CASE REPORT

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A Case of Pulmonary and Central Nervous System Invasive Aspergillosis With Characteristic Radiological Findings

Turkay Akbas,[1] Fatih Karahan,[2] Hayri Ogul,[3] Birgul Onec,[4] Attila Onmez,[2] Nisa Unlu,[3] Ege Gulec Balbay[5]

Abstract

Central nervous system invasive aspergillosis is a rare and fatal infection that accounts for the majority of brain lesions in immunocompromised patients. A 56-year-old man with diabetes mellitus and non-Hodgkin's lymphoma was admitted to the emergency department with a diagnosis of pneumonia-related sepsis. At presentation, cranial computed tomography (CT) and magnetic resonance imaging were normal. However, thoracic CT revealed right lung pneumonia, and antibiotic therapy was initiated. Control CT scans performed on the 13th day of admission—because the patient had subsequently become hypotensive and somnolent— revealed halo signs in the lungs and multiple hypodense lesions within the cerebrum, consistent with invasive aspergillosis. A post-contrast cranial CT scan also revealed vascular enhancement within these hypodense lesions, known as the central vascular sign. In conclusion, central nervous system aspergillosis can be diagnosed by means of tubular enhanced foci in hypodense lesions on contrast-enhanced CT scans.

Keywords: Cranial lesion; Immunosuppression; Invasive aspergillosis; Lymphoma; Sepsis.

[1]Division of Intensive Care, Department of Internal Medicine, School of Medicine, Duzce University, Duzce, Turkiye
[2]Department of Internal Medicine, School of Medicine, Duzce University, Duzce, Turkiye
[3]Department of Radiology, School of Medicine, Duzce University, Duzce, Turkiye
[4]Division of Hematology, Department of Internal Medicine, School of Medicine, Duzce University, Duzce, Turkiye
[5]Department of Pulmonology, School of Medicine, Duzce University, Duzce, Turkiye

Address for correspondence:
Turkay Akbas, MD. Division of Intensive Care, Department of Internal Medicine, School of Medicine, Duzce University, Duzce, Turkiye.
E-mail: turkayakbas@yahoo.com

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Introduction

Central nervous system (CNS) aspergillosis is a rare but fatal CNS infection, mostly affecting immunocompromised patients. Diagnosis requires a high level of awareness and suspicion, since there are no typical clinical signs and symptoms. Patients may present with headache, cranial nerve deficits, dysarthria, changes in mental status, hemiparesis, seizures, and coma.[1] The primary site of infection following hematological dissemination of *Aspergillus* is the lungs in immunocompromised patients, while in immunocompetent individuals, the paranasal sinuses are the primary site of infection following direct invasion from adjacent tissues.[2] Risk factors for CNS aspergillosis are similar to those for invasive pulmonary aspergillosis (IPA). Immunocompromised states include hematological malignancies, allogeneic hematopoietic stem cell transplantation, solid organ transplantation, prolonged corticosteroid use (prednisolone or

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equivalent > 20 mg for > three weeks), prolonged neutropenia (< $0.5x10^9$ neutrophils/L for > 10 days), Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS), and the use of chemotherapy for cancer, as well as immunosuppressive agents for systemic inflammatory disease.[3-6] A number of other disease states can predispose patients to developing invasive aspergillosis (IA). These include chronic renal failure requiring renal replacement therapy, chronic alcohol abuse, chronic obstructive pulmonary disease (COPD) with chronic corticosteroid use, liver cirrhosis/acute liver failure, and diabetes mellitus (DM).[2,4,5] Immunocompetent critically ill patients in the intensive care unit (ICU) are also at risk of developing IA. This is because they exhibit immunosuppressive states following the initial hyper-inflammatory state of sepsis and multiorgan failure, characterized by neutrophil deactivation.[4,7] Additionally, many patients with risk factors for IA are admitted to the ICU, where they may develop the condition during the course of critical illness care. Cranial and lung computed tomography (CT) images assist clinicians in diagnosing IA by revealing specific findings, such as halo and air crescent signs in the lungs, and hypodense lesions with contrast-enhanced tubular structures in the CNS.[4,8] Since the vessels are invaded or thrombosed by *Aspergillus* hyphae, they become particularly apparent on post-contrast radiological images. We describe a case of a patient with non-Hodgkin's lymphoma (NHL) and DM who was admitted to the ICU due to pneumonia-related septic shock, later developed IPA and CNS aspergillosis in the ICU, and exhibited characteristic radiological findings at CT of the brain and lungs.

