Cryptococcal Postinfectious Inflammatory Response Syndrome in an Immunocompetent Host

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Abstract

Cryptococcal-postinfectious inflammatory response syndrome (c-PIIRS) in an immunocompetent host is a rare entity. Unlike cryptococcal-immune reconstitution inflammatory syndrome, in c-PIIRS, macrophage clearance defect can be persistent, and the patient requires prolonged immunosuppressants to control inflammation. Early identification and treatment can reduce the mortality and morbidity in cryptococcal meningitis (CM). Here, we describe c-PIIRS in an apparently healthy individual who developed CM and treated with effective antifungal regimen. After initial improvement, the patient showed clinical and radiological worsening, which could be likely due to PIIRS. The patient was responded to prolonged steroids.

Keywords: Cryptococcal meningitis, immunocompetent, postinfectious inflammatory response syndrome

INTRODUCTION

Cryptococcal meningitis (CM) is a serious central nervous system infection caused by either Cryptococcus neoformans or Cryptococcus gattii.[1] A vigorous immunological response after starting antifungal treatment in cryptococcal infection was initially observed in HIV-infected patients and was termed as cryptococcal-immune reconstitution inflammatory syndrome (c-IRIS).[2] However, in previously healthy individuals, a similar immunological response is rarely seen. Clinical deterioration occurs during effective antifungal treatment due to an aggravated immune response. This condition is known as postinfectious inflammatory response syndrome (PIIRS).[3,4] Manifestations include worsening or relapse of clinical symptoms and/or new radiological findings. Corticosteroids, nonsteroidal anti-inflammatory drugs, interferon-gamma (IFN-γ), thalidomide, and tumor necrosis factor antagonists have been previously used with varying success. Here, we describe cryptococcal-PIIRS (c-PIIRS) in an immunocompetent patient who was successfully managed with steroids.

CASE REPORT

A 61-year-old male presented with a history of holocranial headache, weight loss, and low-grade fever for 1 month. Headache was bilateral, progressive in nature with nocturnal worsening. It aggravated on straining and coughing but was relieved on taking painkillers. Fever was intermittent and low grade. Hearing impairment was also associated with the onset of headache and fever. There was no history of seizures, focal neurological deficit, visual defects, joint pain, high-risk sexual behavior, family history of tuberculosis (TB), and skin rash. There was no history of blood transfusion, dialysis, or intake of any kind of drugs including steroid. The patient had been evaluated for chronic meningitis elsewhere. Magnetic resonance imaging (MRI) brain showed leptomeningeal enhancement, and cerebrospinal fluid (CSF) report showed 280 cells (100% lymphocytes), 442 mg/dl of protein, and 23 mg/dl of glucose with blood glucose – 168 mg/dl. Computer tomography chest and abdomen did not reveal any abnormality.

The patient was started on empirical anti-TB treatment with oral steroids in an outside hospital. As his symptoms did not improve with treatment, he was referred to us for further evaluation and management. On examination, the patient was febrile but hemodynamically stable. Systemic examination showed the presence of meningeal signs, but fundoscopy was unremarkable. All biochemical and hematological parameters were within the normal range. Lumbar puncture showed opening pressure of 250 mm of CSF. Repeat CSF analysis revealed proteins 121 mg/dl, glucose 40 mg/dl (blood glucose – 153), and 110 cells with lymphocyte predominance. CSF for acid-fast bacilli and Gram stain and GeneXpert for TB were negative. Repeat MRI showed only leptomeningeal enhancement (same as previous). However, India ink stain and cryptococcal antigen (latex agglutination test) report came positive.

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Serological tests for HBV, HCV, HIV, syphilis, and Brucella were negative. Autoimmune screening was normal. Serum CD4 count was 818 cells/μl, and blood culture and urine culture were sterile. Whole-body positron emission tomography scan was normal. No evidence of any underlying immunodeficiency or malignancy was found.

Positive cryptococcal antigen test and Indian ink stain and CSF fungal culture showed growth of Cryptococcus neoformans var. grubii. Anti-TB drugs were stopped, and the patient was started on intravenous liposomal amphotericin B (3 mg/kg/day) and oral flucytosine (100 mg/kg/day in 4 divided doses) for the induction course. During the initial 2 weeks of treatment, the patient showed clinical improvement. However, he had acute onset of headache, progressive hearing loss, disorientation, and confusion on day 14. On examination, the patient had altered consciousness with papilledema. Repeat MRI study with contrast showed acute vasculitic infarcts in cerebellar vermis and corpus callosum with diffuse leptomeningeal enhancement [Figure 1 and 2a]. Electroencephalography revealed diffuse delta waves without electrographic seizures. CSF fungal culture was reported negative on day 24. Acute onset of clinical and radiological deterioration with adequate antifungal response led us to suspicion of c-PIIRS, and the patient was initiated on oral prednisolone (1 mg/kg/day). The patient also underwent multiple lumbar punctures to drain CSF and antiedema measures to treat raised intracranial tension. Defervescence of headache and significant neurological improvement was observed over a period of 7 days after commencing steroids. Repeat lumbar puncture showed 38 cells (100% lymphocytes), 107 mg/dl protein, and 51 mg/dl glucose (blood glucose – 167 mg/dl) with CSF opening pressure of 180 mm of CSF. He was treated with liposomal amphotericin B and oral 5-flucytosine for 4 weeks and later switched to oral fluconazole (400 mg) once daily in the maintenance phase and steroid in tapering dosage continued for period of 2 months. The repeat MRI (third) showed decrease in the level of leptomeningeal enhancement [Figure 2b] and no new infarcts. The patient had significant clinical improvement and was discharged in a stable condition.

