



Cryptococcal Post Inflammatory Immune Response Syndrome (PIIRS): A Shrewd Masquerader of Immune Cryptococcal Reconstitution Inflammatory Syndrome (IRIS) in Immunosuppressed Patients

Sriharsha Kanuri^{1*}, Christina C-PA², Anupa Rai¹ and Saeed Baloch²

¹Saint Francis Emory Medical Center Columbus, GA, United States

²Piedmont Medical Center, Columbus, GA, United States

Abstract

Introduction: Cryptococcal meningitis is more common in HIV patients as compared to immunocompetent patients. In immunocompetent patients, despite robust antifungal therapeutic regimens, some patients experience sudden clinical worsening due to Cryptococcal Post Inflammatory Response Syndrome (C-PIIRS). Here, we briefly describe a clinical case and review the current literature on C-PIIRS in immunocompetent patients.

Clinical Case: 64-year-old male with a PMH [Past medical history] of hypertension, myocardial infarction, pulmonary MAC (*Mycobacterium avium* complex), presented with bilateral lower extremity weakness and lethargy. He was diagnosed with cryptococcal meningitis and treated with antifungal therapy and discharged. After discharge he was again readmitted few weeks later with complaints of bilateral lower extremity weakness, mental status changes and lethargy. MRI brain showed new brain lesions. Due to high suspicion for cryptococcal C-PIIRS decision to restart induction antifungal regimen in combination of corticosteroids was made and patient demonstrated clinical recovery.

Discussion: Cryptococcal Post Inflammatory Immune Response Syndrome (C-PIIRS) develops after the resolution of cryptococcal meningitis with sudden appearance of new clinical symptoms, worsening neurological deficits, and new radiological signs in the face of concluded antifungal treatment, and negative fungal cultures. The principal underlying pathophysiological aberration in C-PIIRS is T-lymphocyte-macrophage dissociation.

Conclusion: Clinicians should be cognizant of C-PIIRS in any immunocompetent patient who demonstrates clinical worsening after conclusion of antifungal therapy in cryptococcal meningitis. Corticosteroids in combination with antifungal therapy would be reasonable for favorable clinical outcomes and fair prognosis.

Keywords: Cryptococcal; Clinical symptoms; Antigens

Introduction

Cryptococcal Post Inflammatory Immune Response Syndrome (C-PIIRS) materializes in patients with cryptococcal meningitis secondary to unbalanced and overactive immune activity directed against released fungal antigens and spores [1,2]. Cryptococcal PIIRS is a diagnosis of exclusion and all the possible causes including reinfection, vasculitis, and intracranial masses have to be ruled out.

After initial improvement following treatment of cryptococcal meningitis, patients experience sudden worsening of clinical symptoms, sometimes with new infarcts and intracerebral hemorrhage. Lumbar puncture, imaging studies need to be performed to confirm the diagnosis. This immune mediated damage invokes serious neurological sequelae [3,4], thus increasing the morbidity and mortality in these patients [5]. Taking into account the heightened immune response, clinical studies have shown clinical efficacy in usage of corticosteroids along with antifungal therapy for suppressing hyperexcitable immune attack [6,7]. In this present case, we present a clinical case and take this opportunity to review the literature to briefly discuss the pathophysiology, clinical features

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*Correspondence:

Sriharsha Kanuri, Saint Francis Emory Medical Center Columbus, GA, United States,

E-mail: harsha9009@gmail.com

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and treatment of C-PIIRS.

Case Presentation

Patient is a 64-year-old male with a PMH of hypertension, myocardial infarction, pulmonary MAC status post-treatment. History is obtained via chart review and patient daughters via telephone. The patient does follow the ID team at a major university hospital. He was diagnosed with pulmonary MAC in and completed pulmonary MAC treatment with a course of ethambutol, azithromycin, and rifampicin. At the outpatient follow-up with the ID (Infectious Disease) team, patient complained of fevers and headache.

Cryptococcal antigen collected in the outpatient setting did show up as elevated with 1:160. He was subsequently admitted at university hospital for 3 weeks. During this admission, he did undergo a lumbar puncture, that showed an opening pressure of 17 cm H₂O. CSF analysis further showed glucose 24, protein 179, WBC 4, RBC 14, neutrophil 12%, cryptococcal antigen positive with CSF titer 1:40. He completed induction phase of therapy with amphotericin and flucytosine. Hospital stay was further complicated when he developed aqueductal obstruction and hydrocephalus requiring neurosurgical evaluation and VP (Ventriculoperitoneal) shunt placement. He was then discharged to regional rehab on high-dose fluconazole.

