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PII: S1201-9712(22)00321-6
DOI: https://doi.org/10.1016/j.ijid.2022.05.056
Reference: IJID 6226

To appear in: *International Journal of Infectious Diseases*

Received date: 23 January 2022
Revised date: 17 May 2022
Accepted date: 25 May 2022

Please cite this article as: Elie Haddad , Arnaud Fekkar , Sophie Bonnin , Natalia Shor , Danielle Seilhean , Isabelle Plu , Valérie Touitou , Véronique Leblond , Nicolas Weiss , Sophie Demeret , Valérie Pourcher , Cerebral vasculitis due to Aspergillus sp in immunocompromised patients and literature review, *International Journal of Infectious Diseases* (2022), doi: https://doi.org/10.1016/j.ijid.2022.05.056

Cerebral vasculitis due to *Aspergillus* sp in immunocompromised patients and literature review

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Introduction: (2785 words)

Approximately 1,000,000 (1.47%) people in France are estimated to suffer from serious fungal infections each year. Estimated incidence for invasive aspergillosis is 1.8/100,000 annually based on classical high risk factors(Gangneux et al., 2016). Aspergillosis is a multifaceted disease caused by fungi of the genus *Aspergillus*. The spectrum of aspergillosis is wide; ranges from mere colonization (aspergilloma) to disseminated infection. Understandably, the lungs and paranasal sinuses are the most commonly affected sites in human beings(Aggarwal et al., 2016). *Aspergillus* spp continue to be an important cause of life-threatening infection particularly in immunocompromised patients(Patterson et al., 2016). Early diagnosis of invasive aspergillosis is a challenge and should be based on the integration of clinical, radiological and microbiological data(Ullmann et al., 2018). This fungus has an angioinvasive character and may be the cause of micro- and macro-vascular necrotizing vasculitis(Kosmidis and Denning, 2017). These forms are mainly caused by contiguity (satellite carotid involvement of an ethmoidal or orbital location). There are rarer forms of hematogenous spread which can be the cause of microaneurysms and cerebral emboli(Lampros et al., 2021). Cerebral vasculitis are severe conditions, and their prognosis is directly linked to early recognition and diagnosis. The survival outcome in these cases is poor with mortality of 40% to 80%(Shamim et al., 2007). A wide variety of clinical

presentations, the lack of specific radiologic features, and the relative rarity of this disease make cerebral aspergillosis less recognizable, resulting in a delayed diagnosis and treatment. Furthermore, there are no conclusive recommendations for optimal management of this disease entity(Pushker et al., 2011). We present a case series of aggressive cerebral vasculitis due to aspergillosis in immunocompromised patients presented as a neutrophil aseptic meningitidis.

Clinical cases:

Patient 1:

A 68-year-old male patient is addressed to the infectious diseases ward for fever and headaches. He is known to be hypertensive with hypothyroidism. In his past medical history, he has a chronic lymphocytic leukemia in remission with a rituximab maintenance treatment (500 mg / m^2 of surface bodily). He had a previous history of prostate adenocarcinoma, a cutaneous thoracic melanoma, a dorsal cutaneous melanoma and a gastrointestinal stromal tumor, all treated by surgical excision.

He has been complaining of headaches and recurrent sinusitis for over 6 months and received numerous courses of antibiotics and corticosteroids. A chest X-ray was performed and was normal. A brain magnetic resonance imaging (MRI) was performed and revealed an enlargement of the ventricular system and Sylvian valleys contrasting with the absence of enlargement of cortical sulci. Three weeks later, he complained from a rapidly progressive bilateral loss of visual acuity with a pale fundus and a flat retina. At presentation, a lumbar puncture (LP) was performed, and the cerebral spinal fluid (CSF) revealed 340 white blood cells/µL of which 90% were neutrophils along with hyperproteinorachia (0.93 g/L) and normal glycorachia. Intravenous treatment with amoxicillin (100mg/kg/day), cefotaxime (150mg/kg/day), gentamicin (3mg/kg/day) and acyclovir (15mg/kg/8 hours) were started. An electroretinogram returned

normal and visual evoked potentials were barely discernible from background noise. Three days later, the patient presented with confusion, a paralysis in the abduction of the right eye, a left hemibody negligence, a positive left Babinski, a frontal syndrome, anosognosia and behavioral disorders. Paraneoplastic autoantibodies, angiotensin-converting enzyme, venereal diseases tests, varicella zoster virus IgG and Polymerase Chain Reaction (PCR), cytology and bacteriology were all negative in the CSF.

