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REVIEW

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

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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%.

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Conclusions: *Aspergillus meningitis* may occur in both immunocompetent and immunocompromised patients and run an acute or chronic course. The findings of this systematic review extend the information on this life-threatening infection and could assist physicians in achieving an improved outcome.

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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%.^{1,2} By contrast, *Aspergillus meningitis* is a more seldomly encountered clinical entity and it is found more frequently in immunocompetent rather than in immunocompromised hosts.^{3–8} 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 (Fig. 1). 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 q12). 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 endocanal 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 endocanal inflammation now involving

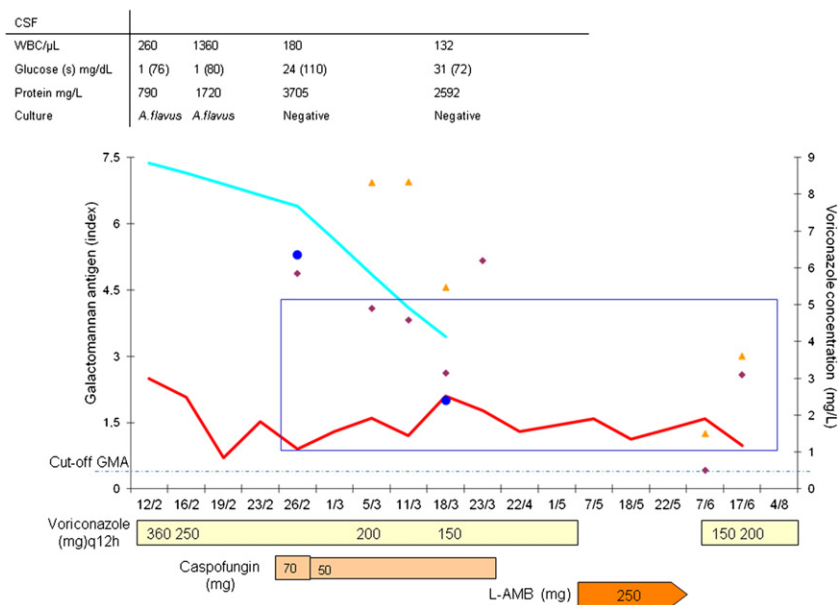


Figure 1 Medication history, clinical course and kinetic of *Aspergillus* antigen in CSF of our case of *Aspergillus flavus* meningitis. The dotted line represents the cut-off value of GM. The light blue line is the index on CSF and the red line on plasma. The blue circle represents the CSF levels of 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.

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 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

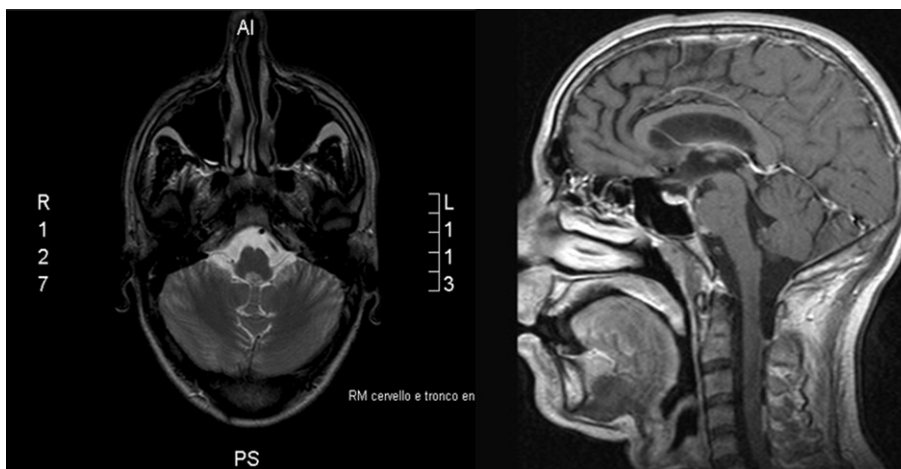


Figure 2 Sagittal and coronal T1-weighted gadolinium-enhanced magnetic resonance scan of the brain of our patient with *Aspergillus flavus* meningitis showing contrast impregnation along the basilar artery in the prepontine cistern.



