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**Aspergillus meningitis: A rare clinical manifestation of central nervous system aspergillosis. Case report and review of 92 cases**

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Accepted 5 November 2012  
Available online 21 November 2012

**KEYWORDS**  
Aspergillus meningitis;  
Galactomannan antigen;  
Diagnosis;  
Therapy

**Summary**  
**Objectives:** To describe the pathogenesis, clinical presentation, cerebrospinal fluid findings and outcome of *Aspergillus* meningitis, meningoencephalitis and arachnoiditis.  
**Methods:** A case of *Aspergillus* meningitis is described. A comprehensive review of the English-language literature was conducted to identify all reported cases of *Aspergillus* meningitis described between January 1973 and December 2011.  
**Results:** Ninety-three cases (including the one described herein) of *Aspergillus* meningitis were identified. Fifty-two (55.9%) were in individuals without any predisposing factor or known causes of immunosuppression. Acute and chronic meningitis was diagnosed in 65.6% of patients and meningoencephalitis in 24.7% of them with the remaining presenting with spinal arachnoiditis and ventriculitis. Cerebrospinal fluid cultures for *Aspergillus* spp. were positive in about 31% of cases and the galactomannan antigen test in 87%. Diagnosis during life was achieved in 52 patients (55.9%) with a case fatality rate of 50%. The overall case fatality rate was 72.1%.
Central nervous system (CNS) infections are well recognized manifestations of disseminated aspergillosis observed in about 10% of immunocompromised patients and with mortality rates greater than 90%. By contrast, Aspergillus meningitis is a more seldomly encountered clinical entity and it is found more frequently in immunocompetent rather than in immunocompromised hosts. Information about Aspergillus meningitis is limited and sparse and to our knowledge no review on this topic has been published so far. We present here a case of Aspergillus meningitis, along with a review of published cases since 1973.

Methods

Case reports of Aspergillus meningitis, meningoencephalitis, arachnoiditis and ventriculitis as well as series of CNS aspergillosis were identified through a search of PubMed and Scopus databases of the English literature, and the reference lists were reviewed for additional cases. Research was conducted from the year 1973 through 2011. Used research terms included “Aspergillus meningitis”, “cerebral aspergillosis”, “central nervous system aspergillosis”, “Aspergillus arachnoiditis”, “mycotic meningitis”. For the purpose of this review a case of meningitis or meningoencephalitis caused by Aspergillus spp. was defined during life as follows: 1) a cerebrospinal culture positive for Aspergillus spp. together with a meningeal or encephalic syndrome; 2) the presence of galactomannan antigen or Aspergillus DNA detected by polymerase chain reaction (PCR) test in the CSF, together with a meningeal syndrome. Post-mortem diagnoses of Aspergillus meningitis were included if the autopsy clearly indicated involvement of the meninges or a picture of meningitis with microscopic identification of Aspergillus hyphae or a positive Aspergillus culture. When inflammation involved the spinal leptomeninges the case was classified as spinal arachnoiditis. Patients were considered immunocompromised if the following conditions were met: 1) HIV/AIDS infection; 2) solid organ transplantation; 3) hematologic diseases with or without bone marrow transplantation; 4) autoimmune diseases treated with steroids or other immunosuppressive drugs; 5) diabetes mellitus; 6) any other condition treated with corticosteroids or immunosuppressive drugs.

Case report

A 34-year-old man was referred to our Infectious Diseases ward on February 9, 2010 from a Neurosurgery Unit where a diagnosis of Aspergillus meningitis had been made. The clinical history was notable for heroin intravenous drug abuse, high alcohol intake, untreated chronic hepatitis C and methadone maintenance therapy (50 mg/day). One month before he was admitted to the Internal Medicine ward of another Hospital to investigate the nature of low back pain, headache and low grade fever (37.5 °C) that had appeared 1 month earlier. Magnetic resonance imaging (MRI) of the brain was negative for parenchymal and meningeal lesions. On the contrary, MRI of the lumbar spine showed abnormal contrast enhancement into the spinal canal between L4 and S1 suggesting an intradural mass lesion conditioning a traction effect on the roots of the cauda equina. A color-doppler echocardiogram showed only a mild mitral regurgitation. Blood and urine cultures were negative as well as a serologic test for HIV. Cerebrospinal fluid (CSF) analysis performed on February 9 is shown in Fig. 1. Gram and Ziehl-Neelsen stains, as well as bacterial and mycobacterial cultures, were negative as was the search for bacterial and Cryptococcus neoformans antigens. Cerebrospinal culture grew Aspergillus flavus that was susceptible to amphotericin B, voriconazole, posaconazole, itraconazole and caspofungin. Aspergillus galactomannan antigen-GM (Platelia Aspergillus, Sanofi Diagnostics Pasteur, Marne-La Coquette, France) was detected both in the CSF and blood with a higher index value in the former (respectively, 7.4 and 2.5). Upon admission to our ward (February 12), the patient had fever (38.5 °C), was alert and complained of frontal headache and photophobia, without neck stiffness. Intravenous treatment with voriconazole was started (6 mg/kg every 12 h (q12h) as loading dose, followed by 4 mg/kg q12h) together with ceftriaxone (2 g q12h). Two weeks later, a control brain and spinal MRI showed meningeal enhancement with cysternal distribution especially in the pre-pontine area around the basilar artery, together with endocanalar pathologic enhancement between L4 and S2 (Figs. 2, 3a and b). A concomitant CSF analysis showed a reduction of WBCs (180/μL, 61% PMNs), improvement of glucose levels (24 mg/dL, serum 110 mg/dL) and a striking increase of protein level (3705 mg/dl), whereas, at this time point, CSF culture turned negative. The GM index was 6.36 in the CSF and 0.9 in the peripheral blood. Because of persistent fever, headache and worsening of the radiological picture, caspofungin (70 mg loading dose, 50 mg maintenance dose) was added to the antifungal regimen with discontinuation of the antibiotic therapy. Voriconazole blood and CSF trough concentrations obtained after 2 weeks of therapy were similar (5.85 and 5.86 mg/L, respectively). Therapeutic drug monitoring was arranged 6 and 10 days later and it showed toxic concentrations of the drug that prompted dosage adjustments despite the absence of any clinical or biochemical signs of voriconazole toxicity. Another CSF examination performed on March 18, disclosed an improvement of all parameters (Fig. 1). Repeated MRI of the brain and spine (March, 17) showed the reduction of the pial and cysternal contrast enhancement but a progression of the endocanalar inflammation now involving
the segments L3 to S2. After a new evaluation by the neurosurgery consultant, who deemed any procedure unfeasible, the patient was discharged after having received 38 days of voriconazole therapy (total cumulative dosage: 21,200 mg) and one month of caspofungin (total cumulative dosage: 1520 mg). The patient was left on maintenance therapy with oral voriconazole at a dosage of 150 mg q12 h due to raised ALT levels (199 U/L), the appearance of visual disturbances and persistently elevated trough voriconazole concentrations (6.2 mg/L). At the end of April, the patient was readmitted to our hospital ward because of persistent abnormal liver function test results and visual disturbances that required discontinuation of voriconazole and its substitution with intravenous liposomal amphotericin B (L-AMB, 250 mg/day). He complained of persistent low back pain that was irradiated to both the lower extremities with preserved deep tendon and superficial reflexes. Repeated attempts to obtain CSF samples by lumbar puncture were unsuccessful. Nerve conduction and electromyography studies showed mild sensorimotor bilateral demyelinating polyneuropathy. A new MRI of the brain and spine (performed on May, 17) was substantially unchanged. During the 30-day therapy with L-AMB, GM was evaluated weekly and showed values ranging from 0.9 to 1.59. Because of the patient’s drug addiction history, it was decided to resume oral voriconazole therapy since the positioning of a permanent intravenous device for L-AMB infusion on an outpatient basis was

Figure 1  Medication history, clinical course and kinetic of *Aspergillus* antigen in CSF of our case of *Aspergillus flavus* meningitis. The dotted line represents the cut-off value of GM. The light blue line is the index on CSF and the red line on plasma. The blue circle represents the CSF levels of voriconazole. The purple diamond and the yellow triangle are respectively the down and peak plasma levels of voriconazole. The blue rectangle denotes the range of expected therapeutic levels of voriconazole.

Figure 2  Sagittal and coronal T1-weighted gadolinium-enhanced magnetic resonance scan of the brain of our patient with *Aspergillus flavus* meningitis showing contrast impregnation along the basilar artery in the preptontine cistern.
judged risky. A dosage of 150 mg every 12 h was started on June 9, showing after a week trough and peak concentrations of 3.4 and 3.6 mg/L, respectively. A new MRI of the brain and spine was performed on August 4, that demonstrated a reduction of pial enhancement along the cervical tract, the conus medullaris and cauda equina with a only a mild volumetric reduction of the endocanalar lumbar abscess. Clinically, the patient was well oriented with a positive bilateral Lasègue sign at the neurologic examination. He was discharged and subsequently lost to follow-up.