The patient was transferred to the neurological intensive care unit where he received a bolus methylprednisolone IV (1 gram/day for 3 days) with plasmapheresis exchange on day 7 of his admission and antifungal therapy (high dose liposomal amphotericin B, 5 mg/kg). A brain MRI was performed and revealed a vasculitis with extensive ischemic lesions in the territory of occluded anterior cerebral arteries including the chiasma and a part of optic nerves and optic radiations (fig1).

The patient died within 24 hours. An autopsy was requested to elucidate the cause of the cerebral vasculitis with optic involvement. Autopsy fixation showed mycelial filament suggestive of *Aspergillus* spp (fig 2). Three days later, a specific PCR for *Aspergillus fumigatus* came back positive in the CSF (116 copies/mL) with a positive galactomannan antigen (>8). The fungal culture returned negative.

The autopsy did not reveal any tumor. Systemic vascular lesions were limited to mild chronic renal arteriosclerosis. There was no significant inflammation or infection in any extra-cerebral organ including the lung and heart. On examination of the brain, the optic tract and the circle of Willis, the vessels of which appeared dilated and thrombosed, were sheathed in the thickened leptomeninges. Bilateral hemorrhagic cortical infarction was observed in the anterior cerebral territory. No infarction was noticed in other regions, especially posterior. The wall of the large basal vessels, and especially that of the anterior cerebral arteries, is the site of fibrin and

neutrophil-rich necrosis in which there are numerous mycelial filaments running through the thickness of the vessel wall. The endothelium is necrotic in places, and the lumen is partially obstructed by clusters of altered polymorphs and mycelial filaments. Very few CD3+ lymphocytes were observed in the infiltrates. No B lymphocytes, plasma cells, granulomas or multinucleated giant cells were seen.

Patient 2:

A 77-year-old female patient complaining of headaches with left hemicrania was hospitalized for high suspicion of Horton's disease in front of a high C reactive protein (CRP) / erythrocyte sedimentation rate (ESR) and treated by oral corticosteroid therapy (0.6 mg /kg/day).

A cerebral MRI revealed a tumorous looking deep cervical lesion of the cavum, infiltrating the parapharyngeal, carotid spaces, with a sigmoid sinus thrombosis associated and lymphadenopathy. The thoraco-abdominopelvic computed tomography (CT) scan found an isolated 7 mm, calcified pulmonary nodule. A cavoscopy with biopsy were performed, which was not contributive.

Corticosteroid therapy was tapered and then resumed at 0.25 mg/kg/day due to headache worsening when stopped.

One month later, the patient consults for increased headache over 3 days, associated with gait problems, walking difficulties and dizziness.

The patient had a fever at 38.4 ° C and was hypertensive (205/100 mm Hg). Neurological examination revealed a dysarthria, a walking instability, and a stiff neck.

A cerebral CT scan found a semi recent stroke of the right vermis. The CSF revealed a meningitis with 1350 white blood cells/µL of which 97% were neutrophils, no bacteria on direct staining or in culture, negative PCR for *Neisseria meningitidis* and *Streptococcus pneumoniae*, a protein level of 0.84 g/L and a normal glucose level. Treatment with cefotaxime 200mg/kg/day was initiated in the context of meningitis, an anti-platelet aggregation with acetylsalicylic acid (250 mg/day) were associated in the context of a recent stroke.

Antibiotic therapy was changed for ceftazidime (2g q 6h) and vancomycin (a bolus of 20mg/kg then 20mg/kg/12 hours) due to the lack of therapeutic response. A brain MRI performed 2 days later revealed numerous recent ischemic lesions,–an increase in the cervical lesion size, with associated jugular thrombosis and internal carotid artery wall after gadolinium enhancement (figure 3).

Three days later, the patient worsened on the neurological status with vertigo, with a psychomotor slowing, associated with an aggravation of the left ptosis.

The patient was transferred to the neurological intensive care unit for monitoring.

Neurological worsening required the use of mechanical ventilation after 4 days. On the control MRI, development of images of cerebral vasculitis with secondarily hemorrhagic transformation on mycotic aneurysms were seen.

On a new LP, the *Aspergillus fumigatus* PCR was positive in the CSF (99 copies/mL) as was the Beta-D glucan (> 500 pg/ml). Intravenous voriconazole (6mg/kg/12 hours on the first day then 4mg/kg/12hours) administration was started.

