

## Case Report:

### Disseminated cryptococcosis in a patient with advanced HIV infection

A. Krishna Prasad,<sup>1</sup> M.V.S. Subbalaxmi,<sup>1</sup> P. Umabala,<sup>2</sup> T. Roshni Paul,<sup>3</sup> Mallikarjun Shetty<sup>1</sup>

Departments of <sup>1</sup>General Medicine, <sup>2</sup>Microbiology, <sup>3</sup>Pathology, Nizam's Institute of Medical Sciences, Hyderabad

#### ABSTRACT

Antiretroviral therapy in human immunodeficiency virus (HIV) patients has prolonged survival and reduced the frequency of opportunistic infections (OI). However, following starting of antiretroviral therapy (ART), some patients experience a paradoxical worsening of clinical condition termed as immune reconstitution inflammatory syndrome (IRIS) an entity, characterized by an excessive inflammatory response to a preexisting antigen or pathogen. *Cryptococcus neoformans* is one of the important pathogens that can cause an IRIS, in patients with low CD 4 cell counts in HIV patients. It is important to consider the possibility of cryptococcal infection in patients with advanced HIV infection, look for cryptococcal antigen in serum and cerebrospinal fluid along with blood culture. Blood cultures should be kept for further incubation for slow growing organisms by as demonstrated in the present case. We herewith report a case of IRIS due to cryptococcal meningitis in a patient with HIV1 infection with very low CD4 counts.

**Key words:** *Cryptococcus*, *HIV*, *AIDS*, *Meningitis*

Krishna Prasad A, Subbalaxmi MVS, Umabala P, Roshni Paul T, Shetty M. Disseminated cryptococcosis in a patient with advanced HIV infection. J Clin Sci Res 2015;4:268-73. DOI: <http://dx.doi.org/10.15380/2277-5706.JCSR.14.015>.

#### INTRODUCTION

Cryptococcal infection is seen among human immunodeficiency (HIV) patients who have CD4<sup>+</sup> counts of <100 cells/iL. Among HIV patients, cryptococcosis most commonly manifests as subacute meningitis or meningo encephalitis. Classic meningeal symptoms and signs, such as neck stiffness and photophobia occur in only one fourth to one third of cases. The incidence of cryptococcal meningitis has declined substantially with the advent of antiretroviral therapy (ART). This is because ART leads to dramatic reductions in plasma viral load, improvement in CD4+ T cell counts and partial restoration of overall immune function. However, some patients experience a clinical deterioration as a consequence of rapid and dysregulated restoration of antigen specific immune responses after starting ART called immune reconstitution inflammatory syndrome (IRIS).<sup>1</sup> The IRIS may present either

by “paradoxical” worsening of symptoms of a known disease, or by “unmasking” of an occult opportunistic infection, which was clinically not apparent prior to starting combination ART.<sup>2</sup> Recognition of IRIS is important, because treatment should be directed towards protecting the patient against the effects of the inflammatory response, without compromising anti-microbial or antiviral therapy.<sup>3</sup>

We report our experience on the successful outcome of a case of disseminated cryptococcal infection in an advanced HIV infection with clinical deterioration following restarting of ART.

#### CASE REPORT

A 27-year-old male patient was diagnosed with HIV-1 infection 5 years ago and was on antiretroviral therapy (ART) consisting of zidovudine 300 mg twice a day, lamivudine 150 mg twice a day and nevirapine 200 mg twice a

Received: 24 March, 2014.

