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Case Report

CASE REPORT

Cytomegalovirus ventriculoencephalitis presenting with hydrocephalus in a patient with advanced HIV infection

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Abstract

A 38-year-old lady with advanced human immunodeficiency virus (HIV) infection presented to the emergency department with headache, vomiting and fluctuating alertness for 3 weeks. On examination, she had tachycardia, bilateral papilledema, restriction of upward gaze, gaze-evoked nystagmus and signs of meningeal irritation. Magnetic resonance imaging of the brain showed hydrocephalus and periventricular high T2-signal regions with restriction on diffusion-weighted imaging. Polymerase chain reaction done on the cerebrospinal fluid obtained after the insertion of an external ventricular drain was positive for cytomegalovirus (CMV). She was treated with intravenous ganciclovir followed by oral valganciclovir with which she made a dramatic recovery. CMV ventriculoencephalitis can present with hydrocephalus in HIV-infected individuals. A high index of suspicion must be maintained to diagnose this disease and start appropriate therapy on time.

INTRODUCTION

Cytomegalovirus (CMV) can cause infections of the central nervous system (CNS) in patients with human immunodeficiency virus (HIV) infection. CD4+ T cells are crucial for keeping a check on uncontrolled CMV replication and deficiency of CD4+ T-cells in advanced HIV infection predisposes these patients to the development of CMV infections [1]. Although the prognosis of this disease was poor in earlier times, the advent of highly active combination antiretroviral therapy (cART) has been a game changer.

CASE REPORT

A 38-year-old woman presented to us with complaints of holocranial headache, loss of weight and appetite for the past 3 weeks. This was followed by a fluctuating level of alertness for the past 1 week. During this time, she had one episode of projectile vomiting, which was not bilious or blood-stained. She did not have fever, photophobia, blurred vision or seizure. One week before her presentation to our center (at the onset of fluctuating alertness and vomiting), she was evaluated at another hospital for these symptoms, where a diagnosis of HIV-1 infection was made. She was started on cART (tenofovir 300 mg, lamivudine 300 mg and efavirenz 600 mg) and a week later referred to us for further management. She did not have any other comorbid illnesses, addictions, allergies or significant family history.

At the time of presentation to the emergency department at our hospital, her pulse rate was 136 beats/minute, blood pressure was 100/60 mmHg in the right upper limb and respiratory rate was 24 breaths/minute. She did not have fever and was drowsy, but arousable. Neurological system examination showed bilateral papilledema. There was restriction of upward

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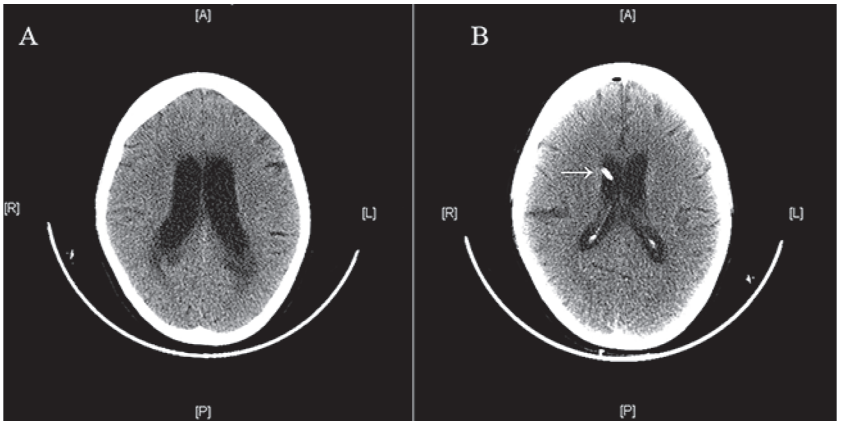

Figure 1: Plain computed tomography of the brain showed moderate communicating hydrocephalus with periventricular hypodensities suggestive of transependymal CSF seepage. (**A**) Before and (**B**) after insertion of ventriculoperitoneal shunt indicated by white arrow.

gaze, bilateral gaze-evoked nystagmus and neck stiffness suggesting meningeal irritation. Examination of other systems was unremarkable.

Since the patient presented with these symptoms and signs in the setting of recently diagnosed HIV infection, a clinical diagnosis of subacute meningoencephalitis was made. The differential diagnosis considered included tuberculous meningoencephalitis, cryptococcal meningoencephalitis, toxoplasmosis, other fungal infections like histoplasmosis and aspergillosis, CMV ventriculoencephalitis, neurosyphilis and HIV encephalopathy. Noninfectious causes, such as carcinomatous meningitis, Kaposi sarcoma, CNS lymphoma, sarcoidosis and immune reconstitution inflammatory syndrome (IRIS), were also considered.