**Discussion**

The treatment of cryptococcal meningoencephalitis is divided into induction, consolidation, and maintenance phases. As per IDSA guidelines, the initial induction phase consists of amphotericin B and flucytosine for 4 weeks in an immunocompetent patient and 2 weeks in an immunocompromised patient. The consolidation and maintenance with fluconazole, for 8 weeks and 1 year, respectively, are similar in both types of patients. In an immunocompetent host, outcome is typically poor in central nervous system cryptococcal infection with reported mortality rates of 16%–44%. In an immunocompetent host, outcome is typically poor in central nervous system cryptococcal infection with reported mortality rates of 16%–44%. Higher rates of mortality in cryptococcal infections in an immunocompetent are mainly due to delay in establishing diagnosis of infection and the vigorous host immune responses. In the present case, initial diagnosis and treatment of CM were delayed due to the first empirical diagnosis and treatment of tuberculous meningitis.

In both immunocompromised and immunocompetent patients, there is a possibility of clinical deterioration after initiation of treatment due to immune responses. Although the clinical presentation is same, the etiopathogenesis for immune responses of cryptococcal infection in an immunocompromised and immunocompetent host is different. In HIV-infected persons and immunocompromised patients, the main mechanism is extreme inflammatory response to residual fungal antigens after reconstitution of the immune system (IRIS). Haddow et al. proposed a diagnostic criterion for two distinct types of c-IRIS; paradoxical c-IRIS and antiretroviral-associated IRIS based on antecedent factors, strict clinical criteria, and exclusion of alternative causes of clinical deterioration.

PIIRS in previously healthy individual is defined as clinical deterioration despite effective antifungal treatment due to aggravated immune response. This syndrome is often reported between 20 and 35 days postonset of infection. In our case, c-PIIRS was considered due to clinical worsening, appearance of new radiological lesions raised ICP despite
effective antifungal treatment (negative fungal culture), and baseline immunocompetent status. A decision was taken to start steroids after discussion with patient’s relatives. Significant clinical recovery within 7 days of steroid initiation vindicated our decision.

PIIRS and c-IRIS have similar clinical presentations, apart from the underlying immune status. PIIRS shares features with c-IRIS including activation of dendritic cell–T-cell synapses and T-cell inflammatory response due IFN-γ and interleukin-6. PIIRS differs from C-IRIS due to lack of effective activation of macrophage leading to macrophage–T-cell dissociation. The macrophage clearance defect can be persistent and may require prolonged immunosuppression to control inflammation-mediated neurological damage.[4] Studies have shown that cellular inflammation progresses gradually in cryptococcal infections and peaks around days 28–35 postinfection when fungal clearance may have already occurred.[6] This is due to delay in crossing of blood–brain barrier by monocytes and T-cells. These CD4+ T-cells help in controlling the fungal burden but may ultimately lead to inflammation and clinical deterioration. If not treated timely, the excessive inflammatory response can be potentially dangerous due to cerebral edema causing neurological damage and herniation. Unfortunately, there are no single criteria available for diagnosis, and one needs to maintain a high index of suspicion in these patients.

There are no recommendations for the treatment of PIIRS. Corticosteroids are generally used to reduce the inflammatory response and raised ICP in most of the case reports. Corticosteroids exert anti-inflammatory effect on immune cells through direct effect on transcription of inflammatory mediators through glucocorticoid responsive element increased transcription of anti-inflammatory mediators and reduced T-cell survival.[7] The dose and duration of therapy with corticosteroids are not defined in c-PIIRS and are commonly individualized, according to the clinical response. The antifungal therapy is continued as per schedule (induction, consolidation, and maintenance phases) and has no bearing on the outcome of PIIRS.

In our case, the patient required steroid treatment for a prolonged period for significant response but tolerated corticosteroid therapy well. At the end of 4 weeks, the patient was discharged at stable condition with maintenance oral steroids. He is being followed on outpatient basis on maintenance dose of antifungal treatment and tapering dosage of steroids and continues to do well.

**Conclusion**

PIIRS in an immunocompetent host can complicate antifungal treatment of cryptococcosis. It should be suspected in the setting of clinical worsening, appearance of new radiological lesions, and raised ICP despite effective antifungal treatment in an immunocompetent host. Early identification and treatment can reduce the mortality and morbidity in CM.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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