

## Challenges of managing HIV cytomegalovirus co-infection in the presence of pancytopenia

Niveditha Vupmandla<sup>1</sup>, Rajendra Prasad Shivaswamy<sup>2</sup>, Subhash Chandra B J<sup>3</sup>, Shashidhara K C<sup>4</sup>

From <sup>1</sup>Medical Student, <sup>2</sup>Associate Professor, <sup>3</sup>Professor and Former Head, <sup>4</sup>Professor, Department of General Medicine, JSS Medical College and Hospital, JSSAHER, Mysuru, Karnataka, India

### ABSTRACT

A 60-year-old male patient who presented with generalized weakness and low-grade fever was diagnosed to be human immunodeficiency virus (HIV) positive with a CD4 count of 17. Routine laboratory investigations revealed pancytopenia. Serum cytomegalovirus (CMV) DNA polymerase chain reaction (PCR) was positive and funduscopy showed CMV retinitis in the right eye. The patient was started on tablet valganciclovir. After 2 weeks, the patient was brought back in an altered sensorium. He was found to have hyponatremia which was corrected. He was started on antiretroviral therapy and tablet valganciclovir was continued. The patient came back again after one and a half months with a urinary tract infection and fissure-in-ano. He was found to have severe neutropenia. Valganciclovir was stopped. He was started on injection granulocyte colony-stimulating factor. The patient clinically improved and his hematological parameters became normal. Patients having HIV and CMV co-infection with pre-existing pancytopenia have to be closely monitored as the medicines used for treatment can exacerbate the existing conditions.


**Key words:** Cytomegalovirus retinitis, Human immunodeficiency virus cytomegalovirus co-infection, Pancytopenia, Valganciclovir

In retroviral-positive patients, cytomegalovirus (CMV) infection happens to be a prevailing opportunistic infection. CMV manifestations in human immunodeficiency virus (HIV)-positive individuals may cause severe end-organ dysfunction involving the central nervous system, eyes, gastrointestinal tract, and respiratory system. Neurological manifestations of CMV infection are diffuse encephalitis, ventriculoencephalitis, cerebral mass lesions involving the brain or transverse myelitis, and polyradiculomyelitis involving the spinal cord [1]. The most frequent ocular lesion seen in HIV-positive patients is CMV retinitis [2]. Symptoms such as anorexia, fever, diarrhea, abdominal pain, wasting, weight loss, and a wide range of lesions ranging from mild inflammation and erosions to esophageal and enterocolic ulcers are seen when CMV infects the gastrointestinal tract. The prevailing cause for lower GI bleeding in retroviral disease-positive patients is due to CMV infection. The earliest manifestation of CMV colitis is bleeding without diarrhea [3]. Conventionally, in starkly immunosuppressed retroviral disease patients, CMV lung infection is seen and has high early mortality due to its association with clinical pneumonitis. The hematological manifestations in HIV-positive

patients with CMV are unclear. This is because according to some studies, HIV/acquired immunodeficiency syndrome (AIDS) is itself a prothrombotic state with an increased incidence of thromboembolism [4,5]. Isolated or multilineage cytopenias due to ineffective hematopoiesis or increased peripheral destruction and fostering cytopenias may encompass some of the hematological manifestations [6]. Anemia being the prime frequent manifestation also happens to be a satisfactory clinical indicator to gauge the underlying immune status in retroviral disease-positive patients. Pancytopenia is also noted. As the disease progresses further, the abnormalities become more extreme. Many opportunistic infections, inflammation, malnutrition, nutritional deficiencies, malignancy, and drug toxicity worsen HIV infection. The current treatment regimens have fewer hematological side effects compared to older treatment regimens [7]. Therefore, CMV coinfection in HIV-positive patients is itself associated [8] with increased progression of the disease.

### CASE REPORT

A 60-year-old male patient presented to the outpatient department with complaints of loss of appetite, easy fatigability, weakness for the past one and a half years, and low-grade fever for 15 days. The

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**Correspondence to:** Rajendra Prasad Shivaswamy, Associate Professor, Department of General Medicine, JSS Medical College and Hospital, JSSAHER, Mysuru, Karnataka, India. E-mail: srpmcd@gmail.com

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patient also gives a history of significant unintentional weight loss of around 10–15 kgs in the past 6 months. He is a reformed alcoholic and had no prior comorbidities.