Figure 3 Sagittal T2 (a) and gadolinium enhanced T1-weighted (T1W) (b) MRI demonstrate pathologic enhancement and endocanal pathologic tissue of the L4-S2 tract.

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 endocanal 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. granulosis* 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 Platelia 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

Table 1 Characteristics of patients with *Aspergillus* meningitis.

Author, year [Reference]	Age/sex	Risk factor/ Underlying disease	Sign and symptoms (time duration)/ Time from TX	Syndrome	Diagnosis/ methods	CSF characteristics	<i>Aspergillus</i> species	CSF Ag GMN (method)	Antifungal treatment (time duration)	Outcome
Meningitis										
Atkinson & Israel, 1973 ⁹	27/M	None/Sarcoidosis	Headache, blurred vision	Meningitis	L/CSF	WBC 144/ μ L (PMNs 10%)	<i>Aspergillus fumigatus</i> (CSF)	NA	5-FLU (3 months)	Alive 2 years after stopping antifungal therapy
Feely et al., 1977 ¹⁰	57/F	Neurosurgery (Trans-sphenoidal Yttrium ⁹⁰ implant)/ Acromegaly	Meningeal signs, left hemiparesis/ 11 months	Meningitis	Pm/Autopsy (purulent basal leptomeningitis + multiple infarcts)	WBC 138/ μ L (PMNs 96%); proteins 850 mg/L	<i>Aspergillus</i> spp. (autopsy culture)	NA	None	Death after 1 day
	37/M	Neurosurgery (Trans-sphenoidal Yttrium ⁹⁰ implant)/ Diabetic retinopathy	Fever, stiff neck, headache, blurred vision/9 months	Meningitis	L/Biopsy (tissue adherent to the screws)	WBC 8800/ μ L (PMNs 90%); protein 330 mg/L	<i>Aspergillus</i> spp. (biopsy)	NA	AMFB (NR)+ removal of implant	Alive
Mohandas et al., 1978 ¹¹	38/M	Neurosurgery/ Maxillary sinusitis	Meningeal irritation, coma/6 days post-operatively	Meningitis	L/Surgery of fungal granuloma	WBC 100/ μ L (PMNs 0%); glucose 35 mg/dL; protein 1160 mg/L	<i>Aspergillus</i> spp. (biopsy)	NA	AMFB (7 days) ev + intrathecal (1 day)	Death after 7 days
Aung et al., 1979 ¹²	22/F	Pregnancy/None	Headache, retrobulbar pain, blurred vision, ophthalmoplegia (22 days after delivery)	Meningitis	L/Biopsy leptomeninges	ND	<i>Aspergillus</i> spp. (biopsy)	NA	Antifungal drugs (not mentioned)	Death after 1 month
Beal et al., 1982 ¹³	47/F	None/Sphenoid sinusitis	Frontal headache (5 months); nuchal rigidity, fever, hydrocephalus	Meningitis	L/biopsy sinus	WBC 120/ μ L (PMNs 63%); glucose 25 mg/dL; protein 620 mg/L	<i>Aspergillus</i> 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 <i>Aspergillus</i> meningitis with exudate in the subarachnoid space of spinal cord)	WBC 2650/ μ L (PMNs 10%); glucose 26 mg/dL; protein 1750 mg/L	<i>Aspergillus</i> spp. (CSF culture after multiple attempts)	NA	AMFB (3 days)	Death after 20 days
Diendogh et al., 1983 ¹⁴	60/M	Neurosurgery (Trans-sphenoidal Yttrium ⁹⁰ 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/ μ L (PMNs 60%)	<i>Aspergillus</i> spp. (autopsy histology)	NA	None	Death after 2 weeks

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Table 1 (continued)