The initial blood investigations showed anemia and leukopenia (Table 1). HIV test detected HIV-1 antibodies, and CD4+ T-cell count was 46 cells/µl. Plain computed tomography of the brain showed communicating hydrocephalus with periventricular hypodensities suggestive of transependymal cerebrospinal fluid (CSF) seepage (Fig. 1). An external ventricular drain (EVD) was inserted to relieve the raised intracranial pressure, and CSF obtained during the procedure was sent for analysis. It showed elevated counts with lymphocytic predominance, elevated protein and normal glucose. Gram stain and India ink preparation did not show any microorganisms, CSF Xpert® MTB/RIF assay was negative, bacterial and fungal cultures did not show any growth and CSF cytospin did not show any abnormal cells. However, CSF polymerase chain reaction (PCR) detected CMV deoxyribonucleic acid (DNA). The EVD was later removed, and a ventriculoperitoneal (VP) shunt was inserted. Subsequently, contrast-enhanced magnetic resonance imaging (MRI) of the brain showed resolution of hydrocephalus. There were numerous periventricular high T2-signal regions with restriction on diffusion-weighted imaging. Similar signals were also seen lining the ependymal surface of the lateral ventricles, which also demonstrated faint enhancement (Fig. 2).

These radiological findings, along with a positive CMV PCR in CSF in the setting of advanced HIV infection, led to a final diagnosis of CMV ventriculoencephalitis and HIV-1 infection (World Health Organization clinical stage IV).

The patient was treated with intravenous ganciclovir for 2 weeks, followed by oral valganciclovir. Her cART regimen comprising once daily tenofovir 300 mg, lamivudine 300 mg and efavirenz 600 mg was continued. Given a CD4+ T-cell count <50 cells/µl, she was also started on primary prophylaxis against *Pneumocystis jirovecii* and Mycobacterium avium–intracellulare complex with daily trimethoprim/sulfamethoxazole and weekly azithromycin, respectively.

The patient had dramatic clinical improvement after relief of raised intracranial pressure with the EVD (later VP shunt) and ganciclovir therapy. At the time of discharge, she had full resolution of neurological deficits and was independently performing all activities of daily living. She was assigned to an HIV counselor for education regarding the need to adhere to therapy, need for regular follow-up and testing of her spouse and children. She is on outpatient follow-up and doing well.

DISCUSSION

CMV ventriculoencephalitis is a rare disease, which almost always occurs in the setting of advanced immunosuppression. CNS infection with CMV was seen in 2% of patients before the era of potent antiretroviral drugs [2]. Now, the incidence can be presumed to be much lower. CD4+ T-cells are required to suppress the uncontrolled replication of CMV, and these cells are depleted in HIV infection [1]. Most reported cases have occurred in the setting of HIV infection and a CD4+ T-cell count of <50 cells/µl [3].

CMV ventriculoencephalitis presents with subacute alteration in level of alertness, cranial neuropathies, gaze-evoked nystagmus and features of raised intracranial pressure due to hydrocephalus. Oculomotor palsy may be seen but is uncommon. Other presentations of CMV-associated CNS infection in HIV-infected individuals include necrotizing polyradiculomyelitis, a Guillain–Barre-like syndrome of ascending weakness with hyporeflexia, motor predominant neuropathy and vasculitis [4–6].

Diagnosis of CMV infection requires demonstration of a cytopathic effect. The cytomegalic cell is a macrophage that contains intranuclear and intracytoplasmic inclusions of CMV particles and resembles 'owl's eyes' [7]. This is a pathologic hallmark of the disease. In our patient, we did not demonstrate the presence of a characteristic cytopathic effect. However, the clinical presentation in the setting of advanced HIV infection, characteristic MRI features, PCR positive for CMV and dramatic response to

Table 1: Lab investigations.

Investigations	Result
Hemoglobin (g/dl)	9.2 (11–15)
Total count ($\times 10^9$ cells/L)	2 (4-12)
Differential count (%)	N 29, L 13, M 8, E1
Platelet count ($\times 10^9$/L)	95 (150-450)
HIV, HBV, HCV serology	Positive for HIV-1 antibodies
CD 4+ T-cell count (cells/µl)	46 (500–1500)
Serum sodium (mmol/l)	131 (135–145)
Serum potassium (mmol/l)	3.3 (3.5–5)
Serum creatinine (µmol/l)	58.34 (53–106)
Serum total/direct bilirubin (µmol/l)	3.93/2.22 (5–21/1.7–5.1)
Serum total protein/albumin (g/l)	76/31 (60–80, 35–50)
AST (U/l)	115 (10–30)
ALT (U/l)	87 (10–40)
Alkaline phosphatase (U/l)	159 (30–120)
CSF counts (/cu mm)	WBC 80 (N12, L56, M24), RBC 630
CSF glucose (mmol/l)	2.72 (Concomitant GRBS: 6.22) (2.5 - 4.4)
CSF protein (mg/dl)	108 (15–45)
CSF cytospin	No abnormal cells
CSF Gram stain and culture	Negative
CSF Xpert® MTB/RIF assay	Negative
CSF India ink preparation and fungal culture	Negative
Serum and CSF cryptococcal antigen	Negative
Toxoplasma IgM and IgG	Negative
CSF PCR for multiple viruses	CMV positive

Normal ranges are given in parenthesis. AST, aspartate aminotransferase; ALT, alanine aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; IgM, immunoglobulin M; IgG, immunoglobulin G.