**Corresponding author:** Dr M.V.S. Subbalaxmi, Associate Professor, Department of General Medicine, Nizam's Institute of Medical Sciences, Hyderabad, India.  
**e-mail:** subbalaxmimvs@yahoo.com



Online access

[http://svimstpt.ap.nic.in/jcsr/oct-dec14\\_files/5cr414.pdf](http://svimstpt.ap.nic.in/jcsr/oct-dec14_files/5cr414.pdf)

DOI: <http://dx.doi.org/10.15380/2277-5706.JCSR.14.015>

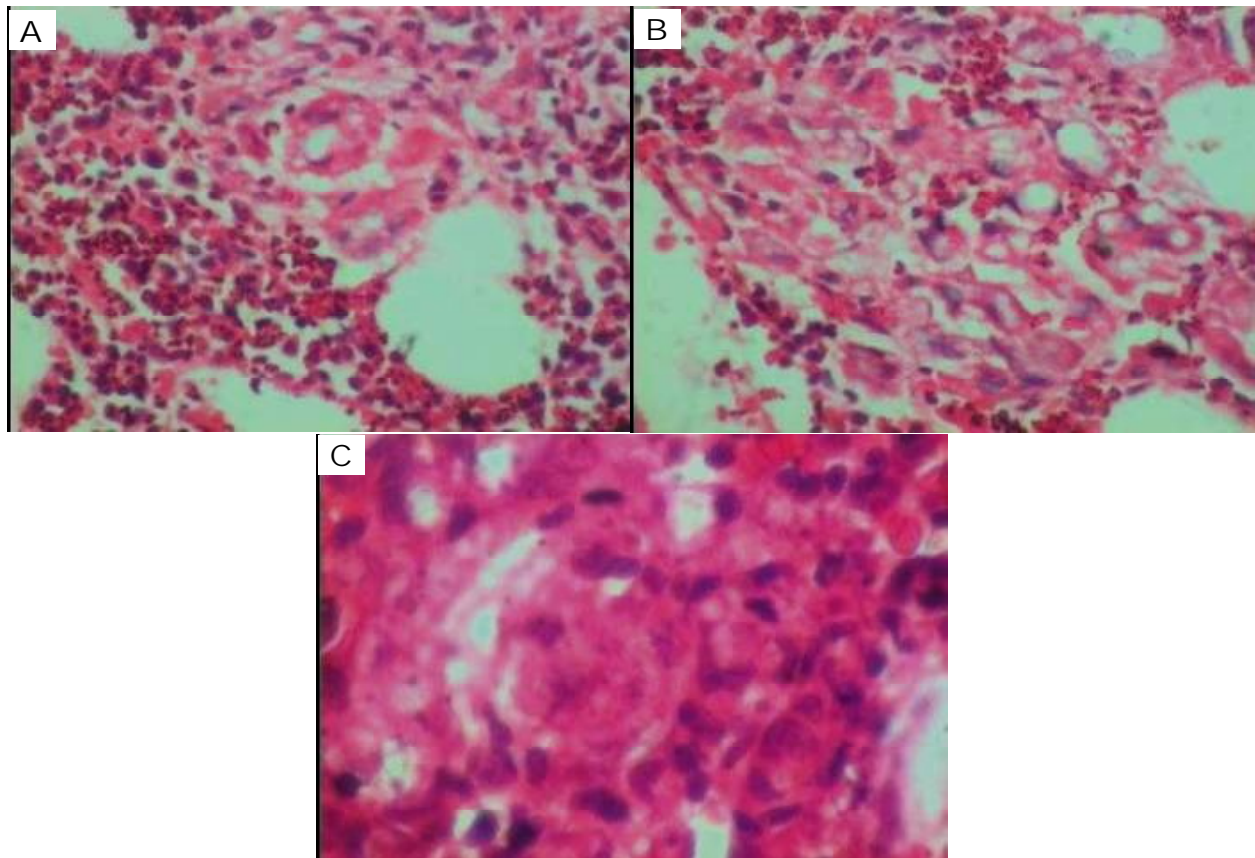


**Figure 1:** Mucoid, cream colored colonies of *Cryptococcus neoformans* on Sabouraud's Dextrose Agar after 48 hours incubation at 30°C