Author, year [Reference]	Age/ sex	Risk factor/ Underlying disease	Sign and symptoms (time duration)/		Diagnosis/ methods	CSF characteristics	Aspergillus species	CSF Ag GMN (method)	Antifungal treatment (time duration)	Outcome
			Time from TX	Syndrome						
Walsh et al., 1985 ⁸	64/F	Steroid treatment/ Cushing syndrome	Meningismus, headache, hemiparesis	Meningitis	Pm/Autopsy : mycotic <i>Aspergillus</i> aneurism & subarachnoid hemorrhage	WBC 15/ μ L (PMNs 0%); glucose 90 mg/dL; protein 1450 mg/L	<i>Aspergillus</i> spp. (autopsy histology)	NA	None	Death after 9 days
Hajjar et al., 1987 ¹⁵	28/M	Neurosurgery/ Acoustic neurinoma	NR/9 days	Meningitis	L/Wound culture	NR	<i>Aspergillus</i> <i>fumigatus</i> (wound culture)	NA	AMFB + 5-FLU (2 months)	Death after 2 months
Asnis et al., 1988 ¹⁶	44/M	None/AIDS	Confusion, generalized seizures	Meningitis	Pm/Autopsy (<i>Aspergillus</i> leptomeningites)	NR	<i>Aspergillus</i> spp. (autopsy histology)	NA	AMFB (20 days)	Death
Carrazana et al., 1991 ¹⁷	44/M	None/AIDS; sphenoid sinusitis	Headache, fever, nausea, ataxia, hemiparesis, seizures	Meningitis	Pm/Autopsy (<i>Aspergillus</i> meningeal infiltration; thrombosis of basilar artery)	NR	<i>Aspergillus</i> spp. (autopsy histology)	NA	None	Death
Komatsu et al., 1991 ¹⁸	61/F	Neurosurgery/ Rathke's cleft cyst	High fever and meningeal signs/12 days after surgery	Meningitis	Pm/Autopsy (<i>Aspergillus</i> meningitis & mycotic aneurism, subarachnoid hemorrhage)	WBC 881/ μ L (PMNs 70%); glucose 46 mg/ dL; protein 540 mg/L	<i>Aspergillus</i> spp. (autopsy histology)	NA	ND	Death after 23 days
Lammens et al., 1992 ¹⁹	39/F	Immunosuppressive therapy/SLE	Headache (1 month), fever (39.5 °C), neck stiffness, Horner syndrome	Meningitis	Pm/Autopsy (<i>Aspergillus</i> basal meningitis & subarachnoid hemorrhage)	WBC 3750/ μ L (PMNs 84%); glucose 32 mg/dL; protein 1000 mg/L	<i>Aspergillus</i> spp. (autopsy histology)	NA	None	Death after 15 days
Torre-Cisneros et al., 1993 ²⁰	31/F	Liver transplant/ End stage liver disease	Seizure ^a	Meningitis	Pm/Autopsy (ischemic infarct; leptomeningeal aspergillosis)	NR	<i>Aspergillus</i> spp. (autopsy histology)	NA	NR	Death
	21/F	Liver transplant/ End stage liver disease	NR ^a	Meningitis	Pm/Autopsy (ischemic infarct; leptomeningeal aspergillosis)	NR	<i>Aspergillus</i> spp. (autopsy histology)	NA	NR	Death
	24/F	Liver transplant/ End stage liver disease	Seizure ^a	Meningitis	Pm/Autopsy (acute leptomeningitis)	NR	<i>Aspergillus</i> spp. (autopsy histology)	NA	NR	Death
	38/M	Kidney transplant/ End stage kidney disease	Seizure ^a	Meningitis	Pm/Autopsy (acute leptomeningitis; haemorrhagic infarcts)	NR	<i>Aspergillus</i> spp. (autopsy histology)	NA	NR	Death

