Case Report

Cryptococcal Meningoradiculitis: An Atypical Presentation after Initiation of Antiretroviral Therapy

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Atypical presentations of cryptococcal infection have been described as clinical manifestations of immune reconstitution inflammatory syndrome (IRIS) in HIV-infected patients following commence of antiretroviral therapy (ART). The authors describe a patient presenting with cryptococcal meningoradiculitis two weeks after initiation of ART. In patients with advanced HIV disease, immune reconstitution induced by ART can precipitate onset of atypical clinical manifestations in those patients with latent cryptococcal infection of the central nervous system.

Keywords: *Cryptococcus, Meningoradiculitis, HIV, Immune reconstitution inflammatory syndrome*

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Cryptococcosis is the most common lethal fungal infection in HIV-infected patients. Antiretroviral therapy (ART) has markedly decreased the mortality in HIV-infected patients[1]. After initiation of ART, some patients experience immune reconstitution inflammatory syndrome (IRIS), a well recognized complication of ART particularly in patients with very low CD4 cell counts[2]. Various studies reported that 8-50% of patients with cryptococcal infection who responded to ART developed cryptococcal IRIS despite the use of fluconazole therapy[3-5]. Cryptococcal IRIS is characterized by atypical manifestations of cryptococcosis in patients experiencing improvement in CD4 cell counts following ART. The authors describe herein an atypical presentation as cryptococcal meningoradiculitis occurring in an HIV-infected patient after initiation of ART.

Case Report

A 36-year-old female with known HIV infection for 11 years presented with a two-week history of progressively difficult walking and numbness in both legs. Her treatment history included a period of antiretroviral therapy with adherence difficulties a year earlier. She had recommended ART with a regimen of stavudine, lamivudine and nevirapine for two weeks prior to her presentation, when her initial CD4 cell count was 17 (3%) cells/mm^3. Her weakness evolved to the point that she could barely walk. She had bladder and bowel disturbances, fever and also malaise. She denied trauma to either the back or a history of any other opportunistic infections. Physical examination revealed a febrile woman without signs of meningeal irritation. Fundi were normal. Examination of her cranial nerves and her upper extremities revealed no abnormalities. Muscle power of the lower limbs showed symmetrical grade III spastic paresis with hyperreflexia. Plantar reflexes were both normal. All modalities of sensation and coordination were intact. A head CT with contrast media was performed and was unremarkable. Magnetic resonance imaging (MRI) of the whole spine showed thickening and clumping of cauda equina nerve roots representing radiculitis (Fig. 1). The cervical cord also showed ill defined hypersignal T2 change without focal enlargement or enhancement extending from C2-C6 level, indications of myelopathy (Fig. 2). A lumbar puncture yielded CSF with no white or red blood cells, a glucose level of 34 mg/dL and total protein of 68 mg/

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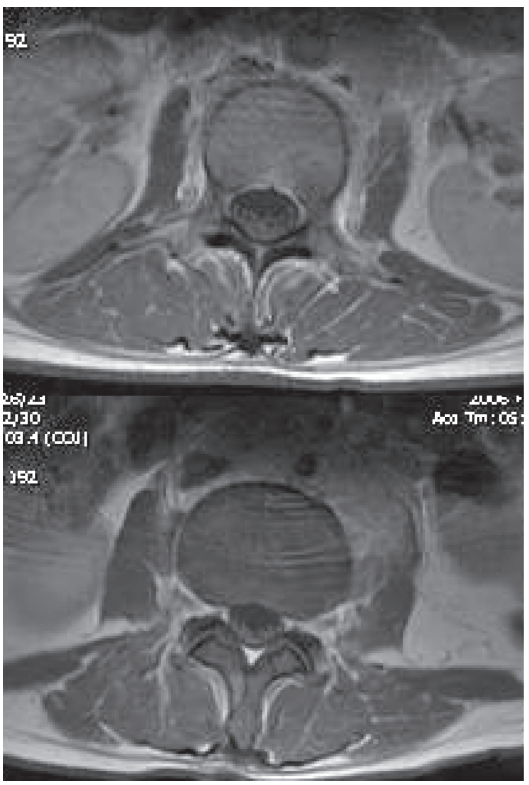

Fig. 1 Axial plane T1-weighted MRI of cauda equina after injection of gadolinium showing thickening and clumping of cauda equina nerve roots representing radiculitis

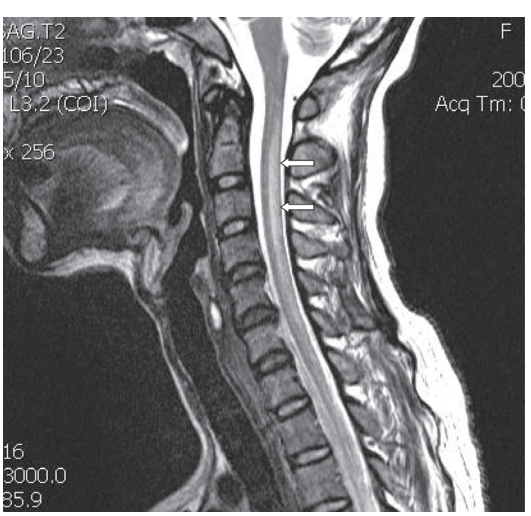

Fig. 2 Sagittal plane T2-weighted MRI of cervical spine after injection of gadolinium showing ill defined hypersignal T2 change without focal enhancement extending from C2-C6 level indicates of myelopathy