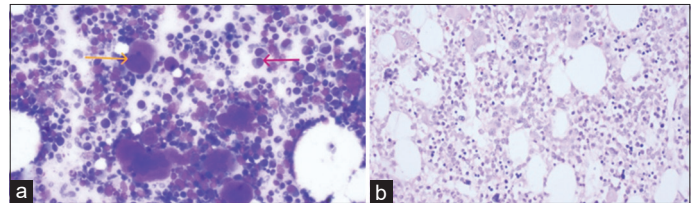
On examination, he had pallor and a poor build with a body mass index of 18.4. He was afebrile with a heart rate of 96/min, blood pressure of 120/70 mm Hg, respiratory rate of 22 cycles/min, and was maintained at room air saturation. Abdominal examination revealed hepatosplenomegaly.

A complete blood count (CBC) on admission showed pancytopenia. On further workup, the patient was incidentally found to be HIV positive with a CD4 count of 17. In the right eye, CMV retinitis was detected on fundoscopy. An increase in plasma cells, cellular bone marrow with trilineage hematopoiesis, and dysplasia was revealed on bone marrow biopsy (Fig. 1). Serum CMV DNA PCR turned positive (8805 copies/ $\mu$  mL). Ultrasound abdomen showed a fatty liver.

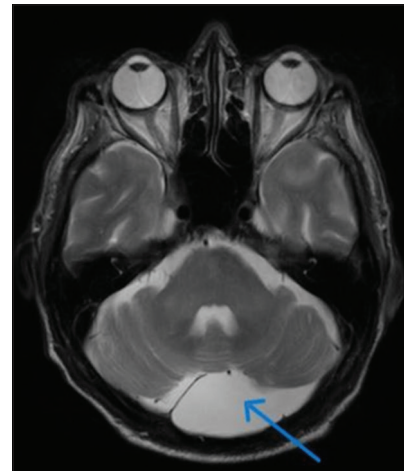
He was started on tablet valganciclovir and cotrimoxazole prophylaxis and was discharged. Twenty days later, the patient was brought to the emergency ward with complaints of irrelevant talk, generalized weakness, difficulty walking, and vomiting. The patient continued to have pancytopenia. Liver function tests showed mild hyperbilirubinemia with hypoalbuminemia and mildly deranged liver enzymes. Renal function test showed hyponatremia and was corrected after which the patient's sensorium improved. Ultrasound abdomen showed a fatty liver with echogenic gallbladder sludge. Computed tomography of head showed a small chronic lacunar infarct in the left external capsule of the lentiform nucleus with a large arachnoid cyst. Magnetic resonance imaging showed chronic small vessel ischemic changes with altered signal intensity in the right uvea and vitreous and an arachnoid cyst in the posterior fossa (Fig. 2).

Neurosurgeon advised conservative management. The nerve conduction study was suggestive of motor and sensory axonopathy. Cerebrospinal fluid (CSF) analysis showed mild elevation in protein with normal cells. A provisional diagnosis of HIV polyneuropathy was made. The patient was initiated on anti-retroviral treatment (tenofovir, lamivudine, and dolutegravir) and valganciclovir was continued on discharge.

The patient was again admitted one and a half months later with a history of fever with burning micturition and bleeding per rectum. On evaluation, the patient had pallor and CBC showed pancytopenia with severe leukopenia (140 cells/cumm). The patient had not come for follow-up monitoring of CBC. The patient was admitted to isolation intensive care unit in view of severe leukopenia. Tablet cotrimoxazole and tablet valganciclovir were stopped in suspicion of their contribution to the persistence of pancytopenia. He was started on injection meropenem and injection Granulocyte CSF and tablet voriconazole. Blood transfusion was done. A surgical examination revealed a fissure in-ano and was treated conservatively. Urine culture grew *Escherichia coli* and sputum culture showed *Acinetobacter baumannii*. During the course in the hospital, the patient developed right epididymo-orchitis with collection, left epididymitis, and bilateral funiculitis. USG-guided aspiration



**Figure 1:** (a) Bone marrow aspirate (Leishman stain) in  $\times 40$  magnification, showing increase in megakaryopoiesis, erythropoiesis and a mild increase in plasma cells (Yellow arrow - megakaryocyte, Magenta arrow - plasma cell); (b) Bone marrow biopsy (hematoxylin and eosin stain) in  $\times 40$  magnification showing cellular bone marrow with trilineage hematopoiesis, trilineage dysplasia, and increase in plasma cells



**Figure 2:** Magnetic resonance image showing arachnoid cyst in the posterior fossa as indicated by the blue arrow

was done and antibiotics were continued. At the time of discharge, hemoglobin percent was 9.3 g %, total count white cell count was 9570 cells/cumm, and platelet count was 1.68 lakhs/cumm all of which indicated a gradual improvement in the blood parameters. After 15 days, the patient came for a follow-up, walking without support, and was symptomatically better.