Miaux et al., 1995 ²¹	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 2000/μL (PMNs 95%); protein 900 mg/L	<i>Aspergillus</i> spp. (autopsy histology)	NA	NR	Death after 5 days
	39/F	Bone marrow transplant; steroid therapy/RAEB	Mental confusion/ 3.5 months	Meningitis	Pm/Autopsy (brain hemorrhagic necrosis; lung involvement)	WBC 2560/μL (PMNs 98%);	<i>Aspergillus</i> spp. (autopsy histology)	NA	NR	Death after 8 days
Adunsky et al., 1996 ²²	74/M	None/None	Fever (38.3°), stuporous, left hemiplegia, dysarthria (1 day)	Meningitis	L/CSF	WBC 2400/μL (PMNs 94%); glucose 10 mg/dL; protein 1500 mg/L	<i>Aspergillus flavus</i> (CSF culture)	NA	AMFB (few days)	Death after few days
Darras-Joly et al., 1996 ²³	68/M	Neurosurgery/ Metastatic cancer	Allucinations, disorientation, hemianopsia/ 5 months after surgery	Meningitis; extradural empyema; abscesses	L/Surgery extradural abscess	NR	<i>Aspergillus fumigatus</i> (extradural abscess)	Negative (NR)	AMFB (2 months) + itraconazole (2 months)	Death after 12 months
	29/M	Neurosurgery/ Acoustic neurinoma	Fever (38 °C), severe headache/ 3 days after surgery	Meningitis; abscess;	L/CSF	WBC 830/μL (PMNs 53%); glucose 48 (s 155) mg/dL; protein 830 mg/L	<i>Aspergillus fumigatus</i> (CSF culture)	Positive (NR)	L-AMB (5 weeks)+ itraconazole (6 months)	Alive after 12 months
Monlun et al., 1997 ²⁴	75/F	Steroid therapy/ Asthma	Fever (38 °C); acute respiratory failure (22 days)	Meningitis	Pm/Autopsy (right haemorrhagic infarct with subcortical vessel invasion and meningeal diffusion by <i>Aspergillus</i> ; pulmonary involvement)	ND	<i>Aspergillus</i> spp. (autopsy histology)	ND	AMFB (3 weeks)	Death 22 days later
Verweij et al., 1999 ²⁵	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	<i>Aspergillus fumigatus</i> (CSF culture, 6th attempt + PCR)	10.4 (Platelia)	Itraconazole 1 week; AMFB (4weeks + AMFB intraventricular; voriconazole (9 weeks)	Alive 12 months after voriconazole discontinuation
Mariushi et al., 1999 ²⁶	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	<i>Aspergillus</i> spp. (CSF culture, 5th attempt)	ND	Fluconazole (2 years)	Alive after 2 years

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Table 1 (continued)

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 ²⁷	58/M	None/Maxillary sinusitis	Confusion, progressive unresponsiveness, 4th nerve palsy 8 days after pneumonia	Meningitis	L/Sinus aspirate/ Autopsy (<i>Aspergillus</i> ventriculitis, meningitis; focal encephalitis; pneumonia)	WBC 3500/ μ L (PMNs 91%); glucose 77 mg/dL(s 102); protein 3370 mg/L	<i>Aspergillus fumigatus</i> (sinus culture)	ND	AMFB (3 weeks)	Death 20 days later	
Nenoff et al., 2001 ²⁸	74/M	Ethmoidectomy and orbitotomy (for <i>A. fumigatus</i> orbital and sinus infection)/Diabetes mellitus	Vomiting, nausea, exophthalmus, somnolent and disoriented/ 7 months	Meningitis	L/Biopsy (orbital apex)/ Autopsy (<i>Aspergillus</i> meningitis, vasculitis internal carotid, mycotic aneurism with subarachnoid hemorrhage)	NR	<i>Aspergillus fumigatus</i> (biopsy)	1:2 (Pastorex)	AMFB+ 5-FLU (few days)	Death 3 weeks after surgical procedure	
Moling et al., 2002 ²⁹	24/M	Kidney transplant (reject); Hemodialysis + steroid therapy/ complement 4 deficiency	Fever (39 °C); confusion; disorientation; right motor hemi-syndrome (2 weeks)	Meningitis	L/CSF	WBC 3200/ μ L; glucose 4 mg/dL	<i>Aspergillus fumigatus</i> (CSF culture, 4th attempt + PCR)	ND	Fluconazole (2 weeks): L-AMB (3 weeks); itraconazole (4 months)	NR	Alive after 7 months; Death after 6 years ^b
Kleinschmidt-De Masters, 2002 ³⁰	40/F	Steroid therapy/ Wegener's granulomatosis	NR	Meningitis	Pm/ Autopsy (<i>Aspergillus</i> acute and chronic basilar granulomatous meningitis; mycotic aneurism; lung, skin, heart involvement)	NR	<i>Aspergillus</i> spp. (autopsy histology)	ND	NR	NR	Death after 68 days
	51/M	Chemotherapy/ Lymphoma	NR	Meningitis	Pm/ Autopsy (<i>Aspergillus</i> basilar meningitis; thrombotic occlusion of arteries)	NR	<i>Aspergillus</i> spp. (autopsy histology)	ND	NR	NR	Death after 4 days
Pandian et al., 2004 ³¹	34/F	Spinal anaesthesia/ None	Fever, headache, vomiting ^c	Meningitis	Pm/ Autopsy (<i>Aspergillus</i> meningitis; mycotic aneurism with subarachnoid hemorrhage)	WBC 640/ μ L (PMNs 76%); glucose 32 mg/dL; protein 3600 mg/L	<i>Aspergillus</i> spp. (autopsy histology)	ND	None	None	Death

