CLINICAL AND TYPICAL IMAGING CHARACTERISTICS OF CRYPTOCOCCAL MENINGITIS IN HIV INFECTED PATIENT: A CASE REPORT

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Although Cryptococcal infection is worldwide distribution, it is more seen in the immunocompromised patients. Cryptococcus neoformans is the most common central neurvous system fungal pathogen in HIV infected patients. Besides clinical features and laboratory tests, imaging findings play an important role in the evaluation of cryptococcal infection. In this paper we present an immunocompromised HIV infected case of C. neoformans meningitis with clinical features and imaging characteristics by MR image.

Keywords: *C. neoformans, Cryptococcus neoformans,Virchow Robin spaces, diffusion weighted imaging, apparent diffusion coefficient, fluid attenuate inversion.*

BACKGROUND

Cryptococcal disease is an opportunistic infection that occurs primarily among people with advanced HIV disease and is an important cause of morbidity and mortality in this disease group. By far the most common presentation of cryptococcal disease is Cryptococcal meningitis, which accounts for an estimated 15% of all AIDS-related deaths globally. And sub-Saharan Africa and Southeast Asia are the areas with the highest number of deaths due to Cryptococcal disease[1]. Cryptococcus neoformans is a fungal pathogen that affects the central nervous system (CNS) in HIV infected patients and patients in other immunocompromised states. It can infrequently be seen in immunocompetent patients as well (Williamson PR, et al 2017)[2]. Two types of cryptococcus are *Cryptococcus.neoformans* and *Cryptococcus* gattii. *Cryptococcus* infection caused by *C.neoformans* accounts for 80% and 20% by *C. gattii*. Infection from *C. neoformans* is most common seen in CNS but *C. gattii* infection is much more seen in lung[3]. *Cryptococcus* is usually acquired by inhalation from the environment, causes pneumonia and it may disseminate hematogenously to the central nervous system. Additionally, skin, eyes, bones, and soft tissue may be affected[2].

The immunosuppressive conditions are major risk factors for *C. neoformans* infections, such as advanced HIV/AIDS (CD4 < 200 cell/µL), organ transplant recipients, advanced malignancy and prolonged corticosteroid usage (Perfect JR et al 2010)[4]. Since *C. neoformans* is typically found in soil, excreta of birds, especially pigeons, thus once involved with these things maybe assumed as a risk factor.

CASE PRESENTATION

In August 2023, a 34-year-old woman was admitted to our hospital who had HIV-positive condition for 10 years and in ARV-treatement for 8 years but had stopped recently. She had suffered intermittent fever, cough, chest pain, dyspnoea, slowdown awareness, weight loss for one month. And she had fever, headaches, sensitivity to light, confusing in a late week. Laboratory studies disclosed the following values: CRP was 80.5 and after 3 weeks was 143.2 mg/L. The CD4 count was 50 cell/µL (1.95%). Lumbar puncture was performed and the cerebrospinal fluid (CSF) findings were as follows: Protein 0.23 g/L, glucose 5.37 mmol/L, Clo 123.5 mmol/L and after ten days : Protein 0.2 g/L, glucose 7.22 mmol/L, Clo: 116.3 mmol/L; *C. neoformans* with Ink stainin,

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culture result in CSF were positive. Microscopic test also revealed spoces like fungus in CSF. HIV viral load test was positive. Other examinations as CSF bacteria, Toxoplasmosis, Mycobacterium tuberculosis PCR were all negative. Brain MRI was performanced after admission and images revealed hyperintensity on T2W, T2 FLAIR images like pseudocysts, no restricted diffusion on DW images and showed no enhancements post gadolinium administration in the bilateral caudate nucleus, putamen, globus pallidus, Virchow Robin spaces, grey matter of insular lobes (Fig.1). No dilation of ventricular system, no other lesions were seen in the brain. A chest CT images revealed interstitial space thickness of bilateral lung superior lobe suggesting pneumonia with pathogen was unknown. Based on the clinical symptoms, laboratory results and image findings, an initial diagnosis of C. neoformans meningitis was suggested. The antifungal and antibacterial treatment was started with Ampholip, Fluconazol, Mizapenem for more than three months. The clinical condition of the patient was improved partially after treatment course and was discharged with consciousness, no fever, no sensitivity to light but still cough and spitting.

