Acta Neurophysiologica

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Case Report *Volume 4 Issue 7*

Invasive Aspergillosis in Hematologic Malignancies: A Case Report and Review of Literature

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Received Date: June 19, 2023; **Published Date:** September 12, 2023

Abstract

We report here a case of 25 year old lady diagnosed with acute lymphoblastic leukemia (ALL) who was on chemotherapy since 5 months, complained to headache. Headache was evaluated. MRI of the brain showed ring enhancing lesion in the left parieto-occipital region. CSF analysis was done- routine biochemical tests, cultures and PCR based tests were done. PCR test was positive for aspergillus species. As the patient was diagnosed with central nervous system (CNS) aspergillosis, she was started on voriconazole. Patient improved clinically.

Keywords: Acute Lymphoblastic Leukemia (ALL); Central Nervous System (CNS); Aspergillosis

Abbreviations: All: Acute Lymphoblastic Leukemia; CNS: Central Nervous System; CSF: Cerebrospinal Fluid; AML: Acute Myeloid Leukemia; IPA: Invasive Aspergillosis.

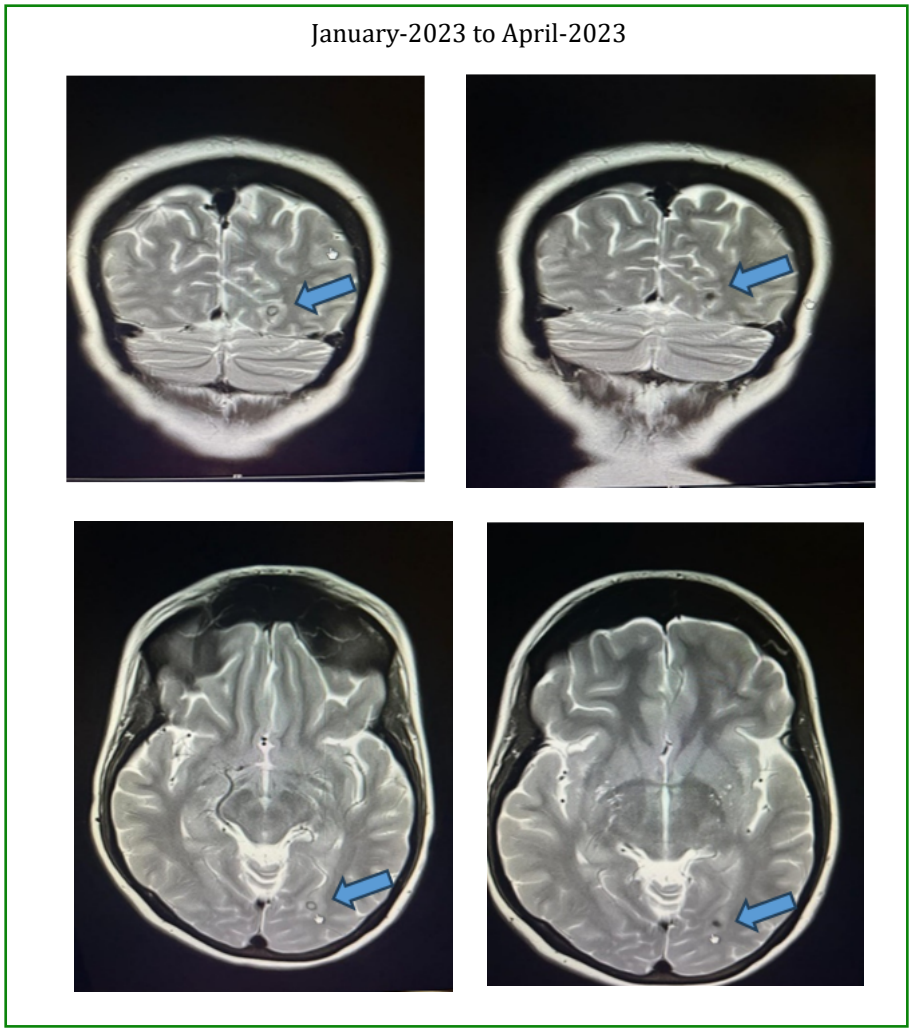
Introduction

Invasive aspergillosis is an air-borne disease and the majority of patients develop pneumonia or sinusitis [1]. However, central nervous system (CNS) aspergillosis occurs at a frequency of 14% to 42% among patients with invasive aspergillosis and acute leukemia or allogeneic stem cell transplantation [2,3]. Moreover, Aspergillus has been identified as the most frequent agent causing brain abscesses in bone marrow transplant patients [4]. The prognosis of invasive aspergillosis is related to the pattern of organ involvement. Localized pulmonary disease has the lowest reported mortality, whereas disseminated or CNS aspergillosis has a mortality approaching 100% [5,6]. In healthy subjects, macrophages and polymorphonuclear leukocytes are effective defences against the ubiquitous Aspergillus [7]. However, in patients with leukemia, the diseased white blood cells impair immune responses, facilitating fungal colonization which becomes manifest with neutropenia, mucosal damage and immunosuppression due to induction chemotherapy [8]. Aspergillus spp. are common in the environment (soil, dust, plants, and decaying vegetable matter) that are inhaled by breathing normal air, and the lungs have the highest chance of exposure to infection [9]. Thus, the portal of entry for Aspergillus usually lies in the respiratory tract and CNS involvement arises as a result of hematogenous spreading from the lung or through direct invasion of the adjacent cranial structure, surgery, contamination of indwelling catheters, and iatrogenic or penetrating trauma [10].