Patient now presents to our hospital 5-6 weeks later with complaints of bilateral lower extremity weakness and lethargy from the regional rehab facility. He was additionally found to be altered on hospital presentation in the ED. He was mildly tachypneic but remaining vital signs were stable with normal white count 7.4. He did have a small AKI with creatinine of 1.59 period. CT scan head completed showed no acute intracranial process with ventricular catheter in place with mild ventriculomegaly. CT stroke protocol completed showing no acute intracranial process. CT head and neck stroke protocol completed showed calcified plaque seen at the origin of the bilateral ICA causing approximately 40% stenosis on the

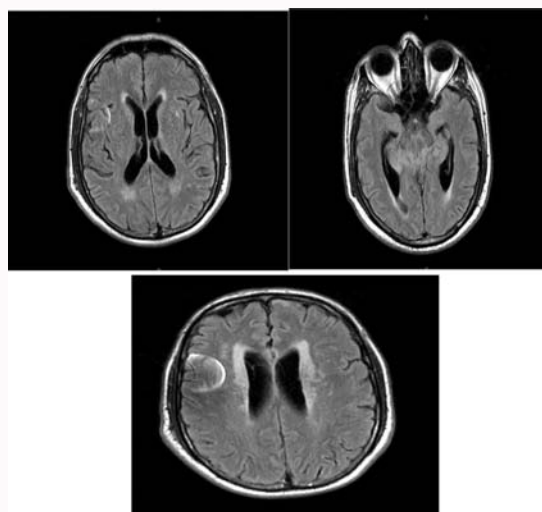


Figure 1: MRI Brain white matter changes.

Small acute infarct in the right cerebellum, the splenium of the corpus callosum on the right and the posterior limb of the left internal capsule. Enhancement is seen in the interpeduncular cistern and prepontine cisterns. Possibility of meningitis should be considered in the differential causing microinfarcts due to the involvement of the microvessels/perforator arteries. Scattered foci of T2 and FLAIR hyperintensity seen in the bilateral periventricular and subcortical white matter suggesting chronic changes probably related to old infarct and combination of microvascular ischemic changes.

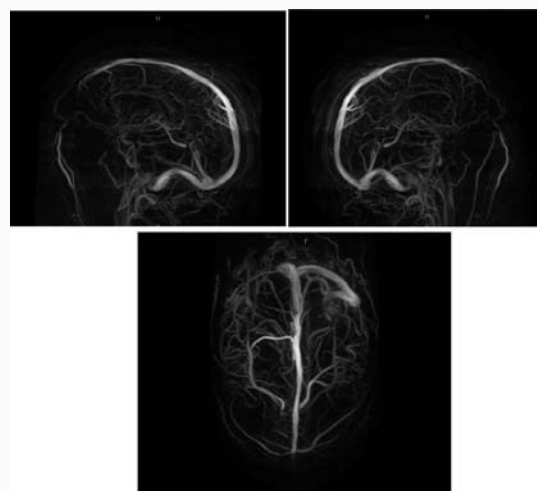


Figure 2: MRI Venogram Head with Contrast: Chronic appearing sinus thrombosis of the right transverse sinus, sigmoid sinus and proximal jugular vein.

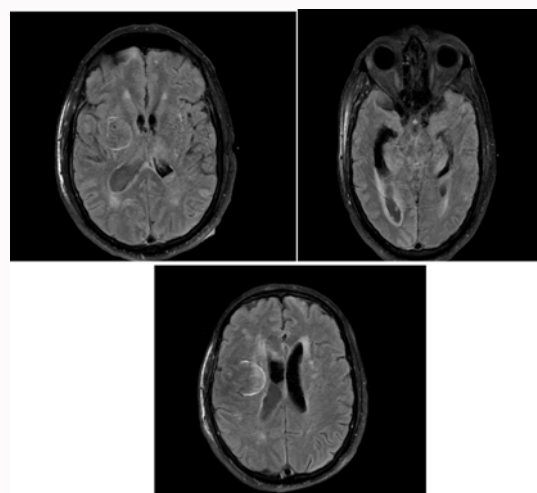


Figure 3: Repeat MRI brain showing intracerebral hemorrhage.

