



Case Report

Unexpected case of cryptococcal meningoencephalitis in a patient with long-standing well-controlled HIV infection

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ABSTRACT

Cryptococcal meningoencephalitis (CM) classically occurs in individuals with advanced HIV infection, solid organ transplants, or other immunocompromising conditions. We report a case of fatal CM in a 78-year-old woman with well-controlled HIV infection who had delayed diagnosis, persistently elevated intracranial pressure and pleocytosis of the cerebrospinal fluid. Initial suspicion for CM was low due to her relatively high CD4⁺ T cell counts, which likely contributed to greater inflammation.

1. Introduction

Cryptococcal meningoencephalitis (CM) is an opportunistic fungal infection that most commonly occurs in individuals with advanced Acquired Immunodeficiency Syndrome (AIDS) and CD4⁺ lymphopenia. There is increasing recognition and diagnosis of cases in non-Human Immunodeficiency Virus (HIV)-infected individuals including those with no apparent immunocompromising condition [1]. While the role of cellular immunity in host defense against cryptococcosis is self-evident [2], there is increasing evidence for a role of humoral immunity in resistance against CM [3]. Clinical presentation, management, and prognosis differ depending on the underlying immune deficit. A potentially detrimental complication of cryptococcosis is a paradoxical inflammatory response in the setting of fungal clearance, known as cryptococcal-immune reconstitution inflammatory syndrome (C-IRIS) in HIV-infected individuals [2] or post-infectious inflammatory response syndrome (PIIRS) in immunocompetent individuals [4]. We report a rare case of CM in a HIV-infected patient with long-standing virologic control and relatively high CD4⁺ T cell counts whose course was complicated by PIIRS-like clinical picture.

2. Case

A 78-year-old HIV-infected African American woman presented to the emergency department with trouble swallowing, nausea and vomiting for 1 week (day –7 to 0). She was recently hospitalized in the same institution (day –30 to day –26) with headache, nasal congestion and

was diagnosed with sinusitis. HIV infection was diagnosed in 1996 and had been well controlled on combination antiretroviral therapy (cART) of emtricitabine, rilpivirine, and tenofovir alafenamide. She had good adherence to cART. Her recent CD4⁺ and CD8⁺ T lymphocyte counts were 435 (39%) and 347 (31%) cells/μL, respectively, and her HIV viral load (VL) had been undetectable for the past 10 years. Her medical conditions included type 2 diabetes mellitus, hypertension and coronary artery disease. She was born in Saint Thomas, US Virgin Islands and had been living in the Bronx, New York. Her baseline (day 0) laboratory values showed: hemoglobin 11.8 g/dL (reference: 12.2–15.3 g/dL), white blood cell count (WBC) 4.1 k/μL (reference: 4.8–10.8 k/μL), lymphocytes 22%, platelets 62 k/μL (reference: 150–200 k/μL), blood urea nitrogen 11 mg/dL (reference: 5–20 mg/dL), and creatinine 0.9 mg/dL (reference: <1.50 mg/dL).

She was admitted to a general medicine floor in stable clinical condition with a normal neurological exam. She underwent endoscopy that showed gastritis (day 5) and her presenting symptoms had improved, but then she developed involuntary movement of her bilateral hands (day 8) that progressed to waxing and waning mental status (day 13), then to complete obtundation and left facial droop (day 15). Magnetic resonance imaging of the brain showed small punctate right parietal subcortical acute infarct, white matter microvascular ischemic disease and mild communicating hydrocephalus. Patient was intubated for airway protection and transferred to the intensive care unit (ICU) (day 15). Electroencephalogram did not reveal epileptic activity. Chest x-ray showed left lower lobe opacity concerning for pneumonia in the setting of an aspiration event. Lumbar puncture (LP) showed opening pressure

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Table 1
Serial cerebrospinal fluid (CSF) opening pressures and analyses.

Day	Opening pressure (cmH ₂ O)	Closing pressure (cmH ₂ O)	WBC counts per mm ³	Protein (mg/dL)	Glucose (mg/dL)	CrAg titer	CSF culture
15	42	10.5	6	85	78	20,480	<i>Cryptococcus neoformans</i> var. <i>grubii</i>
18	56	n/a	74	70	143	n/a	<i>Cryptococcus neoformans</i> var. <i>grubii</i>
20	13	n/a	n/a	n/a	n/a	n/a	n/a
22	16	n/a	n/a	n/a	n/a	n/a	n/a
27	22	10	44	69	38	2560	No growth
44	n/a	n/a	26	n/a	n/a	1280	No growth

(OP) of 42 cmH₂O and closing pressure of 10.5 cmH₂O. WBC of the cerebrospinal fluid (CSF) was 6 cells/μL (reference: <5 cells/μL) (lymphocyte 88%, monocytes 12%), glucose was 78 mg/dL (serum glucose 260 mg/dL), and total protein was 85 mg/dL (reference: 15–60 mg/dL). JC Polyoma virus DNA was <500 copies/mL (reference: < 500 copies/mL) and West Nile virus IgM was not detected. CSF was not tested for the presence of HIV.

