Multiorgan Involvement Due to Cytomegalovirus Infection in AIDS

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Cytomegalovirus (CMV) infection is a relatively late complication of AIDS. Like other viruses contributing to co-morbidity of HIV infection, cytomegalovirus has the propensity to cause multiorgan involvement. We report the case of a 34-year-old seropositive man who presented with bilateral lower limb weakness and symptomatic pallor. He was already on antiretroviral drugs for a month prior to presentation. Detailed clinical examination and laboratory investigations revealed cytomegalovirus polyradiculoneuropathy associated with bone marrow dysplasia. Dysplasia of haematopoeitic cell lines occurs in 30% to 70% of HIV infected patients, and is often indistinguishable from myelodysplastic syndrome. However, in our case, the bone marrow picture reverted back to normal with treatment of the CMV infection, pointing to a possible role of CMV as the causative agent of bone marrow dysplasia. Moreover, CMV has been incriminated as a pathogen producing the immune reconstitution inflammatory syndrome. The onset of the disease in our case one month after initiation of HAART strongly raises the possibility of this being a case of CMV related IRIS. This is the first reported case where IRIS has presented with CMV polyradiculoneuropathy and bone marrow dysplasia. We would like to highlight that in today's era of HIV care, clinicians should be aware of the possibility of multiorgan involvement by CMV, for appropriate management of this disease in the background of AIDS.

Key-Words: AIDS, cytomegalovirus, multiorgan involvement.

A 34-year male patient diagnosed seropositive for HIV-1 in 2003, presented to us in February 2006 with the main complaints of weakness of both lower limbs for 6 weeks. The weakness of his lower limbs was insidious in onset and gradually progressive over this period of time. He could stand on his own but was gradually finding it difficult to walk without assistance associated with a difficulty in getting up from sitting position. He further complained of an inability to feel his footwear and the ground that he was standing on. Moreover, he had involuntary slipping out of footwear on attempted walking. He had no history suggestive of any weakness or sensory loss in his upper limbs. The lower limb weakness was not associated with any sense of tightness, fasciculations, abnormal movements or any back pain. He gave no history suggestive of bladder or bowel involvement. He also complained of exertional dyspnea which had increased over the last four months and was now associated with swelling of both his feet. There was no history of wheeze, orthopnea, chronic diarrhea, postural dizziness or syncope. The patient had no addictions and had been married for 16 years. He has two living children. He describes an episode of skin disease strongly suggestive of zoster involving the ophthalmic division of the left trigeminal nerve about 3 years before. He was diagnosed with extrapulmonary tuberculosis involving the abdominal lymph nodes 14 months before for which he had received 6 months of WHO category 1 antitubercular therapy under Directly Observed Therapy Short-course (DOTS) supervision. He was on antiretroviral therapy for the last 1 month with Stavudine, Lamivudine and Nevirapine. His CD4 count at the initiation of highly active antiretroviral therapy (HAART) was 114 cells/mL.

General survey revealed the presence of moderate pallor and bipedal pitting edema. Examination of the nervous system revealed radiculoneuropathy in both lower limbs, as evidenced by gross wasting, hypotonia, predominantly proximal weakness with a patchy sensory loss involving the L3-S2 dermatomes on the right and L2-S2 dermatomes on the left. The ankle jerks were absent bilaterally and the knee jerks diminished on both sides. The plantar response was bilaterally flexor. There were no features of cranial nerve, cerebellar, pyramidal or extrapyramidal involvement. Both direct and indirect ophthalmoscopy did not reveal any abnormality. Examinations of all the other systems were clinically normal except for the presence of a flow murmur in the pulmonary area.

His baseline biochemical tests revealed a normal fasting plasma glucose urea creatinine and electrolytes, a low serum albumin (2.3 gm/dL) and an elevated alkaline phosphatase (533 IU/mL). The complete heamogram revealed the presence of macrocytic anemia and leucopenia (Table 1). Chest radiographs, abdominal ultrasound and routine urinanalysis revealed no abnormalities. Sensori-motor neuropathy in all four limbs and bilateral S1 radiculopathy was documented on nerve conduction velocity (NCV) studies. Cytomegalovirus (CMV) IgM levels in blood were within normal range but the CMV IgG levels were elevated at 2.813 [< 0.9 Normal]. The cerebrospinal fluid (CSF) analysis showed a predominantly neutrophilic pleocytosis with a cell count of 740 cells/cmm including 70% neutrophils. The CSF protein was elevated at