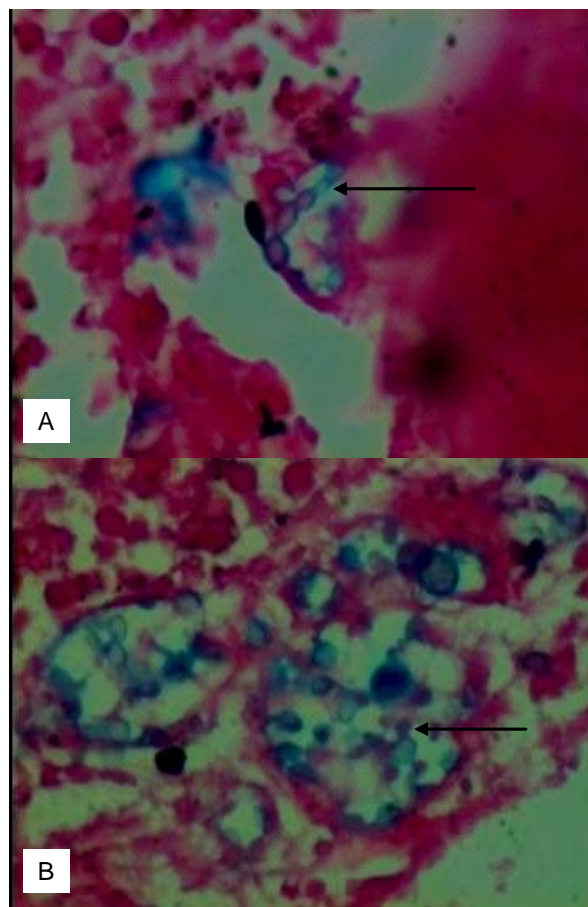
day. He discontinued ART for the last 1 year. He presented to the emergency medicine department of our hospital, a tertiary care teaching hospital in South India with history of fever since 3 months and progressive breathlessness since 10 days. On examination, he was febrile and tachypnoeic. Chest

auscultation revealed bilateral basal crepitations. Patient also had oral thrush. Laboratory investigations showed haemoglobin 10.2 g/dL, total leukocyte count 2,500 mm<sup>3</sup> and platelet count 100,000 mm<sup>3</sup>. Arterial blood gas analysis revealed pH 7.461, carbon-dioxide tension 25.7 mm Hg, arterial oxygen tension 49.2 mm Hg, bicarbonate 17.9 meq/L and oxygen saturation was negative 82.6%. Chest radiograph was normal. Sputum examination was negative for *Pneumocystis jiroveci* and acid-fast bacilli. Mantoux test was also negative. His CD4+ cell count was 46 cells/mm<sup>3</sup> and HIV ribonucleic acid (RNA) viral load was 750,000 copies/mL. Blood cultures (BacTAlert, biomérieux, France) were sterile initially after 5 days incubation but were further incubated to look for the growth of opportunistic organisms.

Clinically a possibility of *Pneumocystis jiroveci* infection was suspected, in view of fever,



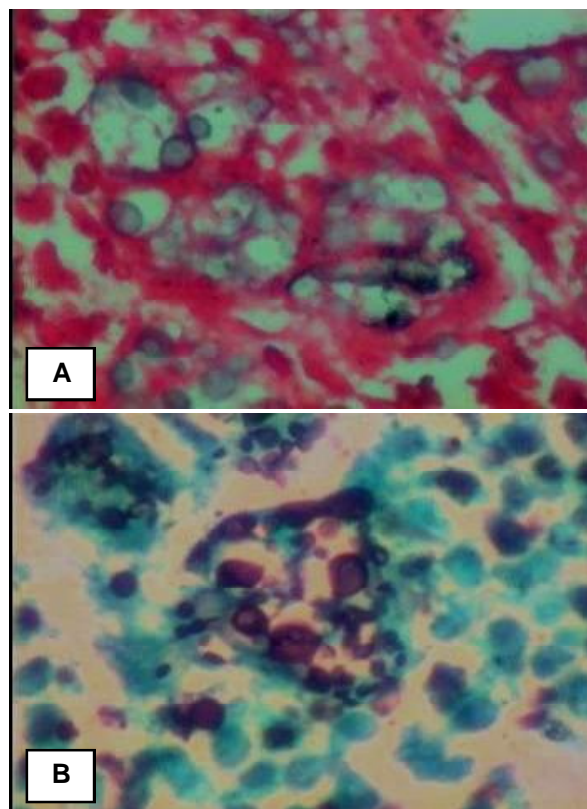
**Figure 2:** Bone marrow biopsy. Photomicrograph showing small aggregates of epithelioid cells forming granulomas [Haemaloxilyn and eosin, × 100 (A and B); × 400 (C)]