Results

A detailed, chronologically ordered summary of 93 cases of Aspergillus meningitis, chronic meningitis/pachymeningitis, meningoencephalitis, arachnoiditis and ventriculitis including the one presented herein (case 46) is shown in Table 1. There were 46 women (50%) and 46 men, with a median age of 37 years (range 3–75 years). Diagnosis was made during life in 52 patients (55.9%) and at autopsy in 41 patients. A diagnosis was obtained more frequently during life among immunocompetent patients (69%) in comparison with immunocompromised individuals (39%) (Table 2).

In almost half of the cases (n = 44) Aspergillus was identified by histology or culture without speciation; all other infections were caused by A. fumigatus (n = 34), A. flavus (n = 8) and A. terreus (n = 3) while A. oryzae, A. granulosus and A. candidus were identified in one case each. Forty-one patients were considered immunocompromised hosts (5 AIDS patients; 3 with autoimmune diseases treated with steroids; 9 solid organ transplant recipients; 10 hematologic patients undergoing chemotherapy or bone marrow transplantation; 5 subjects under steroid therapy for chronic obstructive pulmonary disease (COPD), and Severe Acute Respiratory Syndrome; 7 patients with diabetes and, finally, 1 each with Cushing’s disease and sarcoidosis). In the fifty-two patients without classic risk factors for invasive aspergillosis, central nervous system involvement was presumed to be the result of: direct extension of Aspergillus from the orbit, ear or paranasal sinuses in 6 patients (11.5%); iatrogenic direct inoculation of Aspergillus through spinal anesthesia (13 patients, 25%), neurosurgery (13 patients, 25%) or epidural steroid injections (1 patient). In six intravenous drug abusers (11.5%) the infection was probably acquired by the hematogenous route. Among the remaining subjects, no predisposing factor could be identified in six patients while one patient each were notable for the presence of the following: pregnancy, alcohol abuse, fungal endocarditis and near drowning. The most common syndrome was acute meningitis which was observed in 46 patients, followed by meningoencephalitis (n = 23). A chronic course of meningitis was observed in 15 patients; five patients showed a picture of spinal arachnoiditis (in 1 case with associated meningitis), and 4 ventriculitis (Table 2). An acute course characterized by rapid deterioration of the clinical picture usually ending with death was observed among immunocompromised hosts and in patients who had direct inoculation of the fungus into the cerebrospinal fluid or the subarachnoid space. By contrast, a sub-acute or chronic form of meningitis going unrecognized for several weeks and sometimes displaying a relapsing character was the most frequent presentation among immunocompetent patients, intravenous drug abusers and patients with diabetes. However, the latter clinical picture was also observed among several patients who had undergone neurosurgery.

Cerebrospinal fluid culture was positive for Aspergillus spp. in 31% of cases with a slightly higher prevalence among immunocompetent (36.9%), as opposed to immunocompromised hosts (18.2%) (Table 2). In nine patients, Aspergillus spp. was cultured from CSF only after repeated attempts (median number of lumbar punctures: 4, range 3–9). Antigen-based assays were employed in fifteen patients: GM antigen by use of the Plateia Elisa in 10 patients, with an unspecified assay in 2 patients, with Pastorex assay in 1 patient and 1,3-β-D-glucan in 2 individuals. GM antigen was detected in CSF specimens of 6 out of 8 immunocompetent patients and in all immunocompromised hosts in whom it was assessed (7/7, 100%) with an overall sensitivity of 86.7%. The median CSF GM index was 6.58 (range 2.2–578).

Serum GM was concomitantly measured in 8 cases and turned positive in 3. In 3 patients, CSF GM was serially determined (3–10, median 7), showing a good correlation
| Author, year [Reference] | Age/sex | Risk factor/Underlying disease | Sign and symptoms (time duration)/Time from TX | Syndrome | Diagnosis/methods | CSF characteristics | Aspergillus species (method) | CSF Ag GMN | Antifungal treatment (time duration) | Outcome |
|--------------------------|---------|-------------------------------|-----------------------------------------------|----------|------------------|-------------------|-----------------------|-------------|--------------------------------------|---------|
| Meningitis               |         |                               |                                               |          |                  |                   |                       |             |                                      |         |
| Atkinson & Israel, 1973³ | 27/M    | None/Sarcoidosis              | Headache, blurred vision                      | Meningitis | L/CSF            | WBC 144/µL (PMNs 10%) | *Aspergillus fumigatus* (CSF) | NA          | 5-FLU (3 months)                    | Alive 2 years after stopping antifungal therapy |
| Feely et al., 1977¹⁰     | 57/F    | Neurosurgery (Trans-sphenoidal Yttrium⁶⁰ implant)/Acromegaly | Meningeal signs, left hemiparesis/11 months | Meningitis | Pm/Autopsy (purulent basal leptomeningitis + multiple infarcts) | WBC 138/µL (PMNs 96%); proteins 850 mg/L | *Aspergillus spp.* (autopsy culture) | NA          | None                                 | Death after 1 day |
| 37/M                     |         | Neurosurgery (Trans-sphenoidal Yttrium⁶⁰ implant)/Diabetic retinopathy | Fever, stiff neck, headache, blurred vision/9 months | Meningitis | L/Biopsy (tissue adherent to the screws) | WBC 8800/µL (PMNs 90%); protein 330 mg/L | *Aspergillus spp.* (biopsy) | NA          | AMFB (NR); removal of implant | Alive |
| Mohandas et al., 1978¹¹  | 38/M    | Neurosurgery/Maxillary sinusitis | Meningeal irritation, coma/6 days post-operatively | Meningitis | L/Surgery of fungal granuloma | WBC 100/µL (PMNs 0%); glucose 35 mg/dL; protein 1160 mg/L | *Aspergillus spp.* (biopsy) | NA          | AMFB (7 days) ev + intratechal (1 day) | Death after 7 days |
| Aung et al., 1979¹²      | 22/F    | Pregnancy/None                | Headache, retrobulbar pain, blurred vision, ophthalmoplegia (22 days after delivery) | Meningitis | L/Biopsy leptomeninges | ND                 | *Aspergillus spp.* (biopsy) | NA          | Antifungal drugs (not mentioned) | Death after 1 month |
| Beal et al., 1982¹³      | 47/F    | None/Sphenoid sinusitis       | Frontal headache (5 months); nuchal rigidity, fever, hydrocephalus | Meningitis | L/biopsy sinus | WBC 120/µL (PMNs 63%); glucose 25 mg/dL; protein 620 mg/L | *Aspergillus spp.* (sinus biopsy) | NA          | AMFB (NR)                            | Alive 2 years later |
| 22/F                     |         | Neurosurgery/Medullo-blastoma | Fever (38.8°C), severe headache, meningismus 12 days after neurosurgery | Meningitis | L/CSF; Autopsy (basilar *Aspergillus meningitis with exudate in the subarachnoid space of spinal cord)* | WBC 2650/µL (PMNs 10%); glucose 26 mg/dL; protein 1750 mg/L | *Aspergillus spp.* (CSF culture after multiple attempts) | NA          | AMFB (3 days)                        | Death after 20 days |
| Diendogh et al., 1983¹⁴  | 60/M    | Neurosurgery (Trans-sphenoidal Yttrium⁶⁰ implant)/Diabetic retinopathy | Drowsy, disoriented in time and space, neck stiffness, positive Kernig sign | Meningitis | PM/Autopsy (meningitis; necrotizing vasculitis (pons); fungal invasion of basilar and middle cerebral arteries) | WBC 323/µL (PMNs 60%) | *Aspergillus spp.* (autopsy histology) | NA          | None                                 | Death after 2 weeks |