	21/F	Spinal anaesthesia/ None	Fever, headache, vomiting ^c	Meningitis	Pm/Autopsy (<i>Aspergillus</i> meningitis; mycotic aneurism with subarachnoid hemorrhage)	WBC 678/ μ L (PMNs 65%); glucose 23 mg/dL; protein 3600 mg/L	<i>Aspergillus</i> spp. (autopsy histology)	ND	None	Death
	42/F	Spinal anaesthesia/ None	Fever, headache, vomiting ^c	Meningitis	Pm/Autopsy (<i>Aspergillus</i> meningitis; mycotic aneurism with subarachnoid hemorrhage)	WBC 240/ μ L (PMNs 68%); glucose 23 mg/dL; protein 2400 mg/L	<i>Aspergillus</i> spp. (autopsy histology)	ND	None	Death
	32/F	Spinal anaesthesia/ None	Fever, headache, vomiting ^c	Meningitis	Pm/Autopsy (<i>Aspergillus</i> meningitis; mycotic aneurism with subarachnoid hemorrhage)	WBC 345/ μ L (PMNs 76%); glucose 23 mg/dL; protein 1230 mg/L	<i>Aspergillus</i> spp. (autopsy histology)	ND	None	Unknown
	24/F	Spinal anaesthesia/ None	Fever, headache, vomiting ^c	Meningitis	Pm/Autopsy (<i>Aspergillus</i> meningitis; mycotic aneurism with subarachnoid hemorrhage)	WBC 435/ μ L (PMNs 96%); glucose 32 mg/dL; protein 4200 mg/L	<i>Aspergillus</i> spp. (autopsy histology)	ND	None	Death after 18 months
Larson Kolbe et al., 2007 ³²	51/F	Epidural steroid injections/COPD	Mental status changes; 3rd nerve palsy/2 months	Meningitis	L/Disc aspiration	NR	<i>Aspergillus</i> <i>fumigatus</i> (disc aspiration + vpoas abscess culture)	ND	Caspofungin + oriconazole (4 months)	Death after 5 months
Gunaratne et al., 2007 ^{33,78}	26/F	Spinal anesthesia (Pregnancy)/None	Low grade fever; headache; nausea; vomiting 12 days after sa	Meningitis	Pm/Autopsy	WBC 302/ μ L (PMNs 99%); glucose 56 mg/dl (s 115 mg/dL) ^d ; protein 680 mg/L	<i>Aspergillus</i> <i>fumigatus</i> (autopsy culture)	ND	Fluconazole	Death after 4 weeks
	21/F ^e	Spinal anesthesia (Pregnancy)/None	Fever, chills, neck stiffness 10 days after sa	Meningitis	Pm/Autopsy	WBC 575/ μ L (PMNs 70%); glucose 25 mg/dl (s 90 mg/dL) ^d ; protein 490 mg/L	<i>Aspergillus</i> <i>fumigatus</i> (autopsy culture)	ND	AMFB (4 days)	Death after 4 weeks
	27/F	Spinal anesthesia (Pregnancy)/None	Fever, headache, neck stiffness; diplopia, photophobia 15 days after sa	Meningitis	L/CSF (microscopy)	WBC 720/ μ L (PMNs 3%); glucose 21 mg/dl (s 133 mg/dL) ^d ; protein 680 mg/L	<i>Aspergillus</i> spp. (CSF)	ND	AMFB iv + it (4 weeks) voriconazole (4 weeks)	Alive after 12 months (residual 6th cranial nerve palsy and impaired hearing)

