precipitates with cells (3+) in anterior chamber. Dilated examination revealed a vitreous inflammation with small segment of peri-vascular haemorrhages along the superior arcade with prominent macular star formation on the affected side.

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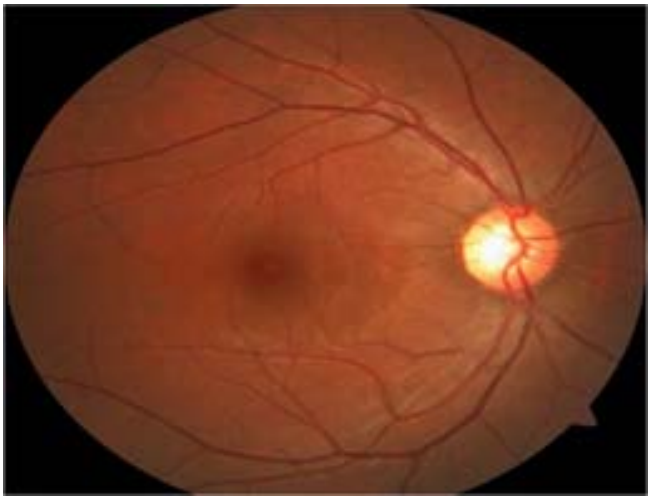
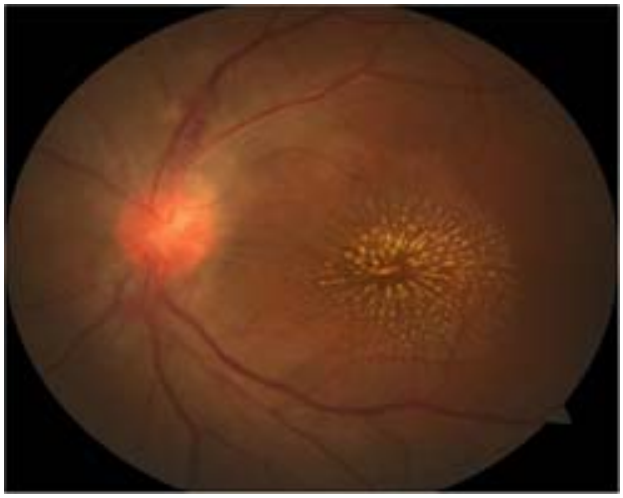
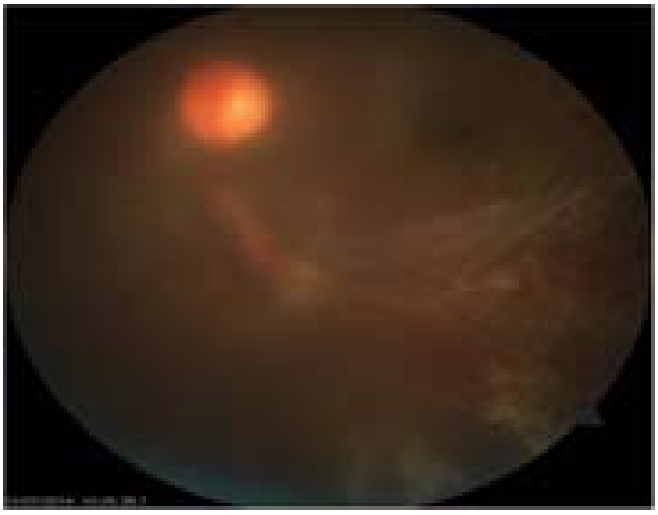
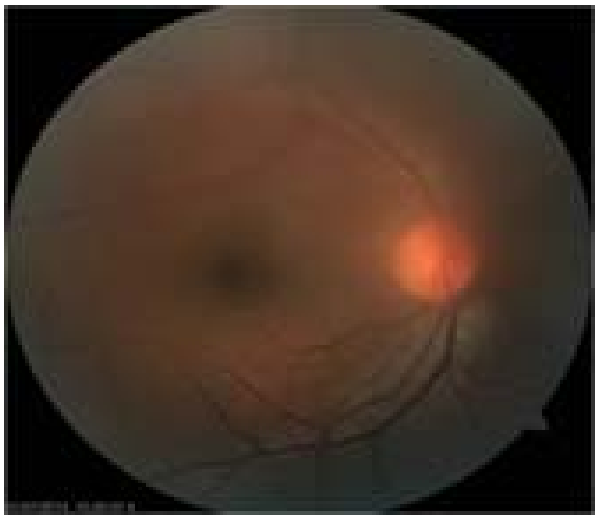