dL. India-ink preparation of CSF revealed rare encapsulated yeast -like fungi. Gram stain and acid fast stains were negative. Cultures from CSF grew *Cryptococcus neoformans*; additional laboratory tests excluded tuberculosis, CMV and herpes simplex virus infections. The cryptococcal latex antigen detection test for Cryptococcus antigen was positive both in the CSF and serum sample. Her blood cultures were also positive for Salmonella group C. Chest radiograph was normal. On admission, her HIV RNA was less than 400 copies/mL and her CD4/cell count was 24 (12%) cells/mm^3. The patient was given intravenous amphotericin B at a dosage of 0.7 mg/kg/day for 19 days, then fluconazole 600 mg/day thereafter. Antiretroviral regimen was left unchanged. Ceftriaxone was administered for Salmonella septicemia and followed with oral ciprofloxacin for 2 weeks. At the time of discharge, spasticity diminished, with motor power returning to 4+/5 in the lower limbs; the bowel and bladder symptoms were resolved.

Discussion

Cryptococcus neoformans is one of the most common opportunistic infections in HIV-infected patients in Thailand[6]. The majority of patients with cryptococcosis usually present with meningitis. Cryptococcosis rarely involved spinal cord and nerve root[7-11]. In the medical literatures, with the use of MEDLINE, we were able to find only one previous report of cryptococcal granuloma in the cauda equine[12]. The present patient was diagnosed with cryptococcal meningoradiculitis within 30 days after initiation of ART. Herpes simplex and CMV infections which are the important causes of radiculitis in HIV-infected patients had been ruled out by extensive investigations. Post-treatment clinical outcome of the presented patient showed remarkable improvement, confirming the resolution of the infection and inflammatory process.

Immune reconstitution inflammatory reactions to cryptococcal infection are now well recognized in the literature. With immune recovery, there is an enhance reaction to latent cryptococcal infection. Recent studies have found that an increased frequency of atypical cryptococcal central nervous system infections can be observed as a consequence of sustained immune-modulating effects of ART[13-17]. Features consistently described in patients with immune reconstitution cryptococcosis are: increased local inflammatory responses, difficulty culturing the yeast *in vitro,*[18] and atypical patterns of disease such as cavitatory lung lesions or mediastinal suppurative lymph nodes[19].

To the authors' knowledge, the present report may represent the first case of atypical presentation of cryptococcosis presenting as meningoradiculitis after commencing ART. Evidence of immune reconstitution after ART initiation was suggested by the increasing number of the CD4 cell count and undetectable HIV RNA. Conclusions concerning the pathogenesis of these entities are still controversial, and two complementary scenarios have actually been proposed[20,21]. The first is that IRIS represents the emergence of a previously quiescent or incubating infection, precipitated by ART-induced immunological changes. Generally, it occurs soon after the institution of ART (within 1-4 weeks), and the pathogens are often recovered and cultured from the site of infection. There are amplified clinical symptoms due to an enhanced inflammatory response. This occurs despite lower burdens of organisms[14]. The second scenario is that IRIS is the consequence of increased levels of circulating immune cells and the accessibility of immune cells to sites of infection where low amounts of pathogen antigens are still present. In this case, IRIS appears after a longer time (>2-4 months) of ongoing antiretroviral therapy, and the opportunistic agent cannot be identified by cultures, but only revealed on special histological specimens, suggesting that microorganisms could replicate at a very low level or even be dead. The presented case seems to belong to the first pathogenetic mechanism. The growth of Cryptococcus in the CSF of the present patient clearly demonstrates latent infection in this case.

In conclusion, as a result of restored immunity, HIV-infected patients receiving antiretroviral therapy may experience atypical clinical manifestations of cryptococcosis. Cryptococcal infection should be included in the differential diagnosis of radiculomyelitis in HIV-infected patients receiving ART. Although radiculomyelitis more commonly presents as an alarming of other opportunistic infections or HIV itself, cryptococcal infection is a treatable disease and specific treatment avoids permanent disability.

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รายงานผู้ป่วยเยื่อหุ้มสมองและรากประสาทอักเสบจากเชื้อราคริปโตคอคคัสหลังได้รับยาต้านไวรัส

อุบลวรรณ จงวุฒิเวศย์, กำธร มาลาธรรม, สมนึก สังฆานุภาพ

หลังจากมีการรักษาด้วยยาต้านไวรัสเอชไอวีอย่างแพร่หลาย ก็เริ่มมีรายงานผู้ป่วยที่มีอาการแสดงของการติดเชื้อคริปโตคอคคัสในผู้ติดเชื้อเอชไอวีที่เปลี่ยนไปจากเดิม โดยถือเป็นอาการหนึ่งของภาวะ Immune reconstitution ผู้นิพนธ์ได้รายงานผู้ป่วยหนึ่งรายที่มีอาการแสดงของเยื่อหุ้มสมองและรากประสาทอักเสบจากเชื้อราคริปโตคอคคัสหลังเริ่มการรักษาด้วยยาต้านไวรัสสองสัปดาห์ในผู้ติดเชื้อเอชไอวีในระยะท้าย หากมีการติดเชื้อราคริปโตคอคคัสแบบซ่อนเร้นในระบบประสาทส่วนกลาง อาจแสดงอาการของการติดเชื้อที่แปลกไปจากอาการแสดงที่พบบ่อยได้หลังเริ่มการรักษาด้วยยาต้านไวรัสเอชไอวี