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Table 1 (continued)

Author, year [Reference]	Age/ sex	Risk factor/ Underlying disease	Sign and symptoms (time duration)/ Time from TX	Syndrome	Diagnosis/ methods	CSF characteristics	<i>Aspergillus</i> species	CSF Ag GMN (method)	Antifungal treatment (time duration)	Outcome
	29/F	Spinal anesthesia (Pregnancy)/None	Fever, headache, vomiting, neck stiffness, photophobia 11 days after sa	Meningitis	L/CSF	WBC 1430/ μ L (PMNs 40%); glucose 45 mg/ dl; protein 330 mg/L	<i>Aspergillus</i> <i>fumigatus</i> (CSF culture)	ND	AMFB 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/ μ L (PMNs 0%); glucose 61 mg/dL (s 109 mg/dL) ^e ; protein 280 mg/L	<i>Aspergillus</i> <i>fumigatus</i> (autopsy culture)	ND	AMB (9 days)	Death after 24 days
Saitoh et al., 2007 ³⁴	33/M	Chemotherapy/AML	Fever, headache, neck stiffness/ 14 days post- chemotherapy	Meningitis	L/CSF	WBC 15/ μ L; glucose 30 mg/ dL; protein 760 mg/L	<i>Aspergillus</i> spp. (PCR + Ag on CSF)	2.2 (s 0.1) (Platelia)	AMFB (1 week); voriconazole (12 months)	Alive after 1 year
Sundaram et al., 2007 ³⁵	22/M	Spinal anesthesia (1 month prior)/ None	Fever, headache, vomiting (2 months), neck stiffness	Meningitis	Pm/Autopsy (<i>Aspergillus</i> purulent meningitis & mycotic aneurism with subarachnoid hemorrhages)	WBC 720/ μ L (PMNs 90%); glucose 37 mg/dL; protein 850 mg/L	<i>Aspergillus</i> <i>fumigatus</i> (CSF culture, 5th attempt) ^f	ND	ND	Death after 68 days
Van de Beek et al., 2008 ³⁶	56/M	Kidney-pancreas transplant/End stage disease; sphenoid sinusitis	Headache, fever (6 weeks); neck stiffness, dysarthria, hemiparesis	Meningitis	L/sphenoid biopsy/Autopsy (<i>Aspergillus</i> meningitis; midline herniation, subarachnoid hemorrhage)	WBC 1200/ μ L (PMNs 94%); glucose 64 mg/dL; protein 7300 mg/L	<i>Aspergillus</i> <i>fumigatus</i> (sphenoid biopsy + autopsy)	6.47 (s 0.39) (Platelia)	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/ μ L (PMN 70%); glucose 1 mg/dL (s 76 mg/dL); protein 7900 mg/L	<i>Aspergillus flavus</i> (CSF culture)	7.4 (s 2.5) (Platelia)	Voriconazole 5 months (+1 month caspofungin); L-AMB 3 months	Alive after 9 months
Chronic meningitis/ pachimeningitis										
Palo et al., 1975 ³⁷	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/ μ L (PMNs 8%); glucose 45 mg/dL; protein 1400 mg/L	<i>Aspergillus</i> <i>fumigatus</i> (CSF culture, 6th attempt) ^f	NA	None	Death 1 month later