Routine investigations carried out revealed a WBC count of 3,700 (N- 63% , L- 33%), haemoglobin (Hb) 9.2 g/dl with normocytic, normochromic cell indices and a platelet count of 162,000/mm^3. Erythrocyte sedimentary rate (ESR) was 38 mm/ 1st hour and blood glucose levels were normal. Due to her clinical background serology tests were performed and Cyto-megalovirus Ig G and Ig M were both positive, HSV serology negative and Venereal Disease Research Laboratory test (VDRL) was non-reactive. Patient was treated with intra-vitreal gancyclovir and was suggested to start intra venous gancyclovir. However patient developed myelo suppression during chemo-therapy for the primary pathology followed by a super added lung infection to which the patient did succumb.

Case 2





Mr. HN 26 year old patient diagnosed with ALL about 1 year ago, after being investigated for pyrexia of unknown origin. He was on maintenance therapy and developed deterioration of vision over 2-3 weeks with associated photophobia and an eye pain more severe on left side.

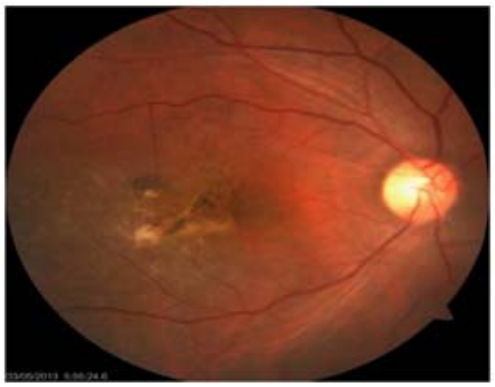
On examination, his visual acuity was 6/60 on left side, and 6/18 on right side. Intra ocular pressure was 20 mmHg in the left side and 16 mmHg in the right. He had a left sided hypopyon and occasional cells on right anterior chamber. Right side patient had an early posterior polar cataract. Dilated fundus examination of the left side revealed vitreous inflammation with areas of burned out necrosis with areas of granular exudates with haemorrhages along peripheral infero-temporal arcade. Routine investigations revealed WBC count of 7,800 / mm^3 (N- 85% L- 14%), Hb 9.0 g/dl with normal cell indices and a platelet count of 140,000 / mm^3. Blood picture showed normocytic normo-chromic anaemia with few megaloblastoid forms with a mild thrombocytopenia.

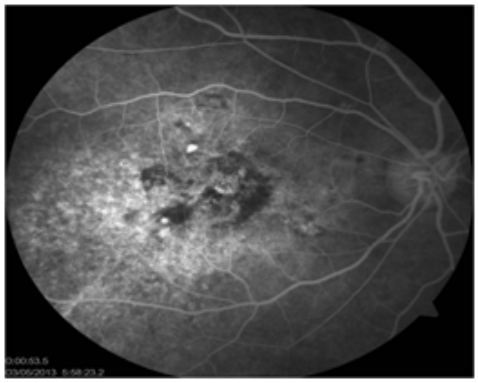
Cytomegalovirus serology revealed reactive Ig G titre and equivocal Ig M titre. Other investigations such as ESR, mantoux, VDRL and HSV serology all were within normal limits. Aqueous paracentesis was done and sample was sent for a real time PCR (qPCR) and patient was treated with intra-vitreal injections of gancyclovir on clinical grounds. qPCR results reported up as strongly positive. As advised by infectious diseases specialist he was started on Intravenous Ganciclovir 14 days and received the regime under medical supervision due to the possibility of myelo-suppression along with tropical steroids. Patient improved clinically following treatment with left sided BCVA improved to $6/9^{-}$ and anterior segment was quiet and vitreous inflammation subsided.