Case Report

25-year-old lady, was diagnosed with T-Acute lymphoblastic leukemia (T-ALL) in September 2022. She was started on chemotherapy with BFM 2002 protocol for treatment of

ALL. When the patient was in consolidation chemotherapy with high dose methotrexate 5g/m2 in January 2023, she complained of headache for a duration 1 week, the headache was insidious in onset, non-progressive, dull boring pain, not associated with vomiting or blurring of vision, on examination- there were no focal neurological deficits, she was evaluated with magnetic resonance imaging of the brain which showed a 0.5x0.5cm ring enhancing lesion. The lesion was located in the parieto-occipital region and was planned to be biopsied, but because it was too small, the procedure was not done. Lumbar puncture was done, and cerebrospinal fluid (CSF) was sent for routine biochemical tests and CSF cell count-01 cells and cell type- lymphocyte, negative for malignancy, protein-61mg/dl, glucose-52mg/dl, AFB stain- negative, CSF cryptococcal antigen- negative, fungal culture- negative. CSF molecular panel by PCR. The molecular panel was reported positive for Aspergillus species. She was diagnosed as possible - CNS aspergillosis (as per recent nomenclature of IFD) and was started with injection Voriconazole 6 mg/kg BD*1 day and anti-edema measures with Inj. Mannitol and Inj. Dexamethasone 4mg IV BD, followed by 4mg IV BD for 5 days and then continued with tablet voriconazole 200 mg BD. Clinically, she became better; her headache decreased. Repeat MRI of the brain was done, and the results point to a reduction in the size of the ring-enhancing lesion. Patient received a total treatment for 24 weeks. Hence early identification and immediately starting her on Voriconazole was lifesaving (Figure 1).



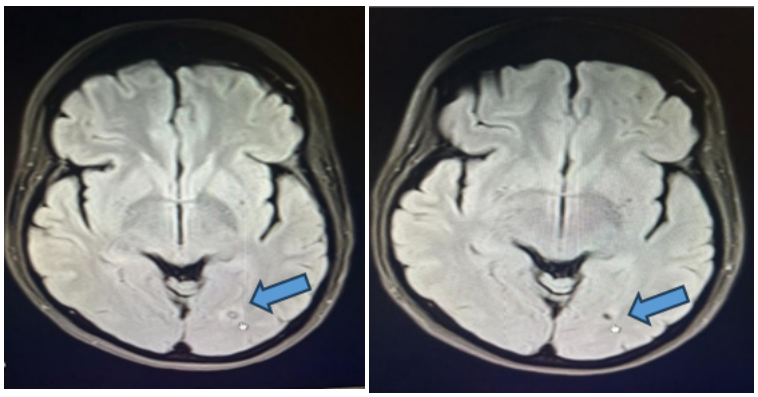


Figure 1: Magnetic resonance imaging of the brain which showed a 0.5x0.5cm ring enhancing lesion located in the parieto-occipital region.

Discussion

For patients with leukemia, especially Acute Lymphoblastic and Myeloid Leukemia (ALL and AML), by receiving intensive cytotoxic chemotherapy and several previous chemotherapy regimens, immunodepression with hypogammaglobulinemia inherent to the primary disease and neutropenia caused by infiltration of bone marrow are at increased risk of CNS aspergillosis [11,12]. The common antifungals used for prophylaxis include fluconazole or posaconazole. There is very limited data on adult ALL patients and the precise antifungal prophylaxis to be used.