The patient died on day 3 with a high suspicion of underlying tumor of the cavum.

The *postmortem* examination of the thoraco-abdominal organs was unremarkable, except for coronary atheromatosis. Histopathological analysis of the cavum, nasal cavities and auditory

canal did not reveal any mycelial filaments. The meninges of the convexity were not thickened, but the optic tract, circle of Willis, and basilar artery were covered by a fibrino-hemorrhagic material. Hemorrhagic infarcts of different stages were observed in various territories associated with a more diffuse ischemic encephalopathy. Examination of the large brain vessels revealed severe arteritis with thrombosis, fibrinoid necrosis, plasma cell infiltrate and multinucleated giant cells, caused by the proliferation of trans-parietal mycelial filaments suggestive of *Aspergillus* spp (Fig 2).

Patient 3:

A 43-year-old male patient with renal transplantation for IgA nephropathy with baseline creatinine at 170 µmol/l, bronchial and miliary tuberculosis and chronic non replicative hepatitis B consulted for neurological symptoms.

The symptoms started with headache, vomiting, associated with a rotational vertigo and an inability to walk, a hearing loss and a tinnitus. He has no fever. The patient consulted in the Emergency Department due to the persistence of these disorders.

On physical exam, he had a right lateral vestibular peripheral syndrome without any sensory-motor deficit. A brain CT scan and MRI did not reveal any abnormality.

The patient was hospitalized for a persistent diffuse headache and a vestibular syndrome.

The LP was performed and showed 45 white blood cells/µL of which 90% were neutrophils and 10% were lymphocytes.

He complained of a right central facial paralysis and a persistent right hearing loss with a vestibular syndrome.

Three days later, the neurological state of the patient deteriorated with the appearance of a right hemicorporeal deficit with brachiofacial predominance. The patient was somnolent and had signs of intracranial hypertension. Brain MRI showed an abscess of the base of the skull, a pathological contrast enhancement of the brainstem, a left capsular ischemic attack, discrete signs of high intracranial hypertension, a vascularization of the base of the skull in the territory of the carotid and the vertebrobasilar (figure 4). A second CSF showed 90 white blood cells/µL with 80% neutrophils and a protein level at 0.46 g/L. Anti-tuberculosis treatment (Isoniazid 3mg/kg/day, Rifampin 10mg/kg/day, Ethambutol 15mg/kg/day and Pyrazinamide 20mg/kg/day) and boluses of IV methylprednisolone (1g/day for 3 days) were started.

Neurological deterioration prompted the realization of an MRI which showed an aggravation of the vasculitis lesions. He presented neurological deterioration towards a state of brain death.

The autopsy showed acute bronchopneumonia and fibrotic retroperitoneal lymph nodes in addition to renal graft interstitial nephropathy. Examination of the brain showed meningeal thickening at the anterior part of the brainstem with ensheathment of the basilar artery and its branches, corresponding to a florid inflammatory cuffing mainly composed of neutrophils penetrating the arteries walls. The lumen was obstructed with a voluminous occlusive thrombus. Numerus mycelial filaments suggestive of *Aspergillus* spp. were identified within the thrombus and the artery walls. Multiple recent hemorrhagic infarcts were observed in the vertebro-basilar territory.

Discussion

We report here 3 cases of invasive aspergillosis occurring in immunocompromised patients and whose clinical expression was dominated by a cerebral vasculitis.

Cerebral invasive fungal affecting large-caliber vessels infection rarely affects healthy individuals. Most affected patients are immunocompromised, immunosuppressed, neutropenic or diabetic (Bhansali et al., 2004). Patients with hematological malignancies are at risk, especially when neutropenic. Risk factors for invasive aspergillosis include neutrophil defects and corticosteroid use(Thurtell et al., 2013). The most common clinical manifestations of cerebral aspergillosis are fever, headache, meningeal irritation, cranial nerve involvement and epilepsy. Headache is often the first symptom of the various types of intracranial *Aspergillus* infection like in our patients (Parikh et al., 2004).