Case Report

A 56-year-old man with DM, suspected of having NHL due to multiple lymphadenopathies, was examined following a tru-cut biopsy procedure performed one month previously. He had not received treatment during this period because examinations for a definitive diagnosis and staging were still ongoing, and his general condition began to deteriorate after the excisional biopsy. He was admitted to the emergency department with complaints of fever (38.9°C), productive cough, and loss of appetite, persisting for a week. Upon admission, the patient was tachypneic (25 breaths per minute), lethargic (Glasgow coma scale [GCS] score of 13), and hypotensive (blood pressure at 95/45 mm Hg). Cranial CT and magnetic resonance imaging (MRI) at presentation were normal. However, a thoracic CT revealed pneumonia in the right lung. Consequently, the patient was admitted to the ICU with a diagnosis of pneumonia-related sepsis, requiring high-dose noradrenaline infusion (0.5 μg/kg/minute). Previous cranial, thoracic, and abdominal CT scans conducted during the NHL diagnosis were normal, except for the para-aortic lymph nodes, which measured 2.5 cm. Piperacillin-tazobactam, teicoplanin, and clarithromycin were initiated as antibiotic therapies in the ICU. Admission laboratory studies indicated thrombocytopenia ($54x10^9$/L), a low partial pressure of oxygen to fractional inspired oxygen ratio (PaO_2/FiO_2=210 mm Hg), and elevated creatinine (1.4 mg/dL). Given the patient's deteriorating state of consciousness and deepening cytopenias, and since CNS involvement could not be ruled out with non-contrast radiological imaging, dexamethasone therapy (32 mg/day, with a planned reduction to 8 mg every three days) was initiated due to the known dramatic response of both cytopenias and CNS involvement to steroid treatment. Cerebrospinal fluid (CSF) analysis was not performed due to thrombocytopenia. The patient responded well to the antibiotics, with his GCS score improving to 15 by day 4, and he became vasopressor-free by day 7. However, he became hypotensive again with a GCS score of 10 on day 13, necessitating the restart of noradrenalin at 0.15 μg/kg/minute. Chest and cranial CT scans showed mass lesions with surrounding halo signs, primarily in the left lung (Figure 1), and multiple new hypodense cerebral lesions in both hemispheres, measuring 1.8 x 2.2 cm, with vascular contrast enhancement, and a

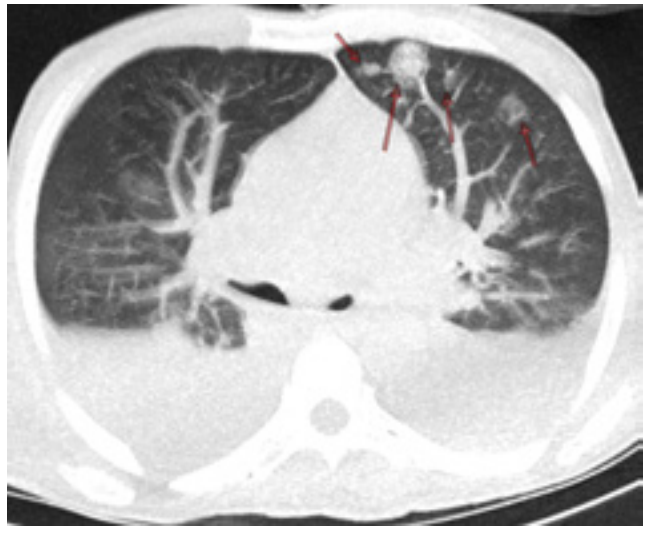

Figure 1. Axial CT scan in the parenchymal window showing multiple nodular lesions (arrows) with peripheral ground glass density.

2.5 x 5.5 cm hemorrhagic lesion in the right temporal lobe (Figures 2A, 2B, and 2C). Radiologically, these lesions in the lungs and CNS were consistent with IA.[8] Lumbar puncture was not performed due to the presence of multiple intracranial lesions, thrombocytopenia, and hemorrhage in the left temporal lobe. The galactomannan test could not be conducted due to its unavailability at the hospital. Voriconazole therapy was initiated following the collection of bronchoalveolar lavage (BAL) fluid on day 14, with a loading dose of 6 mg/kg every 12 hours on the first day, followed by 4 mg/kg every 12 hours intravenously thereafter. This therapy was planned to continue for at least six months. Neurosurgical excision of the lesions was not considered due to the presence of multiple lesions in the bilateral cerebral hemispheres. The patient responded well to voriconazole therapy, and the noradrenaline infusion was stopped on day 19. *Aspergillus fumigatus* was identified in the BAL culture. The patient was transferred to the ward on day 25 with normal vital signs and laboratory parameters, except for thrombocytopenia ($70x10^9$/L), and a GCS score of 13. A control cranial CT performed on day 40 showed resorption of the left temporal lobe hemorrhage and an approximately 25% reduction in the size of the other cranial lesions (Figures 3A and 3B). The patient became hypotensive on day 45 and was readmitted to the ICU. Blood cultures revealed *Klebsiella pneumoniae*, prompting the addition of meropenem to the voriconazole therapy. The patient did not respond to the antibiotherapy and died three days later. The total duration of hospitalization was 48 days, with mortality occurring on the 35th day of voriconazole therapy.

