Acute Stroke as First Manifestation of Cerebral Aspergillosis

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Objectives: To describe the neurological manifestations of invasive aspergillosis presenting with a focal neurological deficit compatible with an acute stroke. *Materials and Methods:* Retrospective analysis of a clinical series of patients between 2011 and 2017 with invasive aspergillosis and neurological symptoms compatible with an acute brain stroke. Clinical and epidemiological data, microbiological results, radiological findings, treatment, and course were recorded. *Results:* Five patients were selected with a mean age of 55.4 years. All patients were immunosuppressed. In 4, systemic infection was unknown. In every case, neurology on call was alerted because of acute focal neurological symptoms. None of the patients received revascularization procedures. Galactomannan antigen was positive in all of the patients and culture was positive in 3. Mortality was 100% despite specific antifungal treatment. *Conclusions:* Acute stroke can be the first manifestation of disseminated aspergillosis. This form of presentation was frequent in our series and should be suspected in immunocompromised patients with acute neurological deficits.

Key Words: Neuroaspergillosis—acute stroke—antifungal therapy—invasive aspergillosis

Introduction

Invasive aspergillosis (IA) is the result of the systemic spread of infection by *Aspergillus* spp. and it is a rapidly progressive, frequently fatal disease that occurs mainly in immunocompromised patients.[1] Central nervous system (CNS) involvement appears in 10%-15% of patients with IA[2] and, when present, has a high mortality despite treatment.[3] There is a wide spectrum of presentations of cerebral aspergillosis, from meningoencephalitis to abscess and granuloma formation.[4] Because of the ability of *Aspergillus* spp. to invade the blood vessel wall, cerebral involvement may present as focal neurological deficits as a consequence of a brain hemorrhage or infarction.[5] The frequency of cerebral aspergillosis presenting as neurological deficits has been reported in pathological series.[6] Additionally acute stroke as presentation of neuroaspergillosis has been communicated as isolated case reports.[7-11]

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We collected 5 cases of IA with cerebral involvement whose first neurological presentation was an acute stroke in the era of reperfusion therapies and we discuss specific diagnostic and therapeutic challenges in these patients.

Patients and Methods

We retrospectively reviewed all the patients diagnosed with IA who presented neurological symptoms in a tertiary care center between 2011 and 2017. These patients fulfilled criteria of proven or probable aspergillosis as per the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group.[12] We selected only those patients that showed acute neurological focal deficits and an activated stroke code alert. Those with subacute or chronic neurological symptoms and those with other presenting manifestations, such as a decreased level of consciousness without focal deficits or epileptic seizures, were excluded. Data collected included epidemiological features, past medical history, clinical data, results of microbiological analysis, complementary tests, treatment received, and clinical course.

Results

Nine patients diagnosed with IA with neurological symptoms were reviewed. Four were excluded due to

their nonictal manifestations (2 as a confusional syndrome and 2 as epileptic seizures). Out of the remaining 5 presenting as acute stroke, 4 were men. The average age was 55.4 years (ranging from 47 to 56 years of age). The characteristics of the patients are summarized in Table 1.

In 4 of the cases (80%), systemic fungal disease was unknown at the moment of neurological consultation. In 1 case, systemic IA had been proven before by a positive skin culture for *Aspergillus.* At neurological onset, only 1 patient had pulmonary infiltrates in chest computed tomography (CT) of unknown aetiology, but on the course of the disease, all of them developed signs of pulmonary aspergillosis.

All patients were immunosuppressed: all had received prolonged (more than 3 weeks) corticotherapy. Three had been diagnosed with acute myeloid leukemia or multiple myeloma and treated with allogenic stem cell transplant followed by immunosuppressants. One of them (case 3) had received intrathecal chemotherapy with methotrexate and cytosine arabinoside and presented the additional risk factor of febril neutropenia for more than 10 days before clinical onset. These 3 patients were receiving antifungal prophylactic treatment at the onset of focal neurological symptoms.