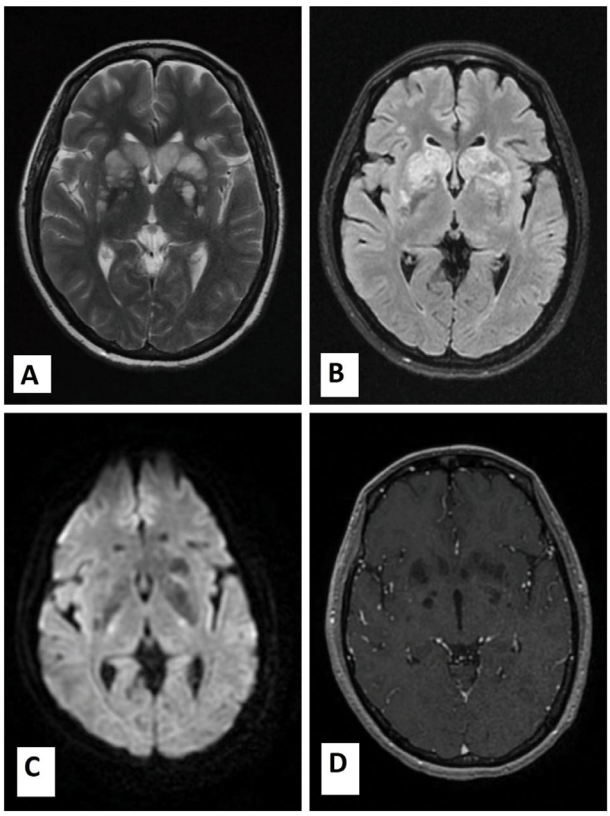
DISCUSSION

Cryptococcal meningitis, which occurs with the entrance into the CNS of the fungus, is seen more in immunocompromised patients, especially with HIV/AIDS patients (Liao CH et al)[5]. Cryptococcal meningitis (CM) is the most severe and common form of cryptococcosis. About 7% - 8% of the HIV-positive patients will have cryptococcal meningitis. The incidence of cryptococcal infection in patients with AIDS varies from 2% to 10% in U.S and western Europe and up to 15% in Africa and Asia. Another study estimated 152,000 cases of Cryptococcal meningitis occur among people with HIV/AIDS worldwide each year, resulting in nearly 112,000 deaths (Rajasingham R et al 4)[6].

Central neurvous system infection caused by C. neoformans may appears with nonspecific symptoms that last for weeks. Therefore, the diagnosis of CM may be challenging and it is often delayed or misdiagnosed. The early symptoms usually of CM include headache, fever, stiff neck, nausea, vomiting; followed by mental changes, visual disturbances, focal paralysis. The critical condition present with seizures, rapidly progressieve coma and death. Our patient case revealed typical symptoms of menigitis as headache, fever, vomiting, slowdown awareness, then an initial diagnosis of CNS infection was suggested.