**Figure 3:** Bone marrow biopsy. Photomicrograph showing budding yeast form of Cryptococci (arrow) (Alcian periodic acid-Schiff,  $\times 400$ )

tachypnoea, bilateral crepitations in lungs and Type 1 respiratory failure. He was started on oxygen inhalation, co-trimoxazole. ART with zidovudine, lamivudine and nevirapine was restarted along with fluconazole. He was discharged in a stable condition after a hospital stay of 15 days.

After 10 days he was readmitted with fever, headache and vomitings of 3 days duration. On general examination, generalized erythematous rash and cervical lymph nodes were detected. Bilateral basal crepitations were noted. Fundus examination showed papilledema. There were no signs of meningeal irritation. Blood cultures sent during the first admission grew *Cryptococcus neoformans* after incubation for 10 days (Figure 1). Bone marrow biopsy was done at the second admission and showed small



**Figure 4:** Bone marrow biopsy. Photomicrograph showing cell wall of cryptococci staining black due to melanin-like activity (Mason Fontana,  $\times 400$ ) (A); and yeast forms of cryptococci (Methanamine silver,  $\times 400$ ) (B)

aggregates of epithelioid cell granulomas few multinucleate giant cells and macrophages (Figure 2) showing the presence of refractile yeast like organisms suggestive of Cryptococcal species. Alcian PAS stain showed thick capsule positive for acid mucopolysaccharide (Figures 3A,B). Methenamine silver and Masson Fontana stained smears showed yeast like organisms of 5-7  $\mu$  in size with unequal budding with narrow bases (Figures 4A,B). Ultra sonogram of the abdomen showed mild splenomegaly. Cerebrospinal fluid (CSF) analysis showed sugar 6 mg/dL, proteins 15 mg/dL and no leucocytes. India ink preparation showed budding yeast cells with capsule resembling *Cryptococcus neoformans* (Figure 5). Latex agglutination for cryptococcal mucopolysaccharide antigen was positive at 1:32 dilutions. Cerebrospinal fluid (CSF)





**Figure 5:** Cerebrospinal fluid. Photomicrograph showing capsulated budding yeast cells of *Cryptococcus neoformans* (India ink preparation,  $\times 400$ )

culture showed growth of *Cryptococcus neoformans*. CD4 cell count during the second admission was 256 cells/mm<sup>3</sup>.

In addition to anti brain oedema measures and intravenous amphotericin B (1mg/kg/day), flucytosine (100mg/kg/day) orally in 4 divided doses was given for 2 weeks. Patient improved and he was discharged on oral fluconazole (400mg) and ART. He is under regular follow up and keeping well after 8 years follow-up.

## DISCUSSION

Widespread use of antiretroviral drugs has dramatically reduced the number of opportunistic infections in patients with HIV. *Cryptococcal neoformans* is the leading infectious cause of meningitis in patients with AIDS. The majority of HIV-associated cryptococcal infections is caused by *Cryptococcus neoformans* and is acquired by inhalation. Most patients present with a picture of subacute meningoencephalitis while seizures and focal neurologic deficits are low. CSF examination shows only modest elevation of WBC, protein and low glucose as seen in our case. The opening pressure of CSF is usually high. Approximately one third of cases also have pulmonary involvement. The respiratory symptoms during the first admission in our case

may be due to the pulmonary involvement by cryptococcus though we did not consider at that time.