(continued on next page)
| Author, year [Reference] | Age/sex | Risk factor/Underlying disease | Sign and symptoms (time duration)/Time from TX | Syndrome | Diagnosis/methods | CSF characteristics | Aspergillus species | CSF Ag GMN (method) | Antifungal treatment (time duration) | Outcome |
|-------------------------|---------|--------------------------------|-----------------------------------------------|----------|------------------|-------------------|-------------------|-----------------|-----------------------------------|---------|
| Walsh et al., 1985³ | 64/F | Steroid treatment/Cushing syndrome | Meningismus, headache, hemiparesis | Meningitis | PM/Autopsy: mycotic Aspergillus aneurism & subarachnoid hemorrhage | WBC 15/µL (PMNs 0%); glucose 90 mg/dL; protein 1450 mg/L | Aspergillus spp. (autopsy histology) | NA | None | Death after 9 days |
| Hajjar et al., 1987¹⁵ | 28/M | Neurosurgery/Acoustic neurinoma | NR/9 days | Meningitis | PM/Autopsy: Aspergillus fumigatus | L/Wound culture | NR | Aspergillus spp. (wound culture) | AMFB + 5-FLU (2 months) | Death after 2 months |
| Asnis et al., 1988¹⁶ | 44/M | None/AIDS | Confusion, generalized seizures | Meningitis | PM/Autopsy (Aspergillus leptomeningites) | NR | Aspergillus spp. (autopsy histology) | NA | AMFB (20 days) | Death |
| Carrazana et al., 1991¹⁷ | 44/M | None/AIDS; sphenoid sinusitis | Headache, fever, nausea, ataxia, hemiparesis, seizures | Meningitis | PM/Autopsy (Aspergillus meningal infiltration; thrombosis of basilar artery) | NR | Aspergillus spp. (autopsy histology) | NA | None | Death |
| Komatsu et al., 1991¹⁸ | 61/F | Neurosurgery/Rathke’s cleft cyst | High fever and meningeal signs/12 days after surgery | Meningitis | PM/Autopsy (Aspergillus meningitis & mycotic aneurism, subarachnoid hemorrhage) | WBC 881/µL (PMNs 70%); glucose 46 mg/dL; protein 540 mg/L | Aspergillus spp. (autopsy histology) | NA | ND | Death after 23 days |
| Lammens et al., 1992¹⁹ | 39/F | Immunosuppressive therapy/SLE | Headache (1 month), fever (39.5 °C), neck stiffness, Horner syndrome | Meningitis | PM/Autopsy (Aspergillus basal meningitis & subarachnoid hemorrhage) | WBC 3750/µL (PMNs 84%); glucose 32 mg/dL; protein 1000 mg/L | Aspergillus spp. (autopsy histology) | NA | None | Death after 15 days |
| Torre-Cisneros et al., 1993¹⁰ | 31/F | Liver transplant/End stage liver disease | Seizure | Meningitis | PM/Autopsy (ischemic infarct; leptomeningeal aspergillosis) | NR | Aspergillus spp. (autopsy histology) | NA | NR | Death |
| 21/F | Liver transplant/End stage liver disease | NR | Meningitis | PM/Autopsy (ischemic infarct; leptomeningeal aspergillosis) | NR | Aspergillus spp. (autopsy histology) | NA | NR | Death |
| 24/F | Liver transplant/End stage liver disease | Seizure | Meningitis | PM/Autopsy (acute leptomeningitis) | NR | Aspergillus spp. (autopsy histology) | NA | NR | Death |
| 38/M | Kidney transplant/End stage kidney disease | Seizure | Meningitis | PM/Autopsy (acute leptomeningitis; haemorrhagic infarcts) | NR | Aspergillus spp. (autopsy histology) | NA | NR | Death |
| Name et al., 1995 | Gender/ Age | Diagnosis | Symptoms | Diagnosis | WBC 2000/μL (PMNs 95%); protein 900 mg/L | Aspergillus spp. (autopsy histology) | NA | NR | Death after 5 days |
|------------------|-------------|-----------|----------|-----------|--------------------------------------|-------------------------------------|-----|----|-------------------|
| Miaux et al., 1995 | 41/M | Bone marrow transplant; steroid therapy/CML | Fever (38 °C), hemiplegia/2 months | Meningitis | Pm/Autopsy (thickening and meningeal inflammation with haemorrhagic necrosis; lung & heart involvement) | WBC 2560/μL (PMNs 98%); Aspergillus spp. (autopsy histology) | NA | NR | Death after 8 days |
| Adunsky et al., 1996 | 74/M | None/None | Fever (38.3 °C), stuporous, left hemiplegia, dysarthria (1 day) | Meningitis | Pm/Autopsy | Aspergillus flavus (CSF culture) | NA | AMFB (few days) | Death after few days |
| Adunsky et al., 1996 | 39/F | Bone marrow transplant; steroid therapy/RAEB | Mental confusion/3.5 months | Meningitis | Pm/Autopsy (brain hemorrhagic necrosis; lung involvement) | WBC 2400/μL (PMNs 94%); glucose 10 mg/dL; protein 1500 mg/L | Aspergillus fumigatus (extradural abscess) | Negative (NR) | AMFB (2 months) + Itraconazole (2 months) | Death after 12 months |
| Adunsky et al., 1996 | 74/M | None/None | Fever (38 °C), acute respiratory failure (22 days) | Meningitis | Pm/Autopsy (right haemorrhagic infarct with subcortical vessel invasion and meningeal diffusion by Aspergillus; pulmonary involvement) | WBC 830/μL (PMNs 53%); glucose 48 (s 155) mg/dL; protein 830 mg/L | Aspergillus fumigatus (CF culture) | Positive (NR) | L-AMB (5 weeks) + 5-FLU (7 weeks); Itraconazole (6 months) | Alive after 12 months |
| Verweij et al., 1999 | 73/F | Mastoidectomy/Otitis media | Fever (39 °C), headache, vomiting, drowsiness, meningismus/NR | Meningitis | L/CSF (sixth attempt) | WBC 2130/μL; glucose 27 mg/dL (47 mg/dL serum); protein 150 mg/L | Aspergillus fumigatus (CSF culture, 6th attempt + PCR) | 10.4 (Platelia) | Itraconazole 1 week; AMFB (4 weeks + AMFB intraventricular; voriconazole (9 weeks) | Alive 12 months after voriconazole discontinuation |
| Mariushi et al., 1999 | 43/F | None/None | Headache, neck stiffness (11 days), fever (37.6 °C), nausea, chills | Meningitis | L/CSF | WBC 329/μL (PMNs 0%); glucose 46 mg/dL; protein 500 mg/L | Aspergillus spp. (CSF culture, 5th attempt) | ND | Flucanazole (2 years) | Alive after 2 years |
| Author, year [Reference] | Age/sex | Risk factor/Underlying disease | Sign and symptoms (time duration)/Time from TX | Syndrome | Diagnosis/methods | CSF characteristics | Aspergillus species | CSF Ag GMN (method) | Antifungal treatment (time duration) | Outcome |
|--------------------------|---------|-------------------------------|-----------------------------------------------|----------|------------------|--------------------|-------------------|-------------------|-------------------------------|---------|
| Arabi, 2001<sup>27</sup> | 58/M    | None/Maxillary sinusitis      | Confusion, progressive unresponsiveness, 4th nerve palsy 8 days after pneumonia | Meningitis | L/Sinus aspirate/ Autopsy (Aspergillus ventriculitis, meningitis; focal encephalitis; pneumonia) | WBC 3500/µL (PMNs 91%); glucose 77 mg/dL; protein 3370 mg/L | Aspergillus fumigatus | ND | AMFB (3 weeks) | Death 20 days later |
| Nenoff et al., 2001<sup>a</sup> | 74/M    | Ethmoidectomy and orbitotomy (for A. fumigatus orbital and sinus infection)/Diabetes mellitus | Vomiting, nausea, exophthalmus, somnolent and disoriented/7 months | Meningitis | L/Biopsy (orbital apex)/ Autopsy (Aspergillus meningitis, vasculitis internal carotid, mycotic aneurism with subarachnoid hemorrhage) | NR | Aspergillus fumigatus (biopsy) | 1:2 (Pastorex) | AMFB + 5-FLU (few days) | Death 3 weeks after surgical procedure |
| Moling et al., 2002<sup>25</sup> | 29/M    | Kidney transplant (reject); Hemodialysis + steroid therapy/complement 4 deficiency | Fever (39°C); confusion; disorientation; right motor hemisindrome (2 weeks) | Meningitis | L/CSF | WBC 3200/µL; glucose 4 mg/dL | Aspergillus fumigatus (CSF culture, 4th attempt + PCR) | ND | Fluconazole (2 weeks); L-AMB (3 weeks); Itraconazole (4 months) | Alive after 7 months; Death after 6 years<sup>b</sup> |
| Kleinschmidt-DeMasters, 2002<sup>24</sup> | 51/M    | Steroid therapy/ Wegener’s granulomatosis | NR | Meningitis | PM/Autopsy (Aspergillus acute and chronic basilar granulomatous meningitis; mycotic aneurism; lung, skin, heart involvement) | NR | Aspergillus spp. | ND (autopsy histology) | NR | Death after 68 days |
| Pandian et al., 2004<sup>31</sup> | 34/F    | Spinal anaesthesia/ None | Fever, headache, vomiting<sup>g</sup> | Meningitis | PM/Autopsy (Aspergillus meningitis; mycotic aneurism with subarachnoid hemorrhage) | WBC 640/µL (PMNs 76%); glucose 32 mg/dL; protein 3600 mg/L | Aspergillus spp. | ND (autopsy histology) | None | Death |
| Age | Gender | Anaesthesia | Diagnosis | Meningitis | WBC | Glucose | Protein | Pathology | AD | Follow-up |
|-----|--------|-------------|-----------|-----------|------|---------|---------|------------|----|-----------|
| 21/F | Spinal anaesthesia | None | Fever, headache, vomiting | Meningitis | WBC 678/μL (PMNs 65%); glucose 23 mg/dL; protein 3600 mg/L | 23 mg/dL | 3600 mg/L | Aspergillus spp. (autopsy histology) | ND | None | Death |
| 42/F | Spinal anaesthesia | None | Fever, headache, vomiting | Meningitis | WBC 240/μL (PMNs 68%); glucose 23 mg/dL; protein 2400 mg/L | 23 mg/dL | 2400 mg/L | Aspergillus spp. (autopsy histology) | ND | None | Death |
| 32/F | Spinal anaesthesia | None | Fever, headache, vomiting | Meningitis | WBC 345/μL (PMNs 76%); glucose 23 mg/dL; protein 1230 mg/L | 23 mg/dL | 1230 mg/L | Aspergillus spp. (autopsy histology) | ND | None | Unknown |
| 24/F | Spinal anaesthesia | None | Fever, headache, vomiting | Meningitis | WBC 435/μL (PMNs 96%); glucose 32 mg/dL; protein 4200 mg/L | 32 mg/dL | 4200 mg/L | Aspergillus spp. (autopsy histology) | ND | None | Death after 18 months |