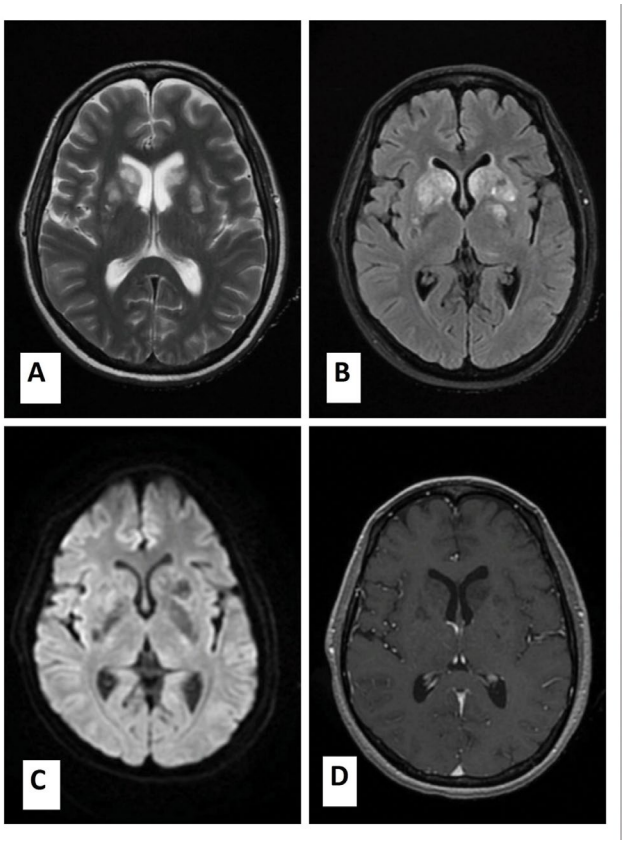
Lumbar puncture is the diagnosis modality of choice for CNS infections. India Ink stainin and Culture for Cryptococcus in CSF remain the definitive criteria for the diagnosis of CM. The fungal culture is the gold standard method, but it can take at least few days. A multiplex PCR assay (Film Array Panel) detect pathogens more rapidly than other methods and it has high sensitivity and specificity (90 % and 97 %, respectively)[5]. Our present case, results were positive with *C. neoformances* and spoces like fungus in CSF, similar to those found in HIV/AIDS patients with cryptococcal meningitis.

Imaging findings of CNS infection by *Cryptococcus* species have been well described in literature. Not all of the cryptococcal meningitis had positive imaging findings. Brain CT/MRI is a useful modalities for diagnosis of CNS infection diseases. Normal brain imaging (47% by CT and 8% by MR) did not exclude cryptococcal meningitis. Approximately 21% - 27% cases had typical cryptococcal meningitis on MRI (Katchanov J et al)[7]. The typical imaging findings of CM include: hydrocephalus and dilated Virchow Robin spaces (VRS), pseudocysts, cerebral infarcts, leptomeningeal or parenchymal enhancing lesions and cryptococcoma(Loyse A et al)[8].



Figue 1. MR images of patient case with T2W (A), T2 FLAIR (B), DWI (C) and post enhancement (D): Pseudocysts dilation and Virchow Robin spaces. No enhancements post post gadolinium administration.

The most common findings were dilation of ventricular system, especially was lateral ventricle and dilation of Virchow Robin spaces (Fig.2). The dilation of ventricular system or hydrocephalus, which results from inflammatory exudates by CSF blockage, is a serious and more common brain images of CM. The fungal polysaccharides may contribute that by blocking CSF outflow and disturbing CSF absorption. Hydrocephalus usually occurs as a late complication in untreated patients[7,8]. Pseudocysts were named as lesions of round or oval hyperintensity on T2W and hypo-intensity on both T1W and FLAIR without restricted diffusion on DWI (iso-or hypointensity)[7]. Pseudocysts can coexist with the dilated perivascular spaces. As infection disseminates along the VRS that adjacent to perforating arteries, perivascular spaces may become large with this mucoid organism. Punctate hyperintensities on T2W representing pseudocysts contain gelatine and dilated perivascular spaces are generally seen in basal ganglia, thalamus, midbrain and cerebellum. These appearances were characteristic for cryptococcal infection of CNS which generally incites no or mild edema or enhancement.



Figue 2. MR images of patient case after treatment, with T2W (A), T2 FLAIR (B), DWI (C) and Post enhancement (D): Slight decrease in size of pseudocysts and Virchow Robin spaces.

Compared with other fungal pathogens, the cerebral infarcts in CM usually occurred in patients with HIV. Acute lacunar infarcts manifested hyperintensity on DWI, hypointensity on ADC (restricted diffusion) and majority of the lesions located at the brain area supplied by perforating artery. Acute infarctions are often accompanied by 'hazy brain base' which indicate that the infarctions might come from vasculitis of perforating arteries due to extension of the fungal invasion along perivascular spaces at brain base (Ruiz A et al)[9].