## DISCUSSION

Cytomegalovirus is the most common viral opportunistic infection in people with AIDS, with clinical disease occurring in up to 40% of patients with progressive HIV infection [9]. CMV can present in various ways, including retinitis, colitis, esophagitis, pneumonitis, and neurological disorders.

Neurological complications in HIV infection are stage specific and vary depending on the individual's stage of systemic HIV infection. The altered immune response, particularly during severe deficiency in cell-mediated defenses seen in late-stage AIDS, is responsible for this stage specificity. In one of the studies, neurological manifestations attributed to HIV itself include tuberculous meningitis (34%), AIDS-related dementia (24%), CNS toxoplasmosis (22%), cryptococcal meningitis (15%), presumed CMV encephalitis (7%), progressive multifocal leukoencephalopathy (PML) (5%), primary CNS lymphoma (5%), and bacterial meningitis (4%) [10]. In addition, peripheral

nervous system disorders, including painful neuropathy, can also occur [11].

Among the neurological manifestations of CMV disease in HIV infection, CMV retinitis is the most common presentation, often diagnosed clinically. Other presentations include encephalitis, polyradiculopathy, and multifocal neuropathy. Neglected CMV retinitis can progress to blindness but can be easily diagnosed through ophthalmological examination. CMV polyradiculopathy may manifest as subacute leg weakness, paresthesia, or urinary retention, progressing to ascending paralysis and potentially fatal outcomes. Multifocal neuropathy typically affects peripheral nerves such as the radial, ulnar, and peroneal nerves, but cranial nerves can also be involved. Ventricular encephalitis may present with confusion, cranial nerve palsies, and hyperreflexia. Diffuse micronodular encephalitis can be challenging to diagnose as patients are often asymptomatic. Detection of CMV DNA in CSF and neuroimaging are important tools for diagnosing polyradiculopathy, encephalitis, and neuropathy [10]. Neutrophilic CSF pleocytosis is a common finding in CMV presentations [12].

CMV infection typically occurs in HIV patients with CD4 counts below 50–100 cells/ $\mu$ L. However, cases of CMV gastrointestinal disease have been reported in patients with CD4 counts >100 cells/ $\mu$ L [13]. CMV retinitis usually occurs when CD4 counts are below 50 cells/ $\mu$ L but other factors such as a rapid decline in CD4 counts, high HIV viral loads, and the presence of CMV viremia may also be correlated with its occurrence. It is important to note that CD4 counts are a surrogate marker for immune dysfunction and do not always reflect functional abnormalities in the immune system. CMV retinitis can still occur even with a normal CD4 count during the latent period between the quantitative restoration of CD4 counts and the actual functional restoration of immunity [14].

Treatment for CMV retinitis involves CMV antiviral therapy, such as systemic or intravitreal therapy [15]. Induction therapy is administered until the retinitis becomes inactive, followed by lower-dose maintenance therapy. Close observation is necessary to evaluate response to therapy and monitor for drug-induced complications. In cases of immediate sight-threatening disease, intravitreal therapy is used in conjunction with systemic therapy. Oral valganciclovir is often preferred due to its good oral bioavailability, ease of administration, and reduced risk of complications compared to intravenous therapy [15]. Both ganciclovir and valganciclovir can cause bone marrow suppression, particularly leukopenia [16]. The severity and frequency of these hematologic abnormalities can vary among different patient populations. However, caution should be exercised when using ganciclovir and valganciclovir in patients with pre-existing cytopenias [17]. Hematopoietic growth factors such as granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage-CSF (GM-CSF) can be utilized to manage myelosuppression caused by drugs such as ganciclovir and valganciclovir [18]. These growth factors are particularly useful when continuous anti-CMV treatment is required, and the potential risks of switching to Foscarnet outweigh the risks of

myelosuppression. By facilitating the dosing of ganciclovir and valganciclovir, hematopoietic growth factors can help to optimize the treatment approach [19]. Furthermore, they can reduce the risk of bacterial infections by enhancing neutrophil chemotaxis and phagocytosis. Importantly, these growth factors are generally well tolerated by patients [20].

## CONCLUSION

Cytomegalovirus infection has to be suspected in an HIV-positive patient whenever the CD4 count is very low. It can involve multiple organs with varied manifestations. There are challenges in the management of CMV infection, especially if the patient is having hematological complications since the drugs used in the treatment of CMV can worsen the pre-existing hematological complications. Strict monitoring of such patients may yield better results.

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