Larson Kolbe et al., 2007

| Age | Gender | Anaesthesia | Diagnosis | Meningitis | WBC | Glucose | Protein | Pathology | AD | Follow-up |
|-----|--------|-------------|-----------|-----------|------|---------|---------|------------|----|-----------|
| 51/F | Epidural steroid injections | COPD | Mental status changes; 3rd nerve palsy | Meningitis | WBC NR (PMNs 99%); glucose 56 mg/dl (s 115 mg/dL); protein 680 mg/L | 56 mg/dl | 680 mg/L | Aspergillus fumigatus (disc aspiration + vpsos abscess culture) | ND | Caspofungin + oriconazole (4 months) | Death after 5 months |

Gunaratne et al., 2007

| Age | Gender | Anaesthesia | Diagnosis | Meningitis | WBC | Glucose | Protein | Pathology | AD | Follow-up |
|-----|--------|-------------|-----------|-----------|------|---------|---------|------------|----|-----------|
| 26/F | Spinal anesthesia | None | Low grade fever, headache, nausea, vomiting 12 days after sa | Meningitis | WBC 302/μL (PMNs 99%); glucose 56 mg/dl (s 115 mg/dL); protein 680 mg/L | 56 mg/dl | 680 mg/L | Aspergillus fumigatus (autopsy culture) | ND | Fluconazole | Death after 4 weeks |

| Age | Gender | Anaesthesia | Diagnosis | Meningitis | WBC | Glucose | Protein | Pathology | AD | Follow-up |
|-----|--------|-------------|-----------|-----------|------|---------|---------|------------|----|-----------|
| 21/F | Spinal anaesthesia | None | Fever, chills, neck stiffness 10 days after sa | Meningitis | WBC 575/μL (PMNs 70%); glucose 25 mg/dl (s 90 mg/dL); protein 490 mg/L | 25 mg/dl | 490 mg/L | Aspergillus fumigatus (autopsy culture) | ND | AMFB (4 days) | Death after 4 weeks |

| Age | Gender | Anaesthesia | Diagnosis | Meningitis | WBC | Glucose | Protein | Pathology | AD | Follow-up |
|-----|--------|-------------|-----------|-----------|------|---------|---------|------------|----|-----------|
| 27/F | Spinal anaesthesia | None | Fever, headache, neck stiffness, diplopia, photophobia 15 days after sa | Meningitis | WBC 720/μL (PMNs 3%); glucose 21 mg/dl (s 133 mg/dL); protein 680 mg/L | 21 mg/dl | 680 mg/L | Aspergillus spp. (CSF) | ND | AMFB iv + it (4 weeks) voriconazole (4 weeks) | Alive after 12 months (residual 6th cranial nerve palsy and impaired hearing) |

(continued on next page)
| Author, year [Reference] | Age/sex | Risk factor/Underlying disease | Sign and symptoms (time duration)/Time from TX | Sydrome | Diagnosis/methods | CSF characteristics | Aspergillus species | CSF Ag GMN (method) | Antifungaltreatment (time duration) | Outcome |
|--------------------------|---------|---------------------------------|-----------------------------------------------|---------|-------------------|-------------------|-------------------|-------------------|-----------------------------------|---------|
| 29/F Spinal anesthesia (Pregnancy)/None | Fever, headache, vomiting, neck stiffness, photophobia 11 days after sa | Meningitis | L/CSF | WBC 1430/μL (PNNs 40%); glucose 45 mg/dL; protein 330 mg/L | Aspergillus fumigatus (CSF culture) | ND | AMF 1 iv + it (2 weeks); voriconazole (16 weeks) | Alive after 12 months (no disability) |
| 38/F Spinal anesthesia (Pregnancy)/None | Fever, neck stiffness 8 days after sa | Meningitis | Pm/Autopsy | WBC 225/μL (PNNs 0%); glucose 61 mg/dL (s 109 mg/dL); protein 280 mg/L | Aspergillus fumigatus (autopsy culture) | ND | AMB (9 days) | Death after 24 days |
| Saitoh et al., 2007 | 33/M Chemotherapy/AML | Fever, headache, neck stiffness/14 days post-chemotherapy | Meningitis | L/CSF | WBC 15/μL; glucose 30 mg/dL; protein 760 mg/L | Aspergillus spp. (PCR + Ag on CSF) (Plateia) | 2.2 (s 0.1) | AMFB (1 week); voriconazole (12 months) | Alive after 1 year |
| Sundaram et al., 2007 | 22/M Spinal anesthesia (1 month prior)/None | Fever, headache, vomiting (2 months), neck stiffness | Meningitis | Pm/Autopsy (Aspergillus purulent meningitis & mycotic aneurism with subarachnoid hemorrhages) | WBC 720/μL (PNNs 90%); glucose 37 mg/dL; protein 850 mg/L | Aspergillus fumigatus (CSF culture, 6th attempt) | ND | ND | Death after 68 days |
| Van de Beek et al., 2008 | 56/M Kidney-pancreas transplant/End stage disease; sphenoid sinusitis | Headache, fever (6 weeks); neck stiffness, dysarthria, hemiparesis | Meningitis | L/sphenoid biopsy/Autopsy | WBC 1200/μL (PNNs 94%); glucose 64 mg/dL; protein 7300 mg/L | Aspergillus fumigatus (sphenoid biopsy + autopsy) | 6.47 (s 0.39) (Plateia) | Voriconazole (NR) | Death after 4 weeks |
| [PR], 2011 | 35/M IVDA (heroin)/Chronic hepatitis C | Fever (37.5 °C), headache, back pain (1 month) | Meningitis & spinal arachnoiditis | L/CSF | WBC 260/μL (PNN 70%); glucose 1 mg/dL (s 76 mg/dL); protein 7900 mg/L | Aspergillus flavus (CSF culture) | 7.4 (s 2.5) (Plateia) | Voriconazole 5 months (+1 month caspofungin); L-AMB 3 months | Alive after 9 months |
| Chronic meningitis/pachimeningitis | | | | | | | | | | |
| Palo et al., 1975 | 69/M None/Diabetes | Headache, fever, diplopia, vertigo hearing loss (6 months) | Chronic meningitis | Pm/CSF; autopsy (granulomatous leptomeningitis and spinal cord involvement) | WBC 103/μL (PNNs 8%); glucose 45 mg/dL; protein 1400 mg/L | Aspergillus fumigatus (CSF culture, 6th attempt) | NA | None | Death 1 month later |
| Reference                      | Gender | Age  | Diagnosis                        | Symptoms                                                                 | Diagnosis                                      | Treatment                          | Outcome                      |
|-------------------------------|--------|------|----------------------------------|--------------------------------------------------------------------------|-----------------------------------------------|------------------------------------|------------------------------|
| Gordon et al., 19766,9        | 34/F   | IVDA (heroin, cocaine)/None     | Bifrontal headache, neck stiffness (weeks), low-grade fever              | Chronic meningitis                                                  | L/CSF WBC 2892/μL (PMNs 80%); glucose 16 (± 110) mg/dL; protein 990 mg/L; ND | Aspergillus oryzae (CSF culture, 7th attempt) | AMFB + 5-FLU (12 months)    | Alive (6 years later; episode of bilateral necrotizing scleritis due to A. oryzae) |
| Mielke et al., 19811,8        | 58/F   | Neurosurgery/Acrromegaly        | Severe headache (4 months), retro-orbital pain, blindness, ophthalhalmoplegia/10 months | Chronic meningitis                                                  | Pm/Autopsy (chronic basilar meningitis by A. fumigatus & C. albicans; mycotic aneurism of the basilar artery with subarachnoid hemorrhage) | Aspergillus fumigatus (autopsy culture) | None                         | Death after 7 days          |
| Weinstein et al., 19829       | 67/M   | None/none                       | Retro-orbital and periorbital pain, vertigo (months); decrease eye vision; weakness; malaise | Chronic meningitis                                                  | L/biopsy sphenoid wing WBC 88/μL (PMNs 6%); glucose 53 (± 97) mg/dL; protein 1130 mg/L | Aspergillus fumigatus (biopsy + culture sphenoid) | AMFB + rifampicin (2 weeks) | Death after 18 days from surgery |
| Salaki et al., 198440         | 32/M   | Steroid treatment/ SLE          | Fever (38°C), frontal headache, lethargy (3 weeks), stiff neck, 6th nerve palsy | Chronic meningitis                                                  | L/CSF + spinal aspirate WBC 1400/μL (92%); glucose 33 mg/dL; protein 1100 mg/L | Aspergillus fumigatus (CSF culture, 4th attempt) | AMFB + 5-FLU (NR)            | Alive                       |
| Woods et al., 199041         | 44/M   | None/AIDS                       | Headache, fever, nausea, vomiting, lethargy, slurred speech, severe back pain (4 months) | Chronic meningitis                                                  | Pm/Autopsy (Aspergillus acute and chronic basilar meningitis; spinal arachnoiditis; pleural, brain, lumbar spinal cord involvement) WBC 80/μL (PMNs 80%); glucose 19 mg/dL; protein 2000 mg/L | Aspergillus fumigatus (autopsy culture) | None                         | Death after 18 days          |
| Murai et al., 199242         | 59/F   | None/Diabetes; Liver cirrhosis; Mondini’s anomaly; otitis media | Headache; hearing loss; multiple nerve palsy (6th, 8th, 9th, 10th, 11th) | Chronic pachymentingitis                                             | L/surgery maxillary sinus WBC 7/μL; protein 660 mg/L | Aspergillus flavus (surgery culture) | Miconazole (2 months); 5-FLU, fluconazole (1 month) | Alive after 4 months         |
| Kurino et al., 199343        | 63/M   | None/Diabetes; otitis media     | Fever, headache, hyperesthesia of face, abducens palsy, deafness         | Chronic meningitis                                                  | Pm/Biopsy granuloma + autopsy WBC 138/μL (PMNs 50%); glucose 87 mg/dL; protein 1007 mg/L | Aspergillus spp. (biopsy + autopsy) | None                         | Death 30 days post-surgery   |