New focal hemorrhages in the posterior thalamus bilaterally. Persisted hemorrhage components to right lateral ventricle. New area of encephalomalacia and fluid in the right frontal lobe adjacent to the shunt catheter with surrounding edema and mass effect flattening the roof of the right frontal horn. Acute infarct in the medial occipital lobe. Extensive new acute infarcts with restricted diffusion in the cerebellar hemispheres bilaterally, posteriorly and sound roof of the 4th ventricle with increased size of the left thalamic infarct

right and 20% stenosis on the left, which are not hemodynamically significant and no large vessel occlusion involving major arteries of the brain is seen. Chest X-ray was negative for acute findings period. X-ray shunt series completed shows shunt remains intact period. MRI of the brain with and without contrast completed showed small acute infarct involving the right cerebellum, the splenium of the corpus callosum on the right, and posterior limb of the left internal capsule with enhancement seen in the interpeduncular cistern and pre-pontine cisterns concerning for meningitis due to microinfarct given the involvement of micro vessels/ perforator arteries (Figure 1).

MRI venogram completed showed chronic appearing sinus venous thrombosis in the right transverse sinus, sigmoid sinus, and proximal jugular vein (Figure 2). MRI cervical spine completed

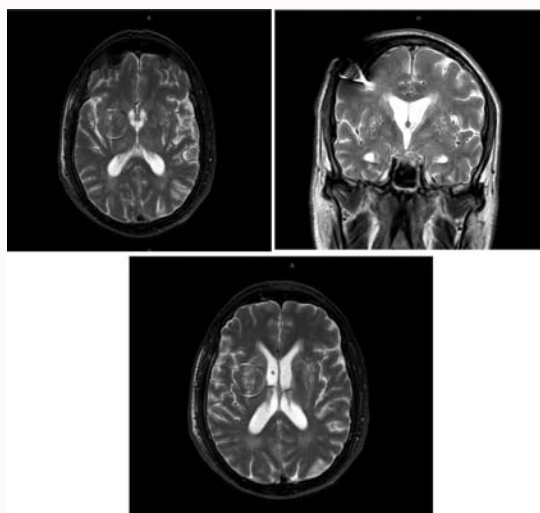


Figure 4: MRI Brain from– New acute infarcts.

showed no cord compression or myelopathic changes. HIV screen was negative. Cryptococcus antigen serum remains elevated 1:40. ID service was consulted for antibiotic recommendations.

After ID has evaluated the patient, they decided to start amphotericin and flucytosine for cryptococcal meningitis. They also consulted neurosurgery and neurology for management of this patient. Once the patient completed the standard induction therapy for cryptococcal meningitis, he was placed on diflucan, 400 milligrams every 24 hours. Moreover, recurrence of cryptococcal meningitis is ruled out. On top of that other causes including infectious vasculitis, stroke, mycotic aneurysms coagulopathy, thrombocytopenia, drug induced bleeding and primary vascular lesions and intracranial masses have been excluded with pertinent diagnostic work up.

As CSF culture did not grow fungus. Furthermore, the presence of newly onset hemorrhage and infarcts indicate PIIRS provoked vasculitis. Since the patient's clinical status has not improved despite starting antifungal therapy, this was presumed to be a classic case of Cryptococcal Post-Inflammatory Immune Response Syndrome (C-PIIRS). Therefore immediately, the ID started treatment with dexamethasone, 10 milligrams every 24 hours for 10 days, then dropped down to 6 milligrams for 7 days, then 3 milligrams for 7 days, and then 1 milligram for 7 days, and then gradually tapering it. As the patient received dexamethasone, the patient gradually recovered, and some of his clinical symptoms have improved drastically. In the next few days, he developed acute change in mental status and repeat MRI showed new acute infarcts, intraventricular hemorrhage and hemorrhage around frontal lobe (Figure 3 and 4). Emergency neurosurgical consultation was made for external ventricular drain placement. The patient was eventually transferred to comfort care and expired after few weeks due to disease complications.

Discussion

80% of the CNS infections are caused by *Cryptococcus neoformans*, while the remaining 20% are caused by *Cryptococcus Gatti* [8]. Studies suggest that, *Cryptococcus Neoformans* has a predilection to infect immunocompromised hosts whereas *C. Gattii* favors immunocompetent hosts [9]. *Cryptococcus* is abundantly found in the soil and is considered to be a plant pathogen of seedlings [8,10]. It typically co-habitats with bird's waste in the soil and thrives

as plant pathogen with *Eucalyptus* and other plant seedlings [8].

As these fungal cysts escape from their natural habitat and become airborne, they can be potentially inhaled by humans. Studies show that, *cryptococcus* airborne particles with sizes between 0.65-2 μM are more likely to be inhaled and get deposited with deeper lung tissues [11]. Importantly, longer periods of incubation of *cryptococcus* within soil is directly proportional to decrease in size of cryptococcal spores to 0.65-2 μM range, thus increasing the probability of lung inhalation [11].