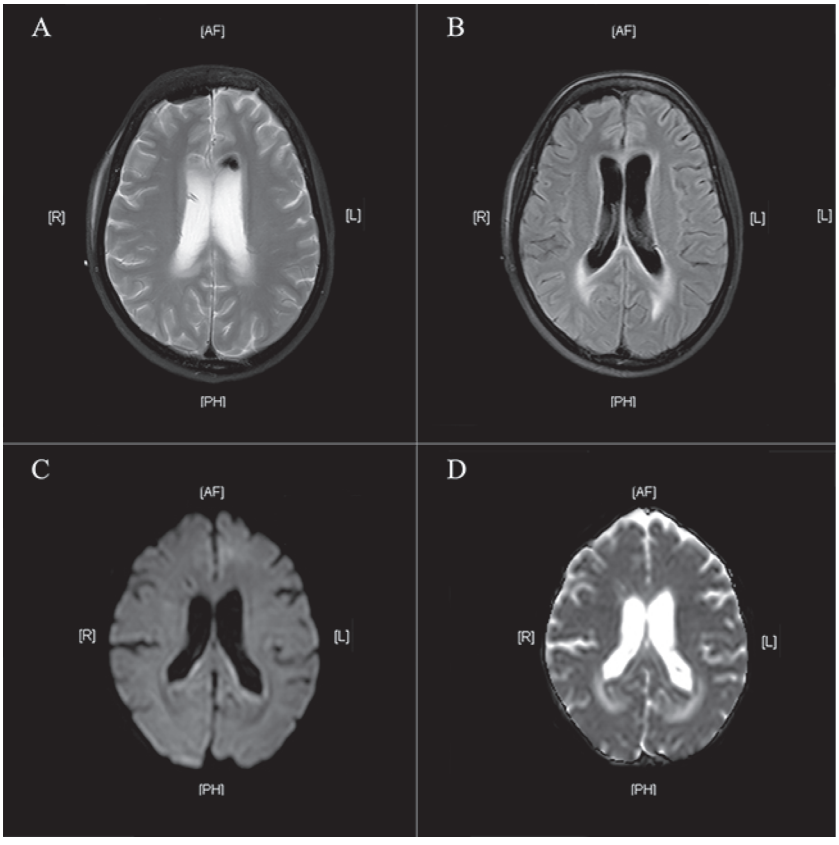

Figure 2: Contrast-enhanced MRI of the brain showing numerous periventricular high T2-signal regions with restriction on diffusion-weighted imaging (DWI). (**A**) T2-weighted image, (**B**) T2 FLAIR (fluid-attenuated inversion recovery) image, (**C**) DWI and (**D**) apparent diffusion coefficient image.

ganciclovir therapy were considered sufficient evidence for the diagnosis. Neuropathological imaging of patients has demonstrated extensive periventriculitis with ependymal and subependymal necrosis [8]. Destruction of the ependyma and inflammation leads to thick fibrinous exudate that accumulates at the base. This basal exudate can block CSF flow by occluding the flow through the aqueduct of Sylvius or by blocking the resorption of CSF by the arachnoid granulation leading to hydrocephalus [8]. This picture is very similar to that seen in tuberculous meningitis. Therefore, a high degree of suspicion needs to be maintained, especially in patients with advanced HIV infection, to differentiate these two diseases. This is especially important because treatment of CNS tuberculosis requires prolonged multidrug therapy with steroids, which may cause clinical worsening of CMV ventriculoencephalitis. Mistaking such a worsening for paradoxical IRIS can add to the confusion.

MRI finding of periventricular enhancement and subependymal high-signal intensities with diffusion restriction may help in differentiating CMV ventriculoencephalitis from other causes of meningoencephalitis in HIV-infected patients [9]. Imaging of the CNS can also help exclude other diagnoses. CSF PCR has high sensitivity and specificity in diagnosing CMV infection of the CNS [10].

Treatment of CMV neurologic disease depends on its severity. Severe disease is treated with a combination of intravenous ganciclovir and foscarnet, while mild disease can be treated with oral valganciclovir. If the patient is cART-naïve, it is recommended to wait for 14 days before starting cART to prevent IRIS. It is crucial to exclude coexistent CMV retinitis before initiation of cART as IRIS at this site can be sight-threatening. Maintenance therapy with oral valganciclovir should be given until CD4+ T-cell counts increase to >100 cells/μl and remain so for at least 6 months.

In conclusion, CMV ventriculoencephalitis is an uncommon but severe CNS infection in HIV-infected individuals that can present with hydrocephalus. Characteristic MRI findings and CMV PCR in the CSF can be used to make a diagnosis of CMV ventriculoencephalitis in the appropriate clinical setting.

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CONFLICT OF INTEREST STATEMENT

None declared.

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ETHICAL APPROVAL

The work meets ethical guidelines and adheres to local legal requirements.

CONSENT

The patient's informed signed consent was obtained.

GUARANTOR

K.J.J. is the guarantor of this paper.

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