Invasive aspergillosis (IPA) is caused by one of the four species of aspergillus- *A. fumigatus, A. flavus, A, niger or A. terreus*. It is increasingly seen in immunocompromised hosts like in those receiving chemotherapy or undergoing SCT or solid organ transplants. The diagnosis of IPA is challenging due to nonspecific nature of the symptoms. CNS aspergillosis can be life threatening as it is a rare and potentially dangerous infection. The primary acquisition route for acquiring aspergillus is the inhalation of fungal conidia, which are spores that subsequently reach the upper and lower respiratory tract. Therefore, the paranasal sinus and the lungs are the most common sites of primary aspergillus infection [11]. However, 40% of patients develop extra pulmonary manifestation, with 10–20% demonstrating CNS involvement [12]. One of the most important risk factors for brain infections are neutropenia and corticosteroid use. In this population, a mortality rate of > 90% has been reported [12]. Patients may present with fever, headache, lethargy, altered mental status, seizures, dizziness, gait disorders or other focal neurological deficits.

However, our results showed that on conventional MRI sequences in patients with leukemia, CNS aspergillosis appears as ring-enhancing lesions, with perifocal edema on MRI. Brain CT has not proven useful in the case of Aspergillus meningitis, which has no parenchymal lesions, while Gadolinium-enhanced MRI of the brain ensures a more efficient diagnosis of the infection [13,14]. As mentioned earlier, CSF analysis was normal in most of the patients because neutropenic patients with fungal meningitis do not always show elevation of the CSF cell count [13]. Detection of Aspergillus DNA from CSF samples is possible and helpful in diagnosing cerebral aspergillosis and can assist in distinguishing this disease from other cerebral conditions with space-occupying lesions in immunocompromised patients. Indeed, the diagnostic gold standard relies on histopathological examination of brain-tissue biopsies, which are rarely performed.

The finding that Aspergillus DNA could be detected in CSF samples but rarely in blood samples supports the hypothesis that PCR is more likely to detect fungal elements at the site of infection than in blood samples, because of the lack of fungemia during antifungal treatment PCR testing of CSF samples is recommended for patients for whom CNS IA is suspected, especially for those whose clinical condition does not allow invasive procedures as a positive PCR result makes the presence of CNS IA in that patient population highly likely Imbert S, et al. [15]. Performance of Aspergillus PCR in cerebrospinal fluid for the diagnosis of cerebral aspergillosis-Seventeen patients had proven/probable invasive aspergillosis according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria, including 12 cases of proven/probable cerebral aspergillosis. Aspergillus PCR in CSF was positive in nine of the twelve patients with cerebral aspergillosis, i.e. 75% sensitivity. In contrast, CSF culture was positive for Aspergillus in only two patients. In the non-cerebral aspergillosis group (60 patients), PCR was positive in one patient, i.e. 98.3% specificity. In this particular population of high-risk patients with suspicion of cerebral aspergillosis,

the disease incidence was 16.7%. Therefore, the positive and negative predictive values of PCR were 90% and 95.2%, respectively. The results of this study indicate that Aspergillus PCR in CSF is an interesting tool that may eliminate the need for cerebral biopsy in patients with suspected cerebral aspergillosis.

Pagano L, et al. [3] Invasive aspergillosis in patients with acute myeloid leukemia: a SEIFEM-2008 registry study, One hundred and forty cases of invasive aspergillosis were collected, with most cases occurring during the period of post-induction aplasia, the highest risk phase in acute myeloid leukemia. The mortality rate attributable to invasive aspergillosis was 27%, confirming previous reports of a downward trend in this rate. Univariate and multivariate analyses revealed that the stage of acute myeloid leukemia and the duration of, and recovery from, neutropenia were independent prognostic factors. We analyzed outcomes after treatment with the three most frequently used drugs (liposomal amphotericin B, caspofungin, voriconazole). No differences emerged in survival at day 120 or in the overall response rate which was 71%, ranging from 61% with caspofungin to 84% with voriconazole.

In this case the patient presented with complaints of headache with the background of underlying haematological malignancy – T-ALL who was on chemotherapy. She was on antifungal prophylaxis with fluconazole due to the financial constraints, she could not be started on higher antifungal prophylaxis. Brain imaging was done with gadolinium enhanced MRI, which showed a ring enhancing lesion. Belonging to developing country like India, the first suspicion was Tuberculosis with other differentials being cryptococcal infection, toxoplasma followed by aspergillosis. CSF analysis was done and sent for routine biochemical tests, AFB staining, India ink preparation which were all negative, so the possibility of TB and Cryptococcus was ruled out. Cultures were negative. Meanwhile, PCR test was done which was positive for aspergillus species. Doing a biopsy on a deep seated small lesion in an immunocompromised patient with neutropenia would do more harm that benefit to the patient, because of which the biopsy was deferred. So we would like to conclude that use of prophylactic antifungals in acute leukemia like ALL and strong clinical suspicion followed by early and reliable diagnostic tests and initiation of appropriate anti-fungal will benefit the patients which is clearly evident clinically and on the MRI brain imaging.

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