All patients had an acute focal deficit and neurologist on call was alerted because of possible in-hospital Code Stroke. In every patient an urgent cranial CT was performed. None of the patients were candidates for thrombolysis with intravenous tissue-type plasminogen activator (IV tPA). Those with normal CT (cases 1 and 4) were beyond time for IV tPA, cases 3 and 5 had established hypodensities, case 3 had associated hemorrhagic focus, and case 2 showed lesions not suggestive of a vascular origin. Magnetic Resonance Imaging (MRI) studies were performed in 4 patients, confirming acute ischaemic brain infarctions in 3 of them (see Fig 1, A-C). Case 2 presented multiple nodular lesions suggesting aspergillomas with combined hemorrhages and ischaemia. Patient 1 stayed in the Stroke Unit until death on day +10 from clinical onset.

Proven IA was diagnosed by direct observation of fungal elements in diseased tissues: cerebral necropsy (Fig 2), bronchial biopsy, and skin cultures (cases 1, 4, and 5 respectively). Probable IA diagnosis was made in 2 patients by detection of galactomanann antigen in other tissue samples. Polymerase chain reaction for *Aspergillus* spp. was performed in 4 cases (1, 3, 4, and 5) being positive in cerebrospinal fluid in case 3 and positive in cerebrospinal fluid and serum in cases 4 and 5. All patients received specific treatment for IA; however mortality in our sample was 100% after 30 days from diagnosis.

Discussion

Many organs can be affected in disseminated aspergillosis. The most devastating complication is cerebral infection which occurs in 10%-15% of the cases[2] with a mortality beyond 90% despite receiving guided antifungal therapy.[11,13] CNS infection can be acquired by hematogenous spread (mainly from a pulmonary focus), by contiguous dissemination from a paranasal sinus infection or by direct iatrogenic inoculation during intracranial invasive procedures.[11] A wide variety of clinical features of CNS infection by *Aspergillus* spp. have been described. Up to 65% of these patients can show focal deficits.[6] However, the frequency of clinical presentation of acute stroke has not been reported in clinical series and has only been described as isolated case reports.[7-11] Our experience suggests that ictal presentation is common in cerebral aspergillosis, as 5 out of 9 cases (55.5%) in this series manifested with sudden neurological deficits. In only 1 of them, this presentation could be considered a stroke mimic since other lesions were present in neurological studies and no cerebral infarctions could be detected in MRI. We could not exclude, however, that vascular invasion caused the ictal symptoms in this patient because hemorrhagic foci were seen within the aspergillomas. Indeed, in 60% of patients with microscopically demonstrated neuroaspergillosis, a combination of mycotic aneurysms, granulomas, and ischaemia is guaranteed.[4] It is well know that *Aspergillus* spp. can generate fungal vasculitis due to its special tropism of the vessel blood wall.[14-16] *Aspergillus* spp. produces a protease enzyme called elastase, which provides the ability to infiltrate the artery wall with intramural hyphae deposit, with secondary narrowing and obliteration of the vessel's lumen-producing ischaemic phenomenons. This disruption of the vessel wall can contribute to mycotic aneurysm formation and rupture with associated hemorrhages.[4,14,17,18,19] The pathology series by Walsh et al. revealed that the most common CNS necropsy findings in patients with brain aspergillosis were subcortical ischaemic infarctions.[6] Typical radiological features of neuroaspergillosis include the combination of ischemia and hemorrhages affecting the basal ganglia, thalamus, and/or corpus callosum. Is also suggestive of IA with CNS involvement to see multiple mass lesions producing hypo to isointense signal on T1-weighted images with mild or no enhancement on postgadolinium sequences and very low signal on T2-weighted imaging with variable edema. Is not unusual to see an irregular dark rim surrounding cavitary lesions on T2-weighted images, which is believed to represent concentrated iron suggesting active proliferation of *Aspergillus,* because iron is an essential element for growth of fungal hyphae.[20] Whenever these features are present, especially in immunosuppressed patients, with acute and progressive neurological deficits, infection by *Aspergillus* spp. should be suspected.

IA is the result of hematogenous spread of *Aspergillus* spp. *Aspergillus fumigatus* is the main agent in the majority (57%) of cases of IA.[21] IA is the principal cause of fungal invasive disease in patients with oncohematological