Once they enter into the human body and migrate to the lungs, they are liable to form latent pulmonary infections and become dormant in immunocompetent hosts [12,13]. These latent infections are characterized by localized chronic inflammation, and cryptococcal granulomas [12]. However, the clinical course changes direction in immunosuppressed host, where these latent cryptococcal granulomas crumble, thence discharging their fungal proteins into the systemic circulation. These unfoldings becomes the impetus for initiation and propagation of systemic cryptococcosis [12,13]. After cryptococcal fungal proteins get on board in the systemic circulation, they have inherent inclination for migration towards brain tissues. This transpires secondary to various mechanisms including trans-cellular passage, intercellular passage, secretion of virulence factors and trojan horse mechanism [14,15]. As cryptococcal fungal proteins gain access to the brain tissues, they instigate intracranial infections due to their innate ability to evade the host defenses, robust cell wall, ability to secrete virulent factors [8,16,17].

Cryptococcus spores and released fungal antigens initially interact with dendritic cells through Mannose-R, β -glucan receptor and TLR-2&9 receptors, thus activating Th1 lymphocytes [18]. Activated Th1 lymphocytes release IFN γ , IL-6, IL-10 and GM-CSF, providing the catalyst for energizing M1 macrophages [18]. Stimulated M1 macrophages secrete TNF- α and IL 12, which will potentiate the killing of fungal spores and antigens [18]. This turn of events will enable the formation of fungal granulomas comprised of CD4 T cells, M1 macrophages and multinucleated giant cells containing *cryptococcus* spores [8].

Before antifungal therapy, fungal proteins residing in the dormant granulomas might be protected immune attack by the robust structural framework of fungal walls such as polysaccharide, strong fungal cell wall and extracellular laccase [18-21]. In C-PIIRS, clinical deterioration after completion of antifungal therapy might be explained by release of fungal antigens from the dormant granulomas which might trigger activation of Th1 T lymphocytes.

GM-CSF is an important cytokine that facilitates M1 polarization, thereby potentiating its phagocytic and lytic activity [22,23]. Due to GM-CSF antibody overproduction in PIIRS, there is will be disordered macrophage activation pathways comprising of under-activation of M1 macrophage and over-activation of M2 macrophage [22, 23]. Materialization of PIIRS will result from predominance of M2 macrophage instead of M1 macrophage due to presence of GM-CSF antibody, thence resulting in blockade of TNF- α and IL 12 secretion [18]. The relative supremacy of M2 phenotype macrophages was identified by predominance of CD68+, CD200R1+ monocytes in autopsy/biopsy studies as well absence of TNF- α and IL 12 in the CSF of PIIRS patients [18]. Analysis of CSF in PIIRS revealed HLA DR+ CD4+ & CD8+ T lymphocytes, natural killer cells, elevated cytokines (IFN-gamma, IL-8 and CXCL10) and increased neurofilament light

chains [24].

Less secretion of proinflammatory cytokines will result in less than adequate pathogen clearance, thus opening the door for disordered immune response [18]. Therefore, defective T-cell immunity and macrophage signalling defects primarily account for transpiration of PIIRS. Moreover, disordered coordination cross-talk between Th1 lymphocytes and activated monocytes might result in M2 polarization and resultant clinical worsening in PIIRS.

Clinical reports suggest that C-PIIRS comes into being approximately 30-45 days after onset of infection [5,25]. This usually eventuates as a consequence of delayed seepage of CD4+ T cells and monocytes across the blood brain barrier to suppress the cryptococcal meningitis related inflammation [5,25]. Gradually as CD4+ T lymphocytes populates adjoining the inflamed foci, they change track to amplify the inflammation, thence launching the commencement of PIIRS [25].

C-PIIRS comes to light as worsening of mental status [18], fading of cognitive skills and new-onset auditory/visual functions in a patient who has been adequately treated with antifungal therapy and proven negative fungal cultures [5,8,18,24]. It is quite different from Cryptococcus Immune Reconstitution Syndrome [C-IRIS] which manifests as clinical decline after 12 months of antiretroviral therapy in HIV patients. Importantly in both PIIRS and C-IRIS, both malignancy and new infection are not accountable for clinical presentations [8].

Patients with cryptococcal meningitis usually present with low grade fever, headache, vision changes, hearing loss, speech deficits, seizures and motor deficits [26].