(continued on next page)
| Author, year [Reference] | Age/sex | Risk factor/Underlying disease | Sign and symptoms (time duration)/Time from TX Syndrome | Diagnosis/methods | CSF characteristics | Aspergillus species | CSF Ag GM1 (method) | Antifungal treatment (time duration) | Outcome |
|--------------------------|---------|-------------------------------|--------------------------------------------------------|------------------|-------------------|-------------------|-------------------|----------------------------------------|---------|
| Mochizuki et al., 2000   | 75/M    | None/Otitis media             | Multiple cranial nerve palsy (2nd, 3rd, 4th), impaired vision (4 months) Chronic pachymeningitis | L/Biopsy         | NR                | Aspergillus flavus (biopsy culture) | ND                | Fluconazole (4 weeks); AMFB (4 months); 5-FLU (4 months); itraconazole (5 months) | Alive after 36 months |
| Moling et al., 2002      | 48/M    | Alcohol abuse/None            | Headache, fever, gait instability, apathy (5 months) Chronic meningitis + ventriculitis + arachnoiditis | L/CSF            | WBC 1880/μL; glucose 20 mg/dL | Aspergillus flavus candidus group (CSF culture) | 6.7 (± 1.7) (Platelia) | AMFB (1 week); rifampicin (several months); voriconazole (10 days); itraconazole (10 months) | Alive after 24 months |
| Kowacs et al., 2004      | 26/M    | Near drowning/None            | Fever (37.2 °C), mild meningismus (4 weeks) Chronic meningitis | L/CSF            | WBC 165/μL (PMNs 69%); glucose 64 mg/dL; protein 778 mg/L | Aspergillus fumigatus (CSF culture, 3rd attempt) | ND                | Fluconazole (12 days); itraconazole + AMFB (44 days) | Death after 56 days |
| Ismail et al., 2007      | 73/M    | None/Diabetes mellitus; pulmonary asbestosis | Headache, left-sided visual loss, scalp tenderness, fatigue (3 weeks) Hypertrophic pachymeningitis | L/Meningeal biopsy | WBC 0/μL; protein 5670 mg/L | Aspergillus flavus (biopsy culture) | ND                | Antifungal treatment (NR) | Death 3 months later |
| Kagawa et al., 2008      | 33/F    | Spinal cord mass lesion       | Headache, low grade fever (5 months), hydrocephalus Chronic meningitis | L/Biopsy VA shunt | WBC 1340/μL; glucose 8 mg/dL; protein 1580 mg/L | Aspergillus spp. (VA shunt biopsy) | ND                | AMFB (NR); fluconazole (NR) | Alive after 15 years (multiple recurrences) |
| Chan et al., 2011        | 59/M    | Diabetes; impaired renal function | Headache, diplopia, hoarseness (2 months) Pachymeningitis | L/Dural biopsy | Glucose 102 mg/dL; protein 1270 mg/L | Aspergillus flavus (culture from dural biopsy) | Positive (β-D-glucan + Platelia) | Voriconazole (2 weeks); caspofungin (4 weeks); voriconazole (8 weeks) | Alive after 7 months |
| Kato et al., 2011        | 42/M    | None/None                     | Headache, right nuchal pain, cranial nerve palsies (2 months) Hypertrophic pachymeningitis | L/CSF            | WBC 43/μL (PMNs 4%); glucose 56 mg/dL; protein 1000 mg/L | Aspergillus spp. (CSF PCR positive) | β-D-glucan (Fungitell) 164 pg/mL; serum < 5 pg/mL | Voriconazole (8 weeks); L-AMB + 5-FLU (2 weeks); fluconazole 8 weeks | Alive after 30 months |
| Meningoencephalitis      | Goldhammer et al., 1974 | 45/M  | None/none                     | Headache (9 months), blurred vision (3 weeks) Meningoencephalitis | Pm/Autopsy       | Disseminated meningoece-phalitis with pituitary abscess and left optic nerve involvement | Aspergillus spp. (microscopy smear of pituitary abscess + autopsy) | ND                | None                     | Death 4 days postoperatively |

**Clinical manifestations of Aspergillus meningitis**
| Study                          | Gender | Age | Diagnosis                      | Symptoms                                                                 | Clinical Presentation | Investigations | Treatment | Outcome       |
|-------------------------------|--------|-----|--------------------------------|--------------------------------------------------------------------------|------------------------|---------------|-----------|---------------|
| Naidoff et al., 1975<sup>51</sup> | 29/F   | 51  | Kidney transplant/ End stage kidney disease | Meningoencephalitis/ disseminated aspergillosis (heart, lung, liver, spleen, thyroid, brain, eye, meninges) | ND | Aspergillus fumigatus (autopsy culture) | None | Death in a few days |
| Kaufman et al., 1976<sup>52</sup> | 31/F   | IVDA (heroin)/ None | Headache (9 months), Meningo-encephalitis blunted vision (2 months), intermittent diplopia, hearing loss | LR/ Lobectomy; CSF/Autopsy (granulomatous basilar leptomeningitis; aspergilloma left frontal gyrus; transtentorial and tonsillar herniation) | WBC 1150/µL (PMNs 83%); glucose 20 (s 119) mg/dL; Aspergillus fumigatus (CSF + frontal granuloma culture) | NA | AMFB (2 weeks) | Death after 3 weeks |
| Horton et al., 1976<sup>53</sup> | 17/F   | 53  | Fungal endocarditis/ Aortic stenosis | Headache, incoordination, right-sided numbness, seizure | Meningoencephalitis PM/Autopsy (mycotic aneurism of the middle cerebral artery with subarachnoid hemorrhage) | NR | Aspergillus fumigatus (CSF culture) | None | Death after 9 days |
| Galassi et al., 1978<sup>54</sup> | 59/F   | 59  | Neurosurgery/ Meningioma | Intermittent fever, seizures, aphasia, hemiparesis/12 months | Meningoencephalitis PM/Autopsy (diffuse purulent meningoc-encephalitis) | NR | Aspergillus fumigatus (CSF culture) | None | Death after 3 months |
| Peacock et al., 1984<sup>55</sup> | 23/M   | 23  | Post-chemotherapy/ Refractory anemia | Fever, headache, lethargia (57 days post-chemo) | Meningoencephalitis LR/ Biopsy (pulmonary); Autopsy (Aspergillus leptomeningitis; necrotizing vasculitis (pons and basal ganglia); tonsillar herniation; necrotizing pneumonia) | WBC 117-1126/µL (PMNs 88–99%); glucose 13–48 mg/dL; protein 540–3460 mg/L; Aspergillus terreus (culture lung biopsy); CSF Aspergillus antigen | Positive (RIA) | AMFB + 5-FLU + rifampicin (NR) | Death after 65 days |
| Ouammou et al., 1986<sup>56</sup> | 3/M    | 3   | Neurosurgery/ Encephalomeningocoele | Fever (37.8 ºC), frontal subcutaneous abscess/3 days | Meningoencephalitis LR/CSF; surgery: meningeal mycetoma. Autopsy: encephalitis (cerebral hemispheres, brain stem) | WBC 52/µL (PMNs 70%); glucose 10 mg/dL; protein 1200 mg/L; Aspergillus fumigatus (CSF culture) | NA | Griseofulvin (3 months) | Death after 3 months |