Meningitis was defined as leptomeningeal or dural thickening combined with focal parenchymal edema[7,8]. FLAIR and contrast enhanced MRI images are the most sensitive sequences to show the meningitis. In the early stage with only edema, no or slight inflammatory reaction was found and with antimycotic therapy, the recovered immunity of the

body can have good inflammatory response to form the cryptococcoma and then circular or linear contrast enhancement. Cryptococcoma can be defined as lesions in which the cryptococcal organisms have involved parenchyma with granuloma consisting of lymphocytes, macrophages and foreign body giant cells[9]. Cryptococcoma is more likely to be seen in immunocompromised patients. Delayed imaging and double dose of contrast materials will better show meningeal and small nodules enhancement[9,10].

Our present case, MR imaging were dilatation of VRS, pseudocysts, no restricted diffusion on DW images and showed no enhancement in bilateral caudate nucleus, central grey neucleus, grey matter of insular lobes. These images characteristics were consistent with clinical, laboratory results and considered presumptively in the diagnosis of CM. Differentiation of cryptococcal meningitis from other entities is necessary. A lots of mimics can distinguish with the cryptococcal meningitis, especially in the patients with HIV/AIDS. The enhanced lesions in the basal ganglia should considered toxoplasmosis, tubeculosis, virus encephalitis or primary lymphoma. Subependymal contrast lesions may be primary lymphoma or Cytomegalovirus encephalitis.

CONCLUSIONS

Cryptococcal meningitis is an opportunistic CNS infection that generally occurred in immunocompromised individuals, especially with HIV positive patients. These patients may suffer from serious complications with high mortality. Therefore, *Cryptococcal* neoformans meningitis should be considered in the diagnosis with images characteristic as pseudocyts, cerebral infarct, hydrocephalus, cryptococcoma in order not to delay diagnosis and treatment.

REFERENCES

1. Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. Supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.WHO.March 2018.

2. Williamson PR, Jarvis JN, Panackal AA, Fisher MC, Molloy SF, Loyse A. Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy. Nat Rev Neurol 2017;13:13-24.

3. Ngamskulrungroj P, Chang Y, Sionov E, Kwon-Chung KJ. The primary target organ of cryptococcus gattii is different from that of cryptococcus neoformans in a murine model. Mbio 2012;3(3):1917-8.

4. Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. Clin Infect Dis 2010; (50):291-322.

5. Liao CH, Chi CY, Wang YJ, Tseng SW, Chou CH, Ho CM, et al. Differentpresentations and outcomes between hiv-infected and hiv-uninfected patients with cryptococcal meningitis. J Microbiol Immunol Infect 2012;45:296-304.

6. Rajasingham R, Govender NP, Jordan A, Loyse A, Shroufi A, Denning DW, et al. The global burden of HIV-associated cryptococcal infection in adults in 2020: a modelling analysis. Lancet Infect Dis 2022 Aug 29.

7. Katchanov J, Branding G, Jefferys L, Arasteh K, Stocker H, Siebert E. Neuroimaging of HIV-associated cryptococcal meningitis: comparison of magnetic resonance imaging findings in patients with and without immune reconstitution. Int J STD AIDS 2016;27(2).

8. Loyse A, Moodley A, Rich P, Molloy SF, Bicanic T, Bishop L, et al.Neurological, visual, and MRI brain scan findings in 87 south african patients with HIV-associated cryptococcal meningoencephalitis. J Infect 2014;70(6):668-75.

9. Ruiz A, Post MJ, Bundschu CC. Dentate nuclei involvement in AIDS patients with CNS cryptococcosis: imaging findings with pathologic correlation. J Comput Assist Tomogr 1997;21(2):175-82.

10. Jain KK, Mittal SK, Kumar S, Gupta RK. Imaging features of central nervous system fungal infections. Neurol India 2007;55(3):241-50.