Screening of plasma and CSF is imperative for confirming the diagnosis and deciding the future plan of action regarding the best line of therapy. Low serum Cryptococcal Antigen (CrAg) titers <1:80 is associated with negative CSF Ag titer and lack of symptoms [27]. Whereas higher serum CrAg titers >1:1280 are linked with positive CSF Ag titer and presence of central nervous system symptoms [27]. Cryptococcal meningitis is frequently associated with elevated CSF pressure >35 mm hg. Patients with elevated intracranial pressure might present with headache, nausea, vomiting, vision changes and papilledema. Since elevated ICP is associated with increased mortality every effort has to be made to reduce the ICP by repeat lumbar puncture and ventricular shunt if needed [27,28]. MRI brain might show leptomeningeal enhancement in sylvian fissures, bilateral cerebral sulci and parenchymal involvement of basal ganglia in patients who developed PIIRS after conclusion of antifungal therapy [26,29,30].

Patients with cryptococcal meningitis are usually treated induction therapy which entails administration of Amphotericin B with Flucytosine for 1-4 weeks [5,27]. This is followed by consolidation (Fluconazole 800 mg/day) and maintenance therapy (Fluconazole 200 mg/day) for 4-8 weeks and 1 year [5,27]. Despite prompt and robust therapy, patients are subjected to have increased mortality (16% to 44%) and morbidity [5,31]. In few subsets of patients, clinical deterioration after starting therapy was noted which can be explained by Post-Infectious Immune Response Syndrome [PIIRS] [5,8,18,24].

Disordered immune response adds credibility for usage of corticosteroids for counteracting disordered immune response and improving clinical response in C-PIIRS. T-lymphocyte-macrophage dissociation and macrophage clearance defect observed in PIIRS

might necessitate prolonged corticosteroid administration to rectify the disordered immune regulation [5,9]. Corticosteroids might downsize the immune response through enhanced production of anti-inflammatory mediators and attenuated T-cell survival [5]. Furthermore, it might reduce raised intracranial pressure, without which it might ultimately result in cerebral edema and herniation [5]. The dose and duration of steroid therapy should be individualized based on the clinical response of the individual patient, with many clinical studies endorsing duration between 2 months-27 months [1,5-7,26,32-36]. Regardless of the duration of the corticosteroid therapy, it is always prudent to assume a cautious approach with longer duration of therapy, keeping in mind the steroid induced side effects including osteoporosis, bone fractures, adrenal insufficiency, aseptic necrosis, ocular hypertension, steroid induced hyperglycemia, weight gain and neuropsychiatric symptoms particularly in elderly patients [26,37,38]. CSF analysis of cryptococcal meningitis PIIRS patients revealed CSF pleocytosis, elevated protein, hypoglycorrhachia, increased CD4+ & CD8+ lymphocytes, NK cells, and IL-6 levels which showed significant improvement with steroid treatment [26]. Clinical indicate that treatment of cryptococcal PIIRS with steroids and antifungal therapy promptly is associated with improvement in vision loss, papilledema, hearing loss, and MRI changes along with reduction in mortality and morbidity [39,40].

Key Points

1. C-PIIRS should be high in differential in any patient showing clinical worsening despite completing antifungal therapy in cryptococcal meningitis.
2. It transpires from exacerbated intracerebral inflammation secondary to CD4+ T lymphocyte-macrophage dissociation.
3. Macrophage clearance defects account for partially finished and disjointed removal of cryptococcal spores and fungal proteins, thus giving rise to heaping up of T-lymphocytes and M2 macrophage adjoining the sites of active inflammation.
4. On the grounds of haphazard cross-talk between inflammatory cells and immune cells, heightened immune response will be rather counterproductive, thence providing the impetus for ushering the outstart of C-PIIRS.
5. Clinicians should be well perceptive of this sporadic clinical phenomenon so that necessary steps can be taken to promptly evaluate and manage this clinical entity.
6. C-PIIRS should be differentiated from C-IRIS as the management differs.
7. Corticosteroids are mainstay of management in C-PIIRS whereas steroids are rarely used in C-IRIS except in severe cases.
8. Antifungal therapy should be commenced as per guidelines of American Society of infectious Diseases in Induction, consolidation and maintenance phases parallelly with steroids in C-PIIRS for favorable clinical outcomes.
9. Repeated lumbar punctures and ventriculoperitoneal shunt should be lessened the heightened intracranial pressure.
10. Elderly patients dependent on steroids for maintaining disease remission should be closely watched for steroid induced side effects.

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