(continued on next page)
| Author, year [Reference] | Age/sex | Risk factor/Underlying disease | Sign and symptoms (time duration)/Time from TX | Syndrome | Diagnosis/methods | CSF characteristics | Aspergillus species | CSF Ag GMN (method) | Antifungal treatment (time duration) | Outcome |
|--------------------------|---------|-------------------------------|-----------------------------------------------|----------|------------------|-------------------|-------------------|------------------|-----------------------------|---------|
| Cox et al., 199057       | 31/M    | None/AIDS                     | Headache, fever (38.2 weeks), confusion, vomiting | Meningoencephalitis | PM/Autopsy | ND | Aspergillus spp. | (autopsy histology) | NA | None | Death after few days |
| Breneman et al., 19925   | 50/M    | IVDA; steroid therapy/COPD    | Fever (38.6°C), dyspnea, headache; stiff neck, progressive mental status change (3 days) | Meningoencephalitis | L/brain biopsy | WBC 4100/µL (PMNs 96%); glucose 33 mg/dL; protein 1340 mg/L | Aspergillus fumigatus | (Brain biopsy culture) | NA | AMFB (few days) | Death after few days |
| Van der Knaap et al., 199358 | 3/M    | None/Galactosemia             | Fever (40°C), nuchal rigidity, convulsions, left hemiparesis | Meningoencephalitis | L/CSF positive antigen | Normal | Aspergillus spp. | (Positive NR) | AMFB + 5-FLU (NR) | Improvement |
| Mikolich et al., 19966   | 25/F    | None/None                     | Worsening headache (3 months); vomiting; photophobia (1 month); papilledema | Meningoencephalitis | L/brain biopsy | WBC 200/µL (PMNs 2%); glucose 40 mg/dL; protein 920 mg/L | Aspergillus fumigatus | (brain biopsy) | NA | Itraconazole (24 months) | Alive after 4 years |
| Darras-Joly et al., 199623 | 17/F   | Neurosurgery/Ependymoma       | Fever (40°C), neck stiffness/7 days after surgery | Meningoencephalitis; ventriculitis | L/Surgical drainage | WBC 1900/µL (PMNs 97%); glucose 36 mg/dL; protein 1100 mg/L | Aspergillus fumigatus | (surgical culture) | Negative (NR) | AMFB (72 days) + Itraconazole (30 days) | Death after 96 days |
| Schwartz et al., 199759  | 18/M    | Chemotherapy/ALL              | Meningism, fever (92 days post-chemotherapy) | Meningoencephalitis | L/Brain biopsy | WBC 1056/µL (PMNs 96%) | Aspergillus spp. | (Brain biopsy) | ND | Itraconazole (4 weeks); voriconazole (6 months) | ND | Death after 6 months |
| Koh et al., 199860       | 15/F    | Chemotherapy/ALL              | Flaccid weakness lower extremities, slurred speech, urinary retention | Meningomioencephalitis | PM/Autopsy (Multifocal leptomeningeal exudates; fungal abscess/necrosis in spinal cord) | ND | Aspergillus spp. | (autopsy histology) | ND | Death 21 days later |
| Payot et al., 199961     | 29/M    | None/AIDS                     | Headache (3 weeks), nausea (1 week), fever (39°C), nuchal rigidity | Meningoencephalitis | PM/Autopsy | WBC 19/µL (PMNs 50%); protein 1080 mg/L | Aspergillus spp. | (autopsy histology) | ND | None | Death after 7 days |
| Fasciano et al., 199962  | 26/M    | Steroid treatment/Chronic asthma | Fever, quadriplegia, areflexia; hydrocephalus (2 weeks) | Meningoencephalitis | L/Brain biopsy | WBC 1300/µL (PMNs 98%); glucose 40 mg/dL; protein 1100 mg/L | Aspergillus fumigatus | (brain biopsy) | ND | AMFB iv and intrathecal + 5-FLU (2 weeks) | Death after 6 weeks |
| Chandra et al., 200063    | 40/F    | None/Ethmoid and sphenoid sinusitis | Headache, fever, vomiting (1 week); left proptosis | Meningoencephalitis | L/Brain biopsy | NR | Aspergillus fumigatus | (biopsy) | ND | ND | ND |
| Study and Authors | Year | Age | Diagnosis | Symptoms | Pathology | Treatment | Outcome |
|------------------|------|-----|-----------|----------|-----------|-----------|---------|
| Viscoli et al., | 2002 | NR  | BMT/Acute lymphoblastic leukemia | Fever, neurological deficit, seizures/5 days post-BMT | Meningoencephalitis | Pm/Autopsy (diffuse meningeal and parenchymal infiltration) | Aspergillus spp. (meningeal and parenchymal) | NR | Death |
| Wang et al.,     | 2003 | 39/M | Steroid treatment/ SARS | Tentorial herniation | Meningoencephalitis | Pm/Autopsy: (Aspergillus meningitis; multiple brain abscess containing aspergillus; disseminated aspergillosis heart, kidney, spleen, pancreas, adrenal glands) | Aspergillus spp. (autopsy histology and culture) | ND | None | Death |
| Roberts et al.,  | 2004 | 71/F | None/Sinusitis | Fever (38.3 °C), severe headache, diplopia, confusion (5 weeks) | Meningoencephalitis | WBC 286/μL (PMNs 38%); glucose 23 mg/dL; protein 850 mg/L | Aspergillus spp. (autopsy histology) | ND | None | Death after 10 days |
| Botturi et al.,  | 2006 | 59/F | Steroid treatment/ Sphenoid sinusitis/ | Headache, diplopia; bilateral 6th nerve palsy (5 weeks) | Meningoencephalitis | WBC 920/μL (PMNs 96%); glucose 0 mg/dL; protein 180 mg/L | Aspergillus spp. (biopsy) | ND | None | Alive after 23 months |
| Gabelmann et al., | 2007 | 43/F | Chemotherapy/AML; sinusitis | NR | Meningoencephalitis | WBC 286/μL (PMNs 90%); glucose 27 mg/dL; protein 830 mg/L | Aspergillus spp. (autopsy histology) | ND | None | Death after 41 days |
| Van de Beek et al., | 2008 | 62/F | Kidney-pancreas transplant/End stage disease | Headache (6 months), Meningoencephalitis altered consciousness | L/Brain biopsy | WBC 286/μL (PMNs 90%); glucose 27 mg/dL; protein 830 mg/L | Aspergillus spp. (biopsy) | ND | None | Alive after 12 days |
| Spinal arachnoiditis | Bryan et al., | 1980 | IVDA (heroin)/None | Headache, nausea, vomiting (weeks), low back pain; hydrocephalus | Spinal arachnoiditis | L/Lumbar biopsy (lesion L3-5) | Aspergillus flavus (immunofluorescence on biopsy) (CSF) | NA | AMFB + rifampicin (10 weeks) | Alive after 14 months |
| Stein et al.,    | 1982 | 24/F | IVDA (heroin)/ Chronic alcoholism | Low back pain (4 months), left leg weakness, frequent headache fever (38 °C); confusion and signs of meningeal irritation | Spinal arachnoiditis | L/CSF | Aspergillus terreus (2 CSF cultures) | NA | AMFB (NR) | Death 26 days after laminectomy |
| Van de Wyngaert et al., 1985 | 30/M | None (splinter stuck on his hand)/None | High fever, painful stiffness of spine, headache, photophobia, nausea | Spinal arachnoiditis | L/CSF | WBC 3200/μL (PMNs 90%); glucose 30 mg/dL; protein 1530 mg/L | Aspergillus fumigatus (CSF) precipitin | NA | AMFB (3 months) + rifampin (10 days) + 5-FLU (3 months) | Alive after 229 days |