CSF cryptococcal antigen (CrAg) test came back positive with a titer of 1:20,480. Subsequently, serum CrAg was checked that came back positive (titer not available). Blood cultures from the time of mental status change came back positive with *Staphylococcus aureus* originating from an abscess over her right arm. Patient was started on intravenous liposomal amphotericin B at 6 mg/kg dose and oral flucytosine (100 mg/kg/day in 4 divided doses) for CM in addition to vancomycin and cefepime (day 16). LP was repeated (day 18) that showed OP of 56 cmH₂O, CSF WBC count of 74/mm³ (reference: <5 cells/μL) (lymphocytes 85%, macrophages 10%, monocytes 5%), glucose 143 mg/dL (serum glucose 324 mg/dL), total protein 70 mg/dL (reference: 15–60 mg/dL), and positive CSF CrAg test (titer not available). CSF cultures from both lumbar punctures grew *Cryptococcus neoformans* var. *grubii*. Serial therapeutic LPs were done as listed in Table 1 with improvement in the OP and clearance of the *Cryptococcus* from the CSF cultures although her WBC count in the CSF remained elevated (range: 26–44/mm³). CD4⁺ T cell counts were repeated that came back at 350 cells/μL and HIV VL remained undetectable. She was continued on cART throughout the course. She remained minimally responsive to verbal and tactile stimuli off sedation throughout her ICU stay. She had a non-contrast computed tomography of the head that did not show any change from prior brain imaging (day 26).

She completed 2-weeks of induction treatment (day 30) and was transitioned to fluconazole 800mg daily for the consolidation phase. She was transferred to the general medicine floor (day 30). Given lack of meaningful neurological recovery, family meeting was held with the palliative care team and a decision was made to proceed with tracheostomy and gastrostomy tube placement (day 34). Her subsequent hospital course was complicated by development of acute deep venous thrombosis, pressure ulcers on her sacrum, aspiration pneumonia, and deterioration in renal function. Her mental status never recovered and the family decided to provide her with comfort care from that time onwards (day 84).

3. Discussion

We report here a surprising case of CM in a HIV-infected patient with long-standing virologic control and relatively high CD4⁺ T cell counts whose course was complicated by elevated intracranial pressure, pleocytosis along with poor neurological recovery despite fungal clearance in the CSF. While there are case reports and reviews of CM in patients with relatively high CD4⁺ counts [5,6], these studies do not report CM cases in a patient with well controlled HIV infection. Not surprisingly, the diagnosis was not suspected earlier in the course and patient had already suffered a severe neurologic damage by the time CM was diagnosed.

The patient had multiple poor prognostic markers of CM including older age, disseminated disease to the CNS, high antigen titer, increased intracranial pressure, and delayed diagnosis that likely led to her poor outcome. Those with relatively higher CD4⁺ T-cell counts ≥100 cells/μL can more commonly present with altered mental status [5]. Her clinical presentation and course were not typical of what has been described in those with advanced HIV-infection or those with no apparent immunocompromising condition. While her presentation of disseminated cryptococcal disease to the CNS with high antigen titer is consistent with how individuals with advanced AIDS may present, the inflammatory response in the CNS and poor neurologic recovery despite fungal clearance is more characteristic of immunocompetent individuals.

The patient did not meet the criteria for C-IRIS as described for HIV-infected patients [2]. However, her clinical course was similar to that of postinfectious inflammatory response syndrome (PIIRS) seen in immunocompetent individuals. PIIRS is known as clinical deterioration despite effective antifungal treatment and fungal clearance due to unrestrained T cell mediated host damage in previously healthy individuals [7]. Some immunocompetent individuals were found to have STAT5-blocking antibodies to granulocyte-macrophage colony-stimulating factor [4]. While CD4⁺ T cells help in controlling the fungal burden, they also contribute to the intense inflammatory response, and rise in interferon-gamma [5], that can lead to neurological deterioration and death [8]. Additionally, the cryptococcus capsule is itself immunosuppressive and immune reconstitution is inevitable with treatment [9]. Experts recommend extended course of induction treatment, trial of corticosteroids and aggressive management of intracranial pressure [2]. Serial measurement of β-D-glucan level in the CSF and/or quantification of viable yeast in the CSF may be helpful in differentiating between uncontrolled infection and paradoxical inflammatory reaction as titers cannot be followed to assess treatment response [10]. As highlighted in our case, the diagnosis of paradoxical inflammatory reaction is a challenging one, often missed or intervened too late. Shunt placement or corticosteroids use was not done in our case.

While not investigated in this case, CSF viral escape, where HIV continues to replicate in the CSF despite peripheral control, may potentially explain the patient's neurological deterioration. A recent study showed 4.4% of HIV-infected volunteers with HIV VL less than 50 copies/mL to have had CSF viral escape. While an uncommon event, it may be associated with CNS inflammation [11]. However, whether CSF viral escape is a risk factor for CM is unknown. A study done in South Africa reported that higher HIV viral burden in the CSF compared with blood was not commonly seen in HIV-CM co-infection nor associated with C-IRIS [12].

Alternatively, age-related immune dysregulation as characterized by an increase in the number of terminally differentiated effector memory CD8⁺ T cells, absent CD28⁺ expression and enhanced secretion of inflammatory cytokines can lead to dysregulation of inflammation [13]. Interestingly, increased frequencies of CD28⁻ CD57⁺ CD8⁺ T cells have been associated with the presence of Kaposi's sarcoma among patients with well controlled HIV infection [14]. Age itself is a poor prognostic marker and a recent study reported higher rates of altered consciousness and recent cerebral infarction as presenting symptoms in those older

than 65-years-old with CM [15]. While importance of cell-mediated immunity is self-explanatory, IgM memory B cells and antibody-based immunity in fungal containment and inflammation has been studied as well [3].

Our case highlights that presentation of CM may be atypical depending on the extent of underlying immune deficit and emphasizes the need for greater understanding of the predisposing risk factors. Others similarly have reported cases of CM in relatively higher CD4⁺ T cell counts and there is increasing evidence that additional immunologic perturbations play a role.

Conflict of interest

None.

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