Usually culture of CSF and blood are diagnostic for cryptococcosis. In our case we could demonstrate growth of the organism in blood, CSF and bone marrow. A particularly useful test is cryptococcal antigen (CRAg) detection in CSF and blood. It is almost invariably detected in CSF at high titer in patients with meningitis or meningoencephalitis. CRAg has high sensitivity and specificity in central nervous system (CNS) disease and disseminated infection but often negative in pulmonary disease.<sup>4</sup>

The deterioration of the condition of our patient with development of new symptoms in the form of headache, fever and vomiting following ART may be due to unmasking IRIS due to cryptococcal infection. The immunopathogenesis of the IRIS is possibly a result of unbalanced reconstitution of effector and regulatory T-cells, leading to exuberant inflammatory response in patients receiving ART.<sup>5</sup> Definition of IRIS includes temporal association between initiation of ART and subsequent development of inflammatory symptoms, usually within 3 months, with evidence of immune restoration in the form of virological and immunological response demonstrated by a decrease in plasma HIV RNA level by more than 1 log<sub>10</sub> copies/mL and an increase in CD4+ T cell count from baseline.<sup>5</sup> Evidence of immune reconstitution is suggested in our patient by new onset headache, significant increase in number of CD4 cells, with positive cryptococcal antigen and cryptococemia.

Specific risk factors for the development of cryptococcal IRIS include shorter duration between cryptococcal diagnosis and ART initiation, low CD4 counts (<100 cells/mm<sup>3</sup>), higher baseline plasma HIV RNA levels; and higher CSF cryptococcal antigen titres, opening

pressures, WBC counts, and glucose levels.<sup>6</sup> Our patient had risk factors for IRIS due to cryptococcal infection in the form of very low CD 4 count (CD4 count of 46 cells/  $\mu$ L), initial high HIV viral load and restarting of ART few days ago. Clinically apparent cryptococcal meningitis was reported within 7-39 days after changing antiretroviral combination therapy.<sup>7</sup> In our case, symptomatic reactivation of cryptococcaemia and cryptococcal meningitis was noted in 10 days after the patient was restarted on ART.

When HIV infected patients present initially with cryptococcal meningitis intracranial pressure may be markedly elevated in patients with cryptococcal meningitis (in excess of 30-50 cm H<sub>2</sub>O), necessitating either repeated large-volume lumbar punctures or shunting procedures. The use of lumbar drainage and selective placement of lumbar peritoneal shunts in the management of elevated intracranial pressure in patients with HIV-associated cryptococcal meningitis can ameliorate the sequelae.<sup>8</sup> Our patient had intense headache, and responded to antifungal treatment and did not require large volume lumbar punctures or shunt procedures.

IRIS due to cryptococcal meningitis is associated with substantial morbidity and mortality.<sup>9</sup> Once the ART is initiated, these patients may return with increasing meningeal symptoms, along with an increased leucocyte count in the CSF, despite having negative CSF cultures and declining CSF antigen titers.<sup>10</sup> It has been suggested to delay ART until CSF sterility is achieved with antifungal combinations such as amphotericin B and flucytosine. However, the exact timing of ART initiation and whether attaining CSF culture sterility is important in avoiding IRIS is not known.

