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

2

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47 **Introduction: (2785 words)**

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

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

69

70 **Clinical cases:**

71 **Patient 1:**

72 A 68-year-old male patient is addressed to the infectious diseases ward for fever and headaches.
73 He is known to be hypertensive with hypothyroidism. In his past medical history, he has a chronic
74 lymphocytic leukemia in remission with a rituximab maintenance treatment (500 mg / m² of
75 surface bodily). He had a previous history of prostate adenocarcinoma, a cutaneous thoracic
76 melanoma, a dorsal cutaneous melanoma and a gastrointestinal stromal tumor, all treated by
77 surgical excision.

78 He has been complaining of headaches and recurrent sinusitis for over 6 months and received
79 numerous courses of antibiotics and corticosteroids. A chest X-ray was performed and was
80 normal. A brain magnetic resonance imaging (MRI) was performed and revealed an enlargement
81 of the ventricular system and Sylvian valleys contrasting with the absence of enlargement of
82 cortical sulci. Three weeks later, he complained from a rapidly progressive bilateral loss of visual
83 acuity with a pale fundus and a flat retina. At presentation, a lumbar puncture (LP) was
84 performed, and the cerebral spinal fluid (CSF) revealed 340 white blood cells/ μ L of which 90%
85 were neutrophils along with hyperproteinorachia (0.93 g/L) and normal glycorachia. Intravenous
86 treatment with amoxicillin (100mg/kg/day), cefotaxime (150mg/kg/day), gentamicin
87 (3mg/kg/day) and acyclovir (15mg/kg/8 hours) were started. An electroretinogram returned

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

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

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

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

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

117

118 **Patient 2:**

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

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

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

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

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

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

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

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

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

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

150 On a new LP, the *Aspergillus fumigatus* PCR was positive in the CSF (99 copies/mL) as was the
151 Beta-D glucan (> 500 pg/ml). Intravenous voriconazole (6mg/kg/12 hours on the first day then
152 4mg/kg/12hours) administration was started.

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

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

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

163

164 **Patient 3:**

165 A 43-year-old male patient with renal transplantation for IgA nephropathy with baseline
166 creatinine at 170 $\mu\text{mol/l}$, bronchial and miliary tuberculosis and chronic non replicative hepatitis
167 B consulted for neurological symptoms.

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

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

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

174 The LP was performed and showed 45 white blood cells/ μL of which 90% were neutrophils and
175 10% were lymphocytes.

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

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

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

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

197

198 **Discussion**

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

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

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

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

227

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

233

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

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

243

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

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

250

251 Diagnosis of invasive aspergillosis may be very challenging, particularly in case of atypical
252 clinical presentation. Cerebral CT scan or MRI are mandatory to exclude focal lesions and to
253 establish the diagnosis(Matsuo et al., 2005). The galactomannan index determination and
254 mycological culture of CSF have been recognized within the European Organization for Research
255 and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute
256 of Allergy and Infectious Diseases Mycoses Study Group criteria for the diagnosis of cerebral
257 aspergillosis(Donnely et al., 2020).

258 Although the detection of *Aspergillus* deoxyribonucleic acid by specific PCR in CSF is not
259 included in the criteria, several publications suggest that it is of great value in case of either
260 primary or secondary cerebral aspergillosis(Imbert et al., 2017). In this setting, it provided up to
261 100% sensitivity, a rate comparable with its performance in blood derived samples (Arvanitis et
262 al., 2014; Imbert et al., 2016) and far above the sensitivity of CSF mycological culture (Reinwald
263 et al., 2013)(Kami et al., 1999).

264

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

269

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

277

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

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

292

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

297

298 **Conclusion:**

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

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

311

312

313 **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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448 Figure 1. Diffusion weighted image shows bilateral stroke in the territory of the anterior cerebral
 449 arteries(A). The occlusion of both vessels can be seen on the time-of-flight sequence (B, arrows).
 450 The right middle cerebral artery irregularity can also be seen (B, arrowhead). Chiasma T2
 451 hyperintensity is also due to the ischemic changes (C, arrow). Meningeal inflammation
 452 (thickening) is shown on the T1 IV+ sequence (D, arrow).

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456 Figure 2. a, d: Anterior communicating artery in patient 1. (a) H&E staining showing extensive
 457 necrosis of the intima (star). (d) Grocott staining shows the mycelial filaments (arrows) that pass
 458 through the thickness of the arterial wall. Scale bars = 80 µm. b, e: basilar artery in patient 2. (b)
 459 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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