(continued on next page)
| Author, year [Reference] | Age/sex | Risk factor/Underlying disease | Sign and symptoms (time duration)/Time from TX | Syndrome | Diagnosis/methods | CSF characteristics | Aspergillus species (method) | CSF Ag GMN (method) | Antifungal treatment (time duration) | Outcome |
|--------------------------|---------|-------------------------------|-----------------------------------------------|----------|------------------|-------------------|---------------------|-----------------------|------------------------|-----------------------|---------|
| Endo et al., 2001 \(^2^\) | 55/M | Neurosurgery/Pituitary adenoma | Diplopia, retro-orbital pain (1 year), loss of vision/9 years | Arachnoiditis; subdural abscess | L/Abscess aspiration | NR | Aspergillus fumigatus (abscess culture) | ND | Fluconazole (4 weeks) | Death after 1 month |
| Genzen et al., 2009 \(^3^\) | 37/F | Spinal anesthesia (12 months prior pregnancy) | Headache (months); fever (37.4 °C), blurred vision, numbness left lower extremity | Arachnoiditis | L/Laminectomy & tissue biopsy | WBC 970/µL (PMN 92%); glucose 50 mg/dL; protein 1010 mg/L | Aspergillus terreus (biopsy culture) | ND | Voriconazole (78 days); voriconazole + caspofungin (54 days); AMFB (6 days); ABLC (50 days) | Alive after 9 months |
| Genzen et al., 2009 \(^4^\) | 73 | | | | WBC 949/µL (PMNs 27%); glucose 29 (s 90) mg/dL; protein 1200 mg/L | Aspergillus flavus (serology) | NA | | | | |
| Hummel et al., 2006 \(^5^\) | 4/F | Chemotherapy/ALL | | Ventriculitis & multiple abscess | L/CSF (Ommaya reservoir) | NR | Aspergillus fumigatus (PCR CSF) | Positive (Platelia) | Voriconazole + caspofungin (5 weeks); intraventricular AMFB (4 weeks); voriconazole (2 months) | Alive after 3 months |
| Antachopoulos et al., 2011 \(^6^\) | 5/F | VP shunt | Fever (40 °C), tonic/clonic seizures | Ventriculitis | L/VP | WBC 400/µL (Neutrophil predominance); glucose 25 mg/dL (s 110 mg/dL); protein 1000 mg/L | Aspergillus fumigatus (Culture VP catheter; PCR CSF) | 5.5 (Platelia) | L-AMB (4 months) + voriconazole (5 months) | Death after 9 months |

**M** = male; **F** = female; **IVDA** = intravenous drug abuser; **CSF** = cerebrospinal fluid; **L** = life; **Pm** = post-mortem; **Ag GMN** = galactomannan antigen; **s** = serum; **WBC** = white blood cells; **PMNs** = polymorphonuclear; **NA** = not available; **ND** = not done; **NR** = not reported; **AMB** = amphotericin B deoxycholate; **SFLU** = 5-fluorocytosine; **L-AMB** = liposomal amphotericin B; **ABLC** = amphotericin B lipid complex; **ALL** = acute lymphoblastic leukaemia; **CML** = chronic myelogenous leukemia; **RAEB** = refractory anemia with excess blasts; **C4def** = hereditary complete C4 deficiency; **PR** = present report; **PCR** = polymerase chain reaction; **VP** = ventriculoperitoneal; **sa** = spinal anaesthesia.

\(^a\) One of these four patients had meningism and headache.
\(^b\) Reported also in reference 77 (updated the follow-up).
\(^c\) Symptoms appeared 2–21 days after spinal anaesthesia (mean 7.8 days).
\(^d\) Random values of blood glucose were reported.
\(^e\) Reported also in reference 78.
\(^f\) Discarded as contaminant.
\(^g\) Reported also in reference 79 (updated the follow-up).
\(^h\) Serological speciation made a result compatible with A. flavus.
with response to therapy. 1-3-β-D-glucan was evaluated in 2 patients with positive results in both. CSF pleocytosis was detected in 61/64 (95.3%) of available specimens with a median cell count of 678/μL and with a neutrophil predominance in 68.4% of cases. Hypoglycorrhachia was shown to be present in 62.5% of cases with a median glucose level of 32.5 mg/dL.

Fifty-six patients received antifungal therapy: amphotericin B deoxycholate (AMFB) alone or associated with 5-fluorocytosine (11 pts), rifampicin (5 pts), itraconazole (3 pts) or fluconazole (1pt) was used in 36 cases; liposomal amphotericin B (L-AMB) was employed in the treatment of 6 individuals; fluconazole was used in five patients (in three patients as the only drug). Two patients received 5-fluorocytosine, alone in one case and with miconazole and fluconazole in the other case. Fifteen patients received voriconazole (in three cases associated with caspofungin), and in 4 following AMFB use. AMFB was the main antifungal employed until 1996 when oral itraconazole was used for the first time. Voriconazole and L-AMB were used for the first time in 1997, whereas caspofungin in 2006.

Of those patients who had received at least one dose of antifungal agent, 30 (51.7%) died after an interval of time ranging from few days up to 6 years. All patients with chronic meningitis were initially treated with antibiotics and had also received anti-tubercular therapy. An overall case-fatality rate (CFR) of 72.1% was observed, with significant differences between immunocompetent (63.5%) as opposed to immunocompromised patients (82.9%) patients.

Autopsy was available in 49 cases and it was the method by which diagnosis was made for 40 patients (81.6%). In twelve cases basilar meningitis was identified; spinal cord involvement was observed in 5 patients; the presence of a mycotic aneurism involving either the internal carotid artery or the basilar artery was shown in 12 patients with concomitant subarachnoid hemorrhage. Transtentorial, tonsillar or uncal herniation was present in three patients.

Discussion

In a 1969 review of the literature, Mukoyama et al., reported 33 cases of aspergillosis involving the CNS of whom 10 had meningitis and 3 had meningoencephalitis. However, Aspergillus isolation failed in all 10 cultured cerebrospinal fluid specimens.7

In a clinical-pathological study of central nervous system aspergillosis only 1 patient had signs of meningeal irritation during life while at autopsy the meninges were focally affected in nearly half of the cases.8

In the present series regarding 93 patients, a picture of pure meningitis was observed in 65.6% of cases, while meningoencephalitis was diagnosed in about 25% of patients.5,6,36,50

In patients with a diagnosis of meningitis fever and headache were the most common presenting symptoms (78.8%) followed by neck stiffness in 28.2% (24/85).3–6,9–76

| Table 2 Characteristics of patients with aspergillus meningitis. |
|---------------------------------------------------------------|
| **Immunocompetent patients, n = 52 (%)** | **Immunocompromised patients, n = 41 (%)** | **Total, n = 93 (%)** |
| Age, years median (range) | 34.5 (3–73) | 39 (4–75) | 37 (3–75) |
| Sex, female (%) | 34 (65.4) | 15/40 (37.5) | 49/92 (53.3) |
| Diagnosis during life | 36/52 (69.2) | 16/41 (39) | 52/93 (55.9) |
| Death after diagnosis in life | 18/36 (50.0) | 9/16 (56.3) | 27/54 (50.0) |
| Total deaths | 33/52 (63.5) | 34/41 (82.9) | 67/93 (72.1) |
| Clinical picture | | | |
| Meningitis | 27 (51.9) | 19 (46.3) | 46 (49.5) |
| Meningoencephalitis | 10 (19.2) | 13 (31.7) | 23 (24.7) |
| Chronic meningitis/pachimeningitis | 8 (15.4) | 7 (17.1) | 15 (16.1) |
| Spinal arachnoiditis | 5 (9.6) | – (0.0) | 5 (5.4) |
| Ventriculitis | 2 (3.8) | 2 (4.9) | 4 (4.3) |
| CSF characteristics | | | |
| Positive culture | 17/46 (36.9) | 4/22 (18.2) | 21/68 (30.9) |
| Positive PCR | 3/3 (100) | 3/3 (100) | 6/6 (100) |
| Median WBCs/μL (range) | 640 (5–8800) | 988 (0–4100) | 678 (0–8800) |
| Neutrophils predominance (≥60%) | 25/37 (67.6) | 14/20 (70) | 39/57 (68.4) |
| Hypoglycorrhachia | 9/14 (64.3) | 1/2 (50) | 10/16 (62.5) |
| Median glucose level (mg/dL) | 30 (1–77) | 33 (0–102) | 32.5 (0–102) |
| Glucose ≤ 25 mg/dl | 16/39 (41.1) | 14/17 (23.5) | 20/56 (35.7) |
| Median protein level (range) (mg/L) | 995 (100–7900) | 1090 (180–7300) | 1007 (100–7900) |
| Median galactomannan antigen (range) | 7.05 (5.5–10.4) | 4.58 (2.2–578) | 6.58 (2.2–578) |
| Positive | 6/8 (75) | 7/7 (100) | 13/15 (86.7) |

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| a 1 patient also had empyema, 1 abscess, 1 spinal arachnoiditis. |
| b 1 patient had concomitant ventriculitis + arachnoiditis. |
| c 1 patient had concomitant subdural abscess. |
| d 1 patient had concomitant multiple abscess. |
However, only 16.5% (14/85) of patients presented with three of the four signs and symptoms of headache, fever, neck stiffness and altered mental status.\textsuperscript{3,10,18–20,25,33–36,40,57,61,66,70} Cranial nerve palsies were reported in 17.6% (15/85) and seizures (11/86) in 12.8% of patients.