The etiologies of aseptic meningitis can be classified in four main groups. The first group includes systemic diseases with meningeal involvement such sarcoidosis, Behcet's disease, Sjogren's syndrome, systemic lupus erythematosus, and granulomatosis with polyangiitis. The second group includes drug-induced aseptic meningitis such as non-steroidal anti-inflammatory drugs, and antibiotics (especially sulfamides, penicillin)(Chu and Eustace, 2018), intravenous immunoglobulins and monoclonal antibodies. The third group consists of neoplastic meningitis whether with solid cancer or with hematological malignancy(Tattevin et al., 2019). The last group includes the infectious causes. The most common cause is viral, most often the enteroviruses, followed by herpes simplex virus-2 and varicella-zoster(Jarrin et al., 2016). Other associated viruses include respiratory viruses (adenovirus, influenza virus, rhinovirus), mumps virus, arbovirus, HIV, and lymphocytic choriomeningitis. Bacterial causes may include partially treated meningitis, parameningeal infection, *Mycoplasma pneumoniae*, endocarditis, *Mycobacterium tuberculosis*, *Borrelia burgdorfi*, Ehrlichiosis, *Brucella*, *Treponema pallidum*, *Bartonella henselae*, and leptospirosis. Rocky Mountain spotted fever and typhus are common rickettsiae on the differential. Fungal causes may include *Candida*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitides*. Parasites causing aseptic

meningitis include *Toxoplasma gondii*, naegleria, neurocysticercosis, trichinosis, and *Hartmannella*(Kaur and Perera, 2021).

Our patients' clinical course of progressive monocular vision loss, inflammation of the optic nerve and the inflammation of the basilar and the verterbro-basilar arteries wall, followed by acute cerebral infarcts in multiple vascular territories, illustrates the complexity of targeting treatment for an optic neuropathy of uncertain cause. In our case, all patients presented with an aseptic neutrophilic meningitis.

It is likely that the optic neuropathy, CSF pleocytosis, and stroke were related to the same pathologic process. Initial clinical and neuroimaging findings were strongly suggestive of a demyelinating or inflammatory condition.

However, development of new neurological symptoms while on steroids would have been unusual for a primary inflammatory process. The differential diagnosis of disseminated aspergillosis is broad and can include demyelination (multiple sclerosis, Neuromyelitis optica), inflammatory (sarcoidosis, Tolosa-Hunt, IgG4, Behcet's disease) disorders and infections (tuberculosis). Neoplastic processes such as lymphomatous and carcinomatosis meningitis are also possibilities(Hersh et al., 2016). All these diagnoses were ruled out for our patients.

In 2 of the 3 cases, the findings that led to the diagnosis of aspergillosis were acquired postmortem, which leads to several comments. First is that aspergillar vasculitis is a difficult entity to diagnose, especially because it is not easily evoked. Diagnostic delays, associated with the deleterious nature of the lesions themselves, contribute to the poor prognosis of the disease.

Finally, the corollary is that a certain number of cases can be expected to remain undiagnosed, which is the case in many invasive mold infections.

Diagnosis of invasive aspergillosis may be very challenging, particularly in case of atypical clinical presentation. Cerebral CT scan or MRI are mandatory to exclude focal lesions and to establish the diagnosis(Matsuo et al., 2005). The galactomannan index determination and mycological culture of CSF have been recognized within 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 criteria for the diagnosis of cerebral aspergillosis(Donnelly et al., 2020).

Although the detection of *Aspergillus* deoxyribonucleic acid by specific PCR in CSF is not included in the criteria, several publications suggest that it is of great value in case of either primary or secondary cerebral aspergillosis(Imbert et al., 2017). In this setting, it provided up to 100% sensitivity, a rate comparable with its performance in blood derived samples (Arvanitis et al., 2014; Imbert et al., 2016) and far above the sensitivity of CSF mycological culture (Reinwald et al., 2013)(Kami et al., 1999).

Our report suggests that in immunocompromised patients, an extensive mycological diagnosis on CSF (including mycological culture, *Aspergillus* PCR, beta-D-glucan research and galactomannan index determination) should be considered in case of so-called aseptic neutrophilic meningitis with no bacteriological and virological evidence.

Antifungal therapy is the mainstay of medical management and must be discussed as soon as possible in similar cases before *Aspergillus* prove due to worse prognosis. Treatment of CNS aspergillosis is controversial with various therapeutic modalities described, but presently there are no universal guidelines for treatment. Medical management with antifungal therapies includes azoles (voriconazole, isavuconazole itraconazole) (Pushker et al., 2011), amphotericin B, echinocandin (fungistatic against *Aspergillus*) are second line therapy. Although regularly initiated, the association of 2 antifungal therapies are not supported by any consensual evidence.