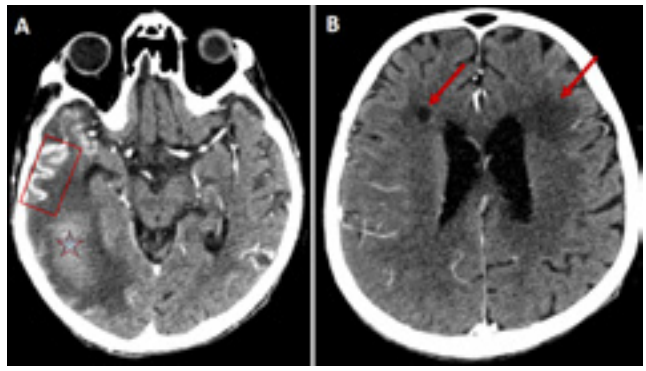

Figure 3 (a, b). Post-contrast control CT scans (A and B) indicating partial resolution of the right temporal hemorrhage (star) and parenchymal aspergillomas (arrows). The axial CT scan (A) also reveals contrast enhancement in the right temporal gyriform region (frame).

Discussion

Aspergillus is a ubiquitous fungus commonly found in the upper respiratory tract, including the external ears. The majority of patients develop invasive lung infections after inhaling spores (conidia). Hematological dissemination of the infection occurs after *Aspergillus* hyphae invade the blood vessels. *Aspergillus* can infect any organ in the body, with the CNS often being the first affected.[1,10] CNS aspergillosis is the most severe sequela of opportunistic fungal infections, with a mortality rate as high as 65%, generally stemming from IPA.[2,9] Angioinvasion by *Aspergillus spp*. typically results in brain infarcts with or without hemorrhage, as well as thrombosis in small arterial vessels caused by *Aspergillus* hy-

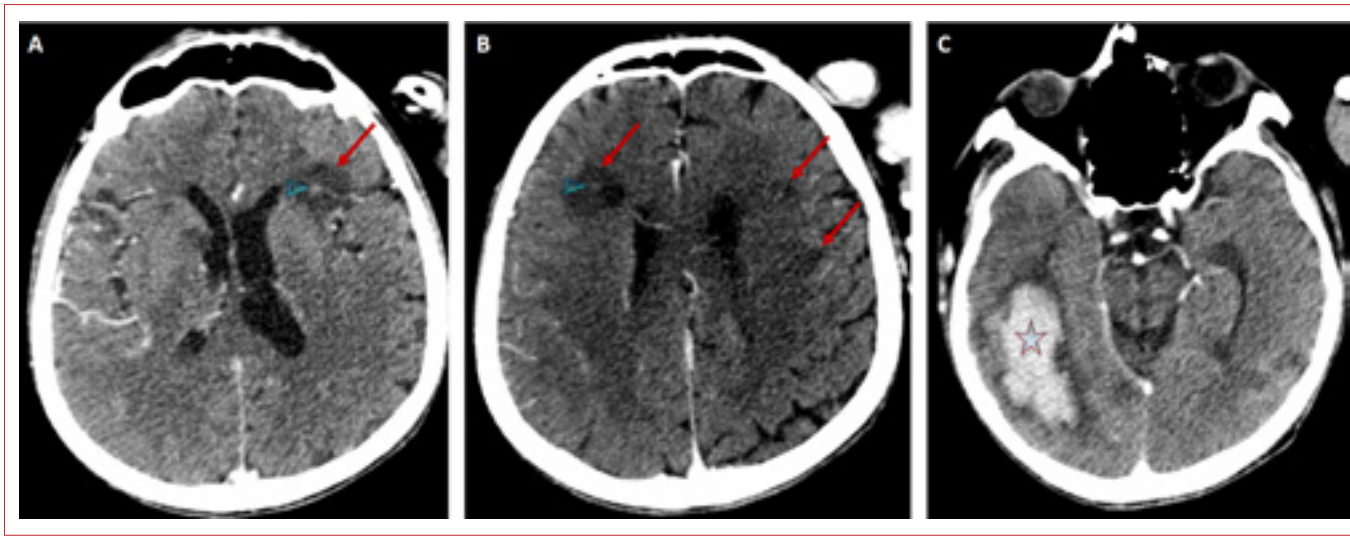

Figure 2 (a-c). Post-contrast consecutive axial CT scans (A and B) revealing multiple hypodense lesions (arrows) with a central vascular sign (arrow heads). The axial CT scan (C) from the brain stem level shows right temporal intraparenchymal hemorrhage (star).