Recurrent meningitis in response to the initiation of ART was reported recently in a patient diagnosed with cryptococcal meningitis

and propose that the recurrent symptoms resulted from a therapy-induced reconstitution of the immune response against residual *Cryptococcus neoformans*.<sup>11</sup> Cryptococcal infection of lymph nodes on histopathological examination was established after starting cART in two separate case reports,<sup>12,13</sup> IRIS should be borne in mind when considering the differential diagnosis in a patient who are recently started on cART.<sup>12</sup>

Paradigm shifts in management of HIV with earlier initiation of ART is expected to decrease the burden of IRIS in developed countries; however, with enhanced rollout of ART in recent years and the enormous burden of opportunistic infections in developing countries like India, IRIS is likely to remain an area of major concern. Management of patients with AIDS should focus on appropriate anti-HIV and specific anti-microbial therapy for opportunistic infections, while closely monitoring for IRIS.

---

## REFERENCES

---

1. French MA, Lenzo N, John M, Mallal SA, McKinnon EJ, James IR, et al. Immune restoration disease after the treatment of immunodeficient HIV-infected patients with highly active antiretroviral therapy. *HIV Med* 2000;1:107-15.
2. Haddow LJ, Easterbrook PJ, Mosam A, Khanyile NG, Parboosing R, Moodley P, et al. *Clin Infect Dis* 2009;49:1424-32.
3. DeSimone JA, Pomerantz RJ, Babinchak TJ. Inflammatory reactions in HIV-1-infected persons after initiation of highly active antiretroviral therapy. *Ann Intern Med* 2000;133:447-54.
4. Aurturo Casadevall. Cryptococcosis. In: Longo DL, Fauci A, Kasper DL, Hauser SL, Braunwald E, Kasper D, et al editors. *Harrison's principles of internal medicine*. New York: McGraw-Hill; 2012;p:1650.
5. Sharma SK, Soneja M. HIV & immune reconstitution inflammatory syndrome (IRIS). *Indian J Med Res* 2011;134:866-77.
6. Mc Combe JA, Auer RN, Maingat FG, Houston S, Gill MJ, Power C. Neurologic immune reconstitution inflammatory syndrome in HIV/

- AIDS: outcome and epidemiology. *Neurology* 2009;72:835-41.
7. Shelburne SA 3rd, Darcourt J, White AC Jr, Greenberg SB, Hamill RJ, Atmar RL, et al. The role of immune reconstitution inflammatory syndrome in AIDS-related *Cryptococcus neoformans* disease in the era of highly active antiretroviral therapy. *Clin Infect Dis* 2005;40:1049-52.
  8. Woods ML, Mac Ginley R, Eisen DP, Allworth AM. HIV combination therapy: partial immune reconstitution unmasking latent cryptococcal infection. *AIDS* 1998;12:1491-4.
  9. Fessler RD, Sobel J, Guyot L, Crane L, Vazquez J, Szuba MJ, et al. Management of elevated intracranial pressure in patients with Cryptococcal meningitis. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998;17:137-42.
  10. Kambugu A, Meya DB, Rhein J, O'Brien M, Janoff EN, Ronald AR, et al. Outcomes of cryptococcal meningitis in Uganda before and after the availability of highly active antiretroviral therapy. *Clin Infect Dis* 2008;46:1694-701.
  11. Jhamb R, Kashyap B, Das S, Berry N, Garg A. Symptomatic relapse of HIV-associated cryptococcal meningitis: recurrent cryptococcal meningitis or *Cryptococcus*-related immune reconstitution inflammatory syndrome? *Int J STD AIDS* 2014;25:369-72.
  12. Tweddle A, Davies SJ, Topping W, Whitehorn J, Falzon M, Miller RF. Nodal cryptococcal immune reconstitution inflammatory syndrome masquerading as tuberculosis in an HIV-infected patient. *Int J STD AIDS* 2012;23:216-8.
  13. Putignani L, Antonucci G, Paglia MG, Vincenzi L, Festa A, De Mori P, et al. Cryptococcal lymphadenitis as a manifestation of immune reconstitution inflammatory syndrome in an HIV-positive patient: a case report and review of the literature. *Int J Immunopathol Pharmacol* 2008;21:751-6.