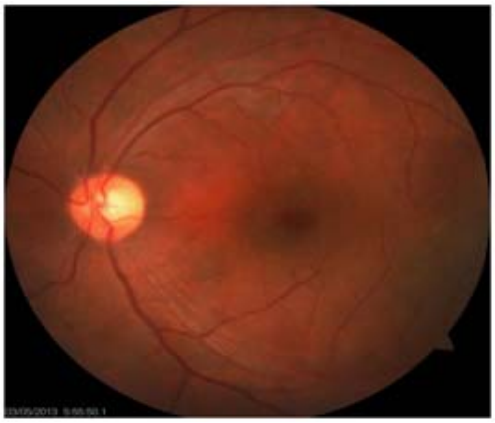
Case 3

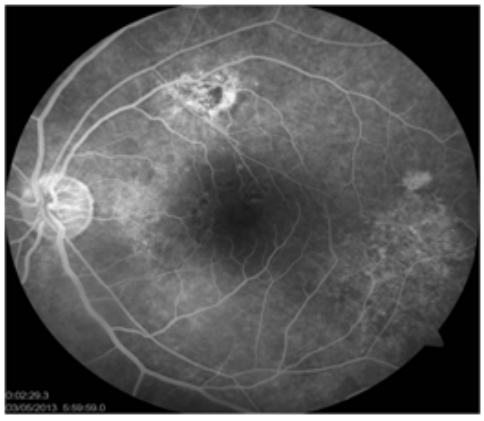
Previously apparently healthy, 47 year old teacher, Mr SR presented with deterioration of vision of about two months duration. His visual acuity was recorded 6/60 on right side and 6/9 on the left. IOP and anterior segment examination was unremarkable. On fundal examination vitreous was inflamed and large whitish yellow exudates found along with a haemorrhagic areas. His routine investigations were normal. CMV IgG and IgM were positive but the rest of the serological tests including HIV screening, HSV antibodies, anti nuclear antibodies (ANA) were negative. Patient was referred to immunologist to assess patient's immune competency and common causes of immune deficiencies were ruled out. Intra vitreal gancyclovir were administered. However patients vision on right side could not be improved beyond 6/36 even after resolution of active inflammation.

Case 4









Mr. LA, 49 years old, self employed patient presented with reduction in vision and ocular discomfort for 2/52 duration. No previous ocular diseases were noted and he was detected to be having elevated blood glucose level 6 months back and was on dietary control only. General examination revealed no significant findings with VA on right side being 6/60 and left side 6/24. He had keratic precipitates and active anterior chamber inflammation. Dilate fundus examinations findings were grade II nuclear sclerosis with vitreal cells, left eye being more severe. Investigations revealed an increased fasting blood glucose value of 148 mg/dl with HbA1c over 10. ANA, VDRL, HSV serology and HIV screening all were negative. CMV serology showed a rising titer done over two weeks apart. A dose of intra vitreal gancyclovir (4mg in 0.1 ml) administered with tropical steroids followed by sub tenon steroid injection to right side and inflammation subsided with BCVA of 6/36 on right and 6/9 on left side.

Discussion

Although CMV ocular infections are mostly associated with immune deficient states and cause essential threat to sight if not treated prompt and properly reported cases of CMV retinitis in apparently "immune competent" patients are found in literature. Systemic review completed by Rafailidis et al. showed 89 articles reporting on severe CMV ocular infections in 290 immunocompetent adults with several other studies[9-11].

Although CMV retinitis commonly seen in advanced stages AIDS (i.e. when CD 4 counts < 50). But many evidences of early occurrences has been documented. Apart from HIV infection other immunodeficiency conditions are also known to associate with CMV ocular infections, haematological malignancies such as leukemia, primary immune deficiencies[12-15].

Clinically most characteristic features of active CMV retinitis would be, perivascular yellow white lesions with focal hemorrhages giving rise to "Cottage cheese and ketchup" appearance or vascular sheathing and perivascular inflammation leading to "frosted branch" appearance, periphery sparing macular involvement in CMV retinitis is also reported as seen with the above case[16-18].

Though not a common etiological agent, CMV also well known to involve anterior segment often mild but at times may even be severe enough to give rise to a hypopyon[19-20].

Awareness of the typical as well as the atypical presentations of ocular CMV infection provide a distinct advantage to the clinician by presenting an opportunity for early identification prompt and proper management leading to prevention of sight threatening complication of CMV ocular infections.

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