phae.[10] Sterile infarcts become septic necrotic areas once the fungus breaches the vessel wall, extending into the ischemic brain parenchyma. In immunocompromised patients, CNS *Aspergillus* infection may manifest as solid or multiple irregular lesions within the hemispheres and/or cerebellum. Conversely, in immunocompetent patients, a reactive mass with a thick fibrous capsule develops around the infected sites to curb the spread of the infection.[2,11] Brain abscesses, epidural abscesses, vasculitis, or stroke-like lesions are more frequently observed in immunocompromised individuals, whereas granulomatous lesions are most common in immunocompetent patients.[8,11]

CNS aspergillosis is classified as definite or probable based on predefined diagnostic criteria.[3] A definitive diagnosis can be made through histological or cultural evidence of *Aspergillus spp*. in brain specimens obtained by needle aspiration/biopsy or from CSF analysis. Given that CNS biopsies are not performed in all cases, a probable diagnosis of CNS aspergillosis relies on host risk factors, clinical manifestations, radiologic findings, mycological testing, and/or positive cultures with *Aspergillus* growth from other sterile sites or BAL samples. The presence of the galactomannan antigen (a cell wall polysaccharide) supports the diagnosis of aspergillosis, albeit with low sensitivity in critically ill patients.[4] Cranial MRI and CT scans are commonly used radiological tests for diagnosing CNS aspergillosis. The presence of contrast enhancements in the lesions can support the diagnosis. Yamada et al.[8] reported that CT examinations revealed contrast enhancement in 25% of cranial lesions, while MRI showed contrast enhancement in 56% of such lesions. Vessels invaded or thrombosed by *Aspergillus* hyphae become visible in post-contrast cranial CT scans. Voriconazole is the first-choice drug for both IPA and CNS aspergillosis, with Amphotericin B being the second-line drug. Neurosurgical interventions, such as draining or excising lesions in suitable cases in addition to antifungal therapy, increase the likelihood of prolonged survival.[2,9,12] Kourkoumperis et al.[2] reviewed 123 patients with CNS aspergillosis and found at least one risk factor for aspergillosis in all cases, with the main comorbidities being DM, hematological malignancy, transplantation, HIV/AIDS, autoimmune diseases, and COPD. Sixty (48.8%) of these 123 patients were on some form of immunosuppressant medication, and 25 (20.3%) were using steroids. The lungs and paranasal sinuses were the primary sites of infection. Targeted therapies included amphotericin B and voriconazole. Neurosurgical procedures, such as abscess drainage, excision of the infected mass, and debridement of bones, were performed in 49 cases. Mortality rates were 28.6% in patients who underwent neurosurgical procedures, compared to 67.5% in those who did not.

The patient in this report had DM and had recently been diagnosed with NHL. He was hospitalized for pneumonia-related sepsis and multiorgan failure. High-dose dexamethasone therapy was initiated in the ICU. Corticosteroids and DM both impair the phagocytic activity of leukocytes.[13,14] As previously discussed, the immune suppression phase of sepsis follows an initial episode of hyper-inflammation, leaving patients susceptible to invasive fungal infections. Our patient, therefore, had four risk factors for IA, including DM, critical illness, NHL, and corticosteroid use. Clinically, IA manifested as hemodynamic instability and changes in mental state toward the end of the second week of hospitalization. Probable CNS aspergillosis was diagnosed due to the presence of host risk factors, clinical features, characteristic radiological findings, and the growth of *Aspergillus fumigatus* from BAL. Following the diagnosis, voriconazole treatment was immediately initiated with a plan to continue therapy for at least six months. Neurosurgical procedures were not performed due to the presence of multiple lesions in both hemispheres of the brain. A control cranial CT scan three weeks later revealed a reduction of approximately 25% in the size of the lesions and resorption of the right thalamic hemorrhage. Unfortunately, the patient succumbed to hospital-acquired *Klebsiella pneumoniae* bacteremia.

Conclusion

CNS aspergillosis represents a severe form of disseminated IA, associated with a high mortality rate that often occurs in conjunction with IPA. Diagnosing this condition requires a high degree of clinical suspicion, as it does not manifest with distinctive signs and symptoms. Additionally, it is crucial to exclude other possible causes of intracranial mass lesions. Cranial CT imaging aids in the diagnosis by identifying contrast-enhanced tubular areas within hypodense lesions. Upon confirmation of the diagnosis, prompt initiation of antifungal therapy is imperative. Furthermore, surgical interventions should be considered in cases where they are deemed appropriate.

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