Review

Imaging characterization of cryptococcal meningoencephalitis

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Received 25 November 2015; revised 28 April 2016; accepted 16 May 2016
Available online

Abstract

Cryptococcus neoformans is the most common opportunistic CNS fungal pathogen in HIV-positive patients. About 7%—8% of the HIV-positive patients will have cryptococcal meningoencephalitis. Imaging plays an important role in the evaluation of cryptococcal infection of the brain. Abnormal findings correlated with higher risk of death. The paper will review the pathogenesis, pathology, imaging characterization and complication combined with cryptococcal meningoencephalitis.

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Keywords: Meningoencephalitis; HIV; MRI; HAART

1. Introduction

Cryptococcus neoformans was first described by Verse’ and then confirmed by Stoddard and Cutler 2 years later [1]. It is reported that the pathogen of cryptococcus is most common seen in nests and droppings of pigeon. Two types of Cryptococcus were grouped including C. neoformans and Cryptococcus gattii [1]. 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 [2].

Although cryptococcal infection is worldwide distribution, it is more commonly seen in the immuno-compromised patients. C. neoformans is the most common opportunistic CNS fungal pathogen in HIV-positive patients [3]. About 7%—8% of the HIV-positive patients will have cryptococcal meningoencephalitis [4,5]. 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 [6—8]. HIV infection is the leading factors along with estimated over 700,000 cases deaths annually and most common in sub-Saharan Africa [9]. Others factors included, long time use of corticosteroids, advanced malignancy, organ transplantation and so on [10,11]. The infection of cryptococcus can also occur in the immuno-competent patients, especially in the C. gattii infection [12]. With the development of immunology, new risk factors in apparently normal cryptococcal patients may be uncovered [13].

2. Pathogenesis of cryptococcal meningoencephalitis

It is important to understand the pathogenesis of the cryptococcus with the increasing rate of AIDS. The cryptococcal infection first initiated in the lung through inhalation of yeast cells. In a host with normal immune, inhaled cryptococci can be eliminated effectively. But in the immuno-compromised patients, the cryptococcal cells can proliferate, disseminate to the central nervous system, heamatogenously crossing the
blood–brain barrier and resulting in meningoencephalitis [14]. There are no effective anti-cryptococcal factors in the cerebral spinal fluid (CSF) and the fungal polysaccharide capsule can also avoid it from host inflammatory response [15].

Parenchymal or sub ependymal invasion of cryptococci are mostly coming through perivascular and subarachnoid space [16–19]. The lesions of basal ganglia are major hematogenously spread. Although any organ can be infected by cryptococci, CNS involvement is much more common and is the most common cause for patients’ death. Another common situation is that the pathogen is dormant, when the patients’ immunity decreased, the cells can be activated and leading to spread [1].

3. Pathology of cryptococcal meningoencephalitis

Three types of pathology could be seen in the cryptococcal meningoencephalitis [19]. First, slight inflammatory reaction combined with lymphocytes and few plasmocytes infiltration in 70% AIDS patients. Second, large amount of gelatinous pseudocysts with lots of C. neoformans in the VRS and adjacent basal brain caused through disseminating from the meningeal infection along the perivascular spaces. Sometimes, the mucinous pseudocysts are small, but larger cysts can also been seen in basal ganglia, cerebellum due to the confusion of smaller lesions. Third, parenchymal involvement from cryptococcus also have minimal inflammatory reaction and large amount of fungal organisms accumulated in the cortex or subcortical white matter through perivascular spaces connected to subarachnoid spaces or micro vessels. All of these process result from the immunodeficiency of phagocytic cell function in the VRS which leads to parenchymal invasion and proliferation.

4. Imaging characterization of cryptococcal meningoencephalitis

Not all of the cryptococcal meningoencephalitis had positive imaging findings. Normal brain imaging (47% by CT and 8% by MR) did not exclude cryptococcal meningoencephalitis. Approximately 21%–27% cases had typical cryptococcal meningoencephalitis on MRI [20]. The typical imaging appearances of cryptococcal meningoencephalitis include: dilated VRS, pseudocysts, cryptococcoma, leptomeningal or parenchymal enhancing lesions and hazy brain base [21–24]. Pseudocysts were named as lesions of round or oval hyperintensity on T2WI and hypo-intensity on both T1WI and FLAIR without restricted diffusion on DWI (iso- or hypo-intensity on DWI and slightly hyper-intensity on ADC) [20,25]. Pseudocysts can coexist with the dilated perivascular spaces (Fig. 1). As infection disseminates along the VRS that adjacent to perforating arteries, perivascular spaces may become large with this mucoid organism. Punctate hyperintensities on T2WI representing pseudocysts 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.

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 [18]. Cryptococcoma is more likely to be seen in immunocompetent patients [26]. Delayed imaging and double dose of contrast materials will better show meningeal and cryptococcoma enhancement [21,27].

Meningitis or meningoencephalitis was defined as leptomeningal or dural thickening combined with focal parenchymal edema (Fig. 2) [20]. FLAIR and contrast enhanced MRI are the most sensitive sequences to show the meningitis or meningoencephalitis. Not all of the meningitis or meningoencephalitis had obvious contrast enhancement and the reason maybe relate with the stage of inflammation and body immunity. 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 [16,17].

