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Concurrent Presence of Cryptococcal Meningitis and Neoplastic Meningitis in a Recipient of Hematopoietic Stem Cell Transplantation: A Case Report

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Abstract

Introduction: Cryptococcal meningitis is a rare disorder that is caused by *Cryptococcus neoformans* in immunocompromised host.
Case Presentation: The case was a 64-year-old man with a history of stem cell transplant for acute leukemia, who presented chronic meningitis caused by *Cryptococcus neoformans* and concurrent neoplastic meningitis with presence of malignant cells only in his cerebrospinal fluid (CSF).
Conclusions: Chronic meningitis in immunocompromised hosts can be due to more than one pathologic etiology and we should do all diagnostic evaluation to rule out all possible differential diagnosis.

Keywords: Cryptococcal Meningitis, Neoplastic Meningitis, Meningeal Co-Infection, Hematopoietic Stem Cell Transplant

1. Introduction

Although cryptococcosis is most often associated with HIV infection, in many centers, especially in more developed countries, the majority of cases occur among non-HIV-infected individuals including transplant recipients and patients, who are receiving immunosuppressive agents (1).

Little information is available regarding central nervous system (CNS) relapse of adult leukemia after allogeneic hematopoietic stem cell transplantation (HSCT) (2).

We presented an extremely rare case of CNS relapse of leukemia five years after HSCT and concurrent cryptococcal meningitis.

2. Case Presentation

A 64-year-old retired man was admitted to the emergency department of Bahman hospital in Tehran, Iran. He complained of transient loss of consciousness. He did not recall the amount of time he was unconscious. He also had a moderately severe, bi-frontal headache and limb paresthesia for the last four months. The most important point in his past medical history was a history of Acute Myeloid Leukemia (AML) (M3) and allogenic stem cell transplant five years ago. He also had a history of GVHD six months after the transplant. He had cyclosporine and prednisone as his prescribed medication.

He had travelled to the USA last year and stayed there for one month. Physical examinations were unremarkable. The results of brain magnetic resonance imaging (MRI) and electroencephalogram (EEG) were normal.

Laboratory evaluations showed a serum white blood count (WBC) of 7000 cell/mm^3 with 58% neutrophil, 24% lymphocyte, 9% monocyte, and 1.7% eosinophil. Peripheral blood smear was normal. Human immunodeficiency virus (HIV) test was negative. Cerebrospinal fluid specimen was colorless, with a normal opening pressure and 4200 cell/mm^3 (90% lymphocyte), glucose 40 mg/dL (with BS: 130) and protein 102 mg/dL. There was no microorganism on Gram stain. India ink preparation showed nothing.

Since the suspicion was infectious meningitis and the patients clinical condition was severe, his treatment was started with broad spectrum antibiotics (vancomycin and meropenem), antiviral (acyclovir) and antituberculosis drugs (isoniazid, rifampin, ethambutol, pyrazinamide) and vitamin B6 were started while waiting for the cytology and cultures of the CSF. We also evaluated his CSF for all the causes of chronic meningitis (the results are shown in Table 1).

Two days later, polymerase chain reaction (PCR) testing of CSF was negative for TB, but PCR for Cryptococcus was

Table 1. Evaluation of Cerebrospinal Results for Chronic Meningitis

Test	Result
AFB stain	Negative
Culture for mycobacteria	Negative
Mycobacterium tuberculosis PCR	Negative
ADA	Normal
Gram staining	Negative
VDRL	Negative
CMV PCR	Negative
Cryptococci PCR	Positive
Cryptococcal Antigen	Weekly positive
India ink	Negative
Culture for fugus	Negative
CMV PCR	Negative
Adenovirus PCR	Negative
EBV PCR	Negative
Wright	Negative
Cytology	Malignant cells were seen
Flow cytometry	leukemic blast: about 90%, with granules and Aure rods
ACE level	Normal

positive and serum cryptococcal antigen was positive as well. Cytology test and flow cytometry of CSF revealed presence of malignant cells (leukemic blast: about 90% with granules and Aure rods) in the CSF, establishing the diagnosis of cryptococcal meningitis and concurrent CNS infiltration. Bone marrow aspiration confirmed AML relapse.

Instead of antibiotics (antiviral and anti-tuberclosis agents) the patient started receiving Amphotericin B, and was scheduled for chemotherapy.

Two weeks after starting antifungal therapy, he felt well and was referred for chemotherapy. Unfortunately four weeks after he received intrathecal chemotherapy his clinical condition was complicated with hospital acquired pneumonia and finally he died from respiratory failure.

3. Discussion

Central nervous system (CNS) infiltration in Acute Myeloid Leukemia (AML) is a rare event with an estimated incidence below 5% at diagnosis. In one study the overall frequency of neoplastic meningitis (NM) throughout the whole treatment period including primary diagnosis, all cytoreductive chemotherapy cycles and also post-transplant course was as high as 15% (3).

Clinical presentation of CNS involvement in AML may be indolent. However, patients with symptoms of increased intracranial pressure such as mental changes and headache, cranial nerve palsies, CNS hemorrhage, symptoms of spinal cord compression, and visual changes should be checked for CNS infiltration with lumbar puncture and radiology imaging studies. Most patients exhibit moderate elevation in protein and moderate decrease in glucose, which was true for our patient's CSF. Computerized tomography (CT) and MRI, can exclude hemorrhage, stroke, and brain tumor. In addition, in case of cranial nerve palsies and negative CSF, MRI can prove very helpful in recognizing signs of CNS infiltration (4). In our case, neither brain MRI nor brain CT scan was indicative of CNS infiltration.

Cryptococcus is an opportunistic fungus that is an important cause of CNS infections among immunocompromised patients, but it has only rarely been reported in non-HIV-positive patients. The most common forms of immunosuppression (other than HIV) include chronic glucocorticoid use, history of organ transplantation, malignancy, as well as sarcoidosis and liver failure (5).

A study has shown that patients with an immunosuppressed condition, especially T-cell suppression, may present less typical clinical manifestations of meningitis (6). The clinical manifestations of cryptococcal meningitis depend largely on the host immune status. Nausea, vomiting, and altered mental status occur in about half of the patients. Signs and symptoms of meningismus affect less than 25% of patients. Visual symptoms, such as diplopia and blindness, occur in about 20% of patients, most often in immunocompetent patients. Seizures and focal neurologic deficits occur in 10% of patients and are generally caused by space-occupying lesions such as cryptococcomas or granulomas (7).

Our purpose to introduce this patient was remembering the important point that in immunocompromised hosts, especially patients, who manifest with neurologic symptoms, diagnostic evaluations should be done completely and all differential diagnosis should be ruled out because of the possibility of more than one pathologic process as an etiologic agent and empiric treatment with antibiotics, antivirals, antifungals, and steroids should be implemented on a case-by-case basis. Also tuberculosis is the leading cause of chronic meningitis in our country, thus we should be aware of its other causes, and even co-infections. Moreover, cryptococcal infections have been infrequently reported from Iran, but all the factors for its existence are available in this part of the world (8) and central nervous system co-infection with tuberculosis and *Cryptococcus neoformans* has also been reported (9).

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