The diagnosis of \textit{Aspergillus} meningitis is very difficult and challenging. In fact, a diagnosis during life was obtained only in 55.9% of patients although with a much higher frequency among immunocompetent patients (69.2\%\textsuperscript{3,6,10,12,15,22,23,25–27,29,32,33,39,44,45,47,52,54,56,58,63–69,73,76,78,79} PR as opposed to immunocompromised individuals (39\%)\textsuperscript{5,9,28,29,34,36,40,42,46,48,55,59,74} This difference might be explained by a more aggressive and acute course of the disease observed in immunosuppressed hosts. A culture-based diagnosis of \textit{Aspergillus} meningitis is hampered by the lack of sensitivity as shown by the 31% of positive results observed in our review of published cases.\textsuperscript{3,9,11,22,23,25,26,29,33,35,37,40,45,52–54,56,70} PR It has been previously suggested that a minimum of 5 mL of cerebrospinal fluid should be cultured when a mycosis is suspected or that repeated culture of large volumes of CSF are critical for successful \textit{in vitro} isolation. However, such large volumes are not easy to obtain in clinical practice.\textsuperscript{80} On the other hand, serial lumbar puncture does indeed seem to succeed by the lack of cerebrospinal fluid only after several attempts.\textsuperscript{3,23,26,29,35,37,40,45}

Non-culture based diagnostic methods for the diagnosis of aspergillosis were employed on CSF in fifteen patients and seem to outperform traditional culture, with an overall sensitivity of 87\%.\textsuperscript{23,25,28,29,34,36,46,69,64,75,76}PR Although a cut-off value of the GM index has not yet been formally established for the diagnosis of CNS aspergillosis, it has been proposed that it might be lower than that used for serum samples due to the lower back-ground reactivity of CSF.\textsuperscript{25,81}

The median CSF GM index in this series was 6.58 which is a value higher than what is usually observed in serum and well above the cut-off of 0.5 when two serial serum determinations are used among immunocompromised patients or the 0.7–1 value when a single determination is employed in non-hematological patients.\textsuperscript{82,83} Notably, when both serum and CSF GM were screened concomitantly, negative results were observed in three cases in serum and the index value was always higher in CSF than in serum.\textsuperscript{29,34,36,64}PR Although serial determinations on CSF were available only in three cases they may provide useful information on the therapeutic response.\textsuperscript{25,29}PR Finally, it seems that the Platelia GM test works well irrespective of the species of \textit{Aspergillus} involved as shown by the cases described by Vervej, Moling and ourselves in whom \textit{A. fumigatus}, \textit{A. candidus} and \textit{A. flavus} were respectively cultured from the CSF.\textsuperscript{25,29}PR

Our review shows that \textit{Aspergillus} meningitis has an ominous prognosis with a global case-fatality rate (CFR) of 72.1% but with a much better outcome among immunocompetent patients in whom a CFR of 63.5% was observed versus a 83% CFR registered among immunocompromised patients. Our data are only slightly better than the 88% CFR reported by Lin et al. in a literature-based survey published before 2001.\textsuperscript{84}

The Infectious Diseases Society of America (IDSA) guidelines recommend voriconazole for the treatment of central nervous system aspergillosis but these recommendations are mainly based upon studies regarding patients with hematological disorders and there is no specific mention as to the treatment of \textit{Aspergillus} meningitis.\textsuperscript{85} In our present review, that encompasses a long period of time before the introduction of voriconazole (\textit{i.e.}, 2002), most patients (64.3\%) were treated with amphotericin B deoxycholate and less than 30\% received voriconazole at some time of their disease.\textsuperscript{32,33,34,36,48,49,67,73–76} PR In a recent analysis conducted by Schwartz et al. on 120 cases of CNS aspergillosis a 47\% response rate and a median survival of 159 days among patients treated with voriconazole was shown.\textsuperscript{86} Voriconazole shows excellent penetration into the CNS as demonstrated by studies conducted in healthy guinea pigs in whom high cerebrospinal fluid to plasma ratio (0.68) together with rapid penetration across the blood brain barrier were observed.\textsuperscript{87} Including the present report, determination of cerebrospinal fluid concentrations of voriconazole were available in four cases, with reported values ranging from 0.8 to 5.86 mg/L and with a CSF/plasma ratio ranging from 38\% to 76 \%.\textsuperscript{25,59}PR Hope recently proposed that in the busy clinical setting, voriconazole therapeutic drug monitoring (TDM) should be obtained at the end of day 2 and subsequently in the first week of therapy.\textsuperscript{88} An association between poor outcome and voriconazole concentrations has been initially observed by Pascual and coworkers.\textsuperscript{89} In addition Miyakis et al. recently showed an 11-fold increased risk of death among patients with invasive mucoses treated with voriconazole who had an initial trough concentration of less than 0.35 mg/L.\textsuperscript{90} By contrast, several studies and expert opinion suggest that the optimal maximum voriconazole concentrations should not exceed 5.5–5.8 mg/L\textsuperscript{89,91,92}

Another crucial issue not yet addressed so far is the optimal length of antifungal therapy in patients with \textit{Aspergillus} meningitis, as well as for cerebral aspergillosis. In our patient, antifungal treatment was administered for 7 months, 5 of which employing voriconazole but, just before losing the patient to follow-up we were uncertain how long it would have been necessary to continue the specific treatment. Our analysis of the literature regarding patients with \textit{Aspergillus} meningitis who were treated with voriconazole shows very different lengths of treatment, ranging from 8–14 weeks to 5–12 months.\textsuperscript{25,32–34,67,74,76}PR

However, it should be pointed out that in most cases the outcome following drug discontinuation is not reported. The long term duration of voriconazole treatment for patients with \textit{Aspergillus} meningitis or with CNS involvement is a matter not only of efficacy but also of toxicity. In this regard, the risk of phototoxicity and, above all, the risk of inducing squamous cell carcinoma should be mentioned.\textsuperscript{93} Caspofungin was employed in 5 patients, (in 4 of whom in combination with voriconazole), but its role, if there is any, as a single agent in the treatment of aspergillus meningitis is hampered by the lack of significant penetration across the blood–brain barrier of this drug.\textsuperscript{94} Except one apparently successful case, flucytosine has been used only in association with AMB and its role in the treatment of aspergillosis remains anecdotal.\textsuperscript{9,95}

In conclusion, our review shows that \textit{Aspergillus} meningitis is a rare clinical entity that is much more frequently observed among immunocompetent patients. It is characterized by CSF neutrophil pleocytosis in 68\% of cases and...
hypoglycorrhachia in 62% of cases. Cultures of CSF are positive only in one third of cases, but the GM antigen test is very useful, with a sensitivity reaching 87%. Although our data show a poor prognosis, we believe that the more widespread use of diagnostic methods with greater sensitivity (e.g., PCR and GM), together with the availability of voriconazole therapy, may allow improved outcomes provided that the diagnosis is achieved earlier. The optimal length of antifungal therapy however remains to be determined.

**Funding**

No particular funding was received to support this work.

**Conflict of interest**

Spinello Antinori none Mario Corbellino none Luca Meroni none Federico Resta none Salvatore Sollima none Massimo Tonolini none Anna Maria Tortorano none Laura Milazzo none Lorenzo Bello none Elisa Furfaro none Massimo Galli none Claudio Viscoli none.

**Acknowledgments**

We thank Rosamaria Rotolo, Virginia Zanzottera, and Rossella Garlaschelli of the Biblioteca “Alberto Malliani” of the University of Milano for their excellent help in the retrieval much of the articles.

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