‘Hazy brain base’ sign can also been detected on MRI which was defined as an uniform and symmetrical hazy T2 signal increase on the basal brain such as basal ganglia, midbrain, thalamus and hypothalamus (Fig. 3). These areas are belonging to the anterior and posterior perforate substances where the perforating arteries enter the brain. The lesions show symmetrical hyperintensity on both T2WI and FLAIR. Hazy brain base was supposed to represents brain edema due
to fungal material penetration to the basal parenchyma along with perivascular spaces [20]. In the pre-era of using HAART, the inflammatory response around cryptococcomas is mild or absent due to the status of immunodeficiency of the patients [20]. With antifungal treatment and recovery of the immunity, the body can have ability to confine the infection to form abscesses or granulomas. Some papers reported that all patients under immune reconstitution had leptomeningeal enhancement and some combined with parenchymal involvement [20,28]. And meningeal enhancement correlated with high CSF white blood cell count (WBC). Other papers reported that cerebral atrophy had been less seen because of the decreased incidence of HIV-associated dementia after using HAART [41]. The treatment of HAART may have great effect on the imaging appearances of cryptococcal meningoencephalitis due to its verified effect on the local production of IL-8 and fungal virulence [9,10,42]. But some other papers did not find the effect of HAART on the imaging appearances. This needs further large cohort study to confirm and compare the prognosis with the different imaging characterization.

Cryptococcal infection can also occur in the HIV-negative patients and the predisposing factors are diabetes [29-32]. The basic imaging of cryptococcal infection in HIV-negative is similar to that of HIV-positive [33]. They are more likely to present with cryptococcomas, and contrast enhancement of cryptococcomas and meninges might occur more often as a result of an immunologic reaction by the host [34]. The main findings are meningoencephalitis and polycranial neuritis [32]. The main difference is that most HIV-negative patients with CNS cryptococcal infection will recover totally with appropriate therapy but HIV-positive patients will persist or aggravate pending on the immunity of the patients [32,33].

Imaging plays an important role in the evaluation of cryptococcal infection of the brain. Some literature reported abnormal findings correlated with higher risk of death [35,36]. MRS is a new technique that can also be applied in the evaluation of cryptococcal infection. Increased lactate and decreased NAA, choline and creatine suggested neuronal injury and gliosis [37-39]. Some paper reported that high concentration of alpha-trehalose is specific for diagnostic of Cryptococcus neoformans [40].

### 5. Complications of cryptococcal meningoencephalitis

Cerebral ischemic vascular disease can also combined with cryptococcal meningoencephalitis. Acute lacunar infarcts manifested hyperintensity on DWI and hypointensity on ADC.
(restricted diffusion) and majority of the lesions located at the brain area supplied by perforating artery. Acute infarction 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. 4% of patients with cryptococcal meningoencephalitis can have cerebral infarctions the acute stage or during the treatment [18].

Intracranial hypertension (ICH) is one of the most severe neurological complications and morbidity and mortality are high [41,42]. Approximately 50% of patients with cryptococcal meningoencephalitis had ICH and with intracranial pressure over than 200 mm H2O [42]. The mechanism for the ICH maybe related with the occlusion of CSF outflow from a great burden of yeasts and polysaccharide staying the arachnoid villi. Lumber puncture or inadequate CSF drainage maybe risks for the development of brain stem herniation [43], CT or MRI revealed normal or decreased size of ventricles. MRI sagittal imaging can clearly detect the brain stem herniation.

Hydrocephalus is the most common complication. The reason for the obstructive hydrocephalus may be related with cryptococcomas within the choroid plexus or subependymal area [22,33,44].

Calcification was rare but can be detected and this can be regarded as a sequela from chronic infection [17,23].

6. Interaction between Immune reconstitution syndrome and cryptococcal meningoencephalitis after HAART

Immune reconstitution syndrome (IRS) was defined as emergence of a past quiescent or incubating infection after HAART therapy [45-47]. IRS is a serious complication associated with cryptococcal meningoencephalitis. It can occur within 1-4 weeks or 2-4 months after institution of HAART [20]. One paper reported that a case with recurrent cryptococcal meningoencephalitis combined with IRS eight years after the initial diagnosis of cryptococcal meningoencephalitis [35,46]. 10%—42% of CM patients will develop IRS and 66% of them will die from it. In China the occurrence of IRS is about 17.5% in CM patients. The pathogenesis of these entities is still controversial. The definitive diagnostic criteria and therapeutic guidelines for IRS still need further investigation. Combination of antifungal and corticosteroid therapy may be effective and worthwhile [12,13].

7. Differentiation of cryptococcal meningoencephalitis from other entities

Lots of mimics can combine with the cryptococcal meningoencephalitis, especially in the patients with AIDS. The enhanced lesions in the basal ganglia should considered toxoplasmosis or primary lymphoma. Subependymal contrast lesions may be primary lymphoma or cytomegalovirus encephalitis.

In a word, there are some of the important imaging findings of the cryptococcal meningoencephalitis, including: diluted VRS, pseudocysts, cryptococcoma, leptomeningeal or parenchymal enhancing lesions and hazy brain base. Therapy of HAART can help patients gain immunity and it has a great effect on the imaging appearances of cryptococcal meningoencephalitis with more contrast enhancement. IRS could also coexist with the cryptococcal meningoencephalitis and combined treatment of antifungal and corticosteroid therapy may be effective and worthwhile.

References