Voriconazole is now recognized as a first choice agent for invasive aspergillosis by the Infectious Diseases Society of America and there are several reports supporting its efficacy in cerebral aspergillosis("Management of granulomatous cerebral aspergillosis in immunocompetent adult patients: a review. - PubMed - NCBI," n.d.).

Voriconazole may be a more suitable option for angioinvasive aspergillosis because of better tolerance and lower toxicity compared with amphotericin B(Herbrecht et al., 2002). In case of cerebral vasculitis, antifungal treatment is associated with corticosteroids alone or in combination with immunosuppressives (azathioprine or cyclophosphamide)(Berlit et al., 2019). Isavuconazole was compared with voriconazole in a randomized, blinded, multicentric study for the treatment of invasive aspergillosis among individuals 18 and older. Although most patients in both groups had adverse events, patients in the isavuconazole group had less hepatobiliary, ocular, skin, and psychiatric adverse events than in the voriconazole group (42% vs 60%, respectively). Furthermore, discontinuation of isavuconazole was lower than voriconazole (8% vs 14%, respectively)(Cadena et al., 2021; Maertens et al., 2016).

Even with aggressive medical and surgical therapy in such cases, the prognosis of invasive fungal infection is poor, perhaps because of the delays in the diagnosis and the initiation of treatment. Prognosis is largely dependent on early diagnosis, extent of invasion and the host's immune status(Lee et al., 2011).

Conclusion:

Aspergillus spp can infect the central nervous system through several pathways, and the clinical manifestation of cerebral aspergillosis is atypical and necrotizing arteritis of the large cerebral vessels can progress promptly in immunocompromised patients. Early diagnosis is the only opportunity to improve the chances of improvement to the treatment given in a timely manner. Occurrence of neutrophilic meningitis in immunocompromised patients require eliminating aspergillosis infection using PCR and galactomannan. If the infection is confirmed or highly evocative, we recommend urgent initiation of antifungal chemotherapy with the goal of preserving life and the structures of vital function. With proper follow-up, the prognosis of these patients would improve.

The authors declare they have no conflict of interests.

The authors declare they have no funding resource.

Ethical approval was not sought for the present study because our study is descriptive in focus.

Declaration of interests

314 The authors declare that they have no known competing financial interests or personal
315 relationships that could have appeared to influence the work reported in this paper.

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Figure 1. Diffusion weighted image shows bilateral stroke in the territory of the anterior cerebral arteries(A). The occlusion of both vessels can be seen on the time-of-flight sequence (B, arrows). The right middle cerebral artery irregularity can also be seen (B, arrowhead). Chiasma T2 hyperintensity is also due to the ischemic changes (C, arrow). Meningeal inflammation (thickening) is shown on the T1 IV+ sequence (D, arrow).

Figure 2. a, d: Anterior communicating artery in patient 1. (a) H&E staining showing extensive necrosis of the intima (star). (d) Grocott staining shows the mycelial filaments (arrows) that pass through the thickness of the arterial wall. Scale bars = 80 µm. b, e: basilar artery in patient 2. (b) Intimal necrosis (star) is associated with a giant cell inflammatory reaction (arrow heads). (e)

460 The Period acid Schiff (PAS) staining shows mycelial filaments in contact with giant cells (arrow
461 heads). Scale bars = 40 µm. c, f. (c) Intimal necrosis is associated with an occlusive thrombus
462 (star). Scale bar = 40 µm. (f) The Period acid Schiff (PAS) staining shows mycelial filaments
463 accumulated under the elastic fibers and which cross them. Scale bar = 20 µm.

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465 Figure 3. 3DT1 weighted gadolinium enhanced gradient echo (A) and spin echo sequence (B)
466 showing diffuse left pharyngeal infiltration (A, arrowhead) in its central part. Left carotid artery
467 focal stenosis (A, arrowhead) and abnormal wall thickening (B, arrow) as well as the left sigmoid
468 sinus thrombosis (B, arrowhead) are shown. Diffusion weighted images (C, D) showing multiple
469 recent ischemic lesions. Computed Tomography scan revealing subarachnoid bleeding (E, arrow)
470 with middle cerebral artery aneurysm (F, arrow) and focal stenosis (F, arrowhead).

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474 Figure 4. 3DT1 IV+ sequence (A) demonstrating basilar artery wall enhancement and adjacent
475 leptomeningeal gadolinium focal thickening (A, arrow) Time of flight sequence showing multiple
476 stenosis of the cerebral arteries (B, arrows). Multiple recent ischemic lesions are seen on the
477 diffusion weighted images (C, D).

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