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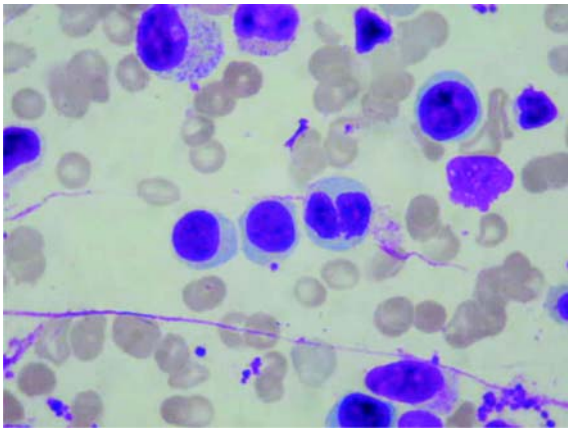
172mg/dL and the sugar levels corroborated with normal values. The CSF CMV DNA PCR was positive, while the CSF Mycobacterial and Herpes Simplex Virus (HSV) PCR were negative. The HIV 1 viral load following admission was 3,000 copies/mL. A bone marrow histopathological examination was performed which showed a cellular marrow with depressed erythropoeisis, features of dyserythropoeisis, normal maturation of granulocytes, increased megakaryopoeisis and features of dysplasia along with a moderately increased plasma cell percentage of 6%-8%. The impression of the pathologist was myelodysplastic syndrome [MDS-RA].

Vitamin B12 assay was normal (374pg/mL). His CD4 count at this time was 128 cells/mL. Viral markers for hepatitis band C were non-reactive as serum toxoplasma antibodies were. The blood counts at 4 weeks of follow-up showed significant improvement over pretreatment values (Table 1).

He was diagnosed to be a case of acquired immunodeficiency syndrome (AIDS) with cytomegalovirus polyradiculoneuropathy and HIV associated myelodysplastic syndrome (MDS-RA).

He was treated with parenteral gancyclovir at a daily dose of 5 mg/kg body weight, to which he showed marked improvement with a weight gain of 8 kg [17%] over the initial 14 days of therapy. He is now ambulatory and on maintenance dose of gancyclovir.

Figure 1. Bone marrow dysplasia due to CMV infection in AIDS.



Discussion

End organ disease due to CMV occurs late in the course of HIV infection and various neurologic diseases like ventriculoencephalitis and ascending polyradiculopathy are common [1]. The incidence of CMV disease has declined rapidly and significantly from 7.34 cases per 100 patient years (py) in the pre-HAART era to 0.75 cases per 100 py in the HAART era [2]. Our patient had already been on HAART for four weeks with a viral load of 3,000 copies/mL, suggesting appropriate response to anti-retroviral therapy. Interestingly normal neurological assessment of the upper limbs did not corroborate with the NCV study, highlighting sub-clinical neurological involvement by CMV in HIV infection. The short duration of Stavudine based HAART and the cessation of anti-tubercular drugs eight months prior to the onset of neurological symptoms, rationally rules out drug induced neuropathy. CMV-specific IgM remains undetectable early in the course of primary or reactivation CMV disease, which explains this finding in our patient.

Dysplasia of one or more haematopoeitic cell lines occurs in 30% to 70% of HIV infected patients, and is often indistinguishable from myelodysplastic syndrome [3]. Anemia with HIV is common in our country, but marrow dysplasia has been rarely documented. The pathophysiology of bone marrow involvement includes infection of more than one haematopoeitic cell lines. CMV infects bone marrow progenitor cells, making them less responsive to colony stimulating factors and also affects the marrow stromal cells causing decreased local production of haematopoeitic growth factors [4]. However, direct infectious bone marrow affection (with either HIV or CMV), leading to bone marrow dysplasia is recorded in medical literature as a rare cause of myelodysplastic syndrome [5]. Documentation of CMV associated bone marrow dysplasia in HIV patients has not been published from this subcontinet. Although reactivation of CMV infection is less likely than primary infection to be clinically important, the temporal profile of CMV mediated multiorgan involvement following four weeks of HAART strongly suggests an immune

Table 1. Complete haemograms before and after treatment with gancyclovir

	Pre-treatment (6 months)	Post-treatment
Haemoglobin (gm/dL)	9.2	13.4
WBC count (X 10^9/L)	3.6	4.9
Differential count	$N_{73}L_{11}M_{13}E_{01}B_{00}$	$N_{62}L_{33}M_{02}E_{04}B_{00}$
Platelets (X 10^9/L)	485	412
MCV (fl)	105	78.6
MCH (pg)	36.6	26.1
MCHC (g/L)	34.4	33.2
ESR (mm/h)	42	24

reactivation pathogenesis. However, CMV has been rarely incriminated as a pathogen producing the recently identified Immune Reconstitution Inflammatory Syndrome (IRIS) [6].This case combines the neurological and hematological associations of CMV disease in a HIV patient and underlines the significance of identifying CMV as an opportunistic pathogen, etiologically related to several HIV – related clinical syndromes.

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