Gordon et al., 1976 ^{3,79}	34/F	IVDA (heroin, cocaine)/None	Bifrontal headache, neck stiffness (weeks), low-grade fever	Chronic meningitis	L/CSF	WBC 2892/ μ L (PMNs 80%); glucose 16 (s 110) mg/dL; protein 990 mg/L;	<i>Aspergillus oryzae</i> (CSF culture, 7th attempt)	NA	AMFB+ 5-FLU (12 months)	Alive (6 year later; episode of bilateral necrotizing scleritis due to <i>A. oryzae</i>) ⁸
Mielke et al., 1981 ³⁸	58/F	Neurosurgery/Acromegaly	Severe headache (4 months), retro-orbital pain, blindness, ophthalmoplegia/10 months	Chronic meningitis	Pm/Autopsy (chronic basilar meningitis by <i>A. fumigatus</i> & <i>C. albicans</i> ; mycotic aneurism of the basilar artery with subarachnoid hemorrhage)	ND	<i>Aspergillus fumigatus</i> (autopsy culture)	NA	None	Death after 7 days
Weinstein et al., 1982 ³⁹	67/M	None/none	Retro-orbital and periorbital pain, vertigo (months); decrease eye vision; weakness; malaise	Chronic meningitis	L/biopsy sphenoid wing	WBC 88/ μ L (PMNs 6%); glucose 53 (s 97) mg/dL; protein 1130 mg/L	<i>Aspergillus fumigatus</i> (biopsy + culture sphenoid)	NA	AMFB + rifampicin (2 weeks)	Death after 18 days from surgery
Salaki et al., 1984 ⁴⁰	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/ μ L (92%); glucose 33 mg/dL; protein 1100 mg/L	<i>Aspergillus fumigatus</i> (CSF culture, 4th attempt)	NA	AMFB + 5-FLU (NR)	Alive
Woods et al., 1990 ⁴¹	44/M	None/AIDS	Headache, fever, nausea, vomiting, lethargy, slurred speech, severe back pain (4 months)	Chronic meningitis	Pm/Autopsy (<i>Aspergillus</i> acute and chronic basilar meningitis; spinal arachnoiditis; pleural, brain, lumbar spinal cord involvement)	WBC 80/ μ L (PMNs 80%); glucose 19 mg/dL; protein 2000 mg/L	<i>Aspergillus fumigatus</i> (autopsy culture)	NA	None	Death after 18 days
Murai et al., 1992 ⁴²	59/F	None/Diabetes; Liver cirrhosis; Mondini's anomaly; otitis media	Headache; hearing loss; multiple nerve palsy (6th, 8th, 9th, 10th, 11th)	Chronic pachymeningitis	L/surgery maxillary sinus	WBC 7/ μ L; protein 660 mg/L	<i>Aspergillus flavus</i> (surgery culture)	NA	Miconazole (2 months); 5-FLU, fluconazole (1 month)	Alive after 4 months
Kurino et al., 1993 ⁴³	63/M	None/Diabetes; otitis media	Fever, headache, hyperesthesia of face, abducens palsy, deafness	Chronic meningitis	Pm/Biopsy granuloma + autopsy	WBC 138/ μ L (PMNs 50%); glucose 87 mg/dL; protein 1007 mg/L	<i>Aspergillus</i> spp. (biopsy + autopsy)	NA	None	Death 30 days post-surgery

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Table 1 (continued)

Author, year [Reference]	Age/ sex	Risk factor/ Underlying disease	Sign and symptoms (time duration)/		Diagnosis/ methods	CSF characteristics	Aspergillus species	CSF Ag GMN (method)	Antifungal treatment (time duration)	Outcome
			Time from TX	Syndrome						
Mochizuki et al., 2000 ⁴⁴	75/M	None/Otitis media	Multiple cranial nerve palsy (2nd, 3rd, 4th), impaired vision (4 months)	Chronic pachymeningitis	L/Biopsy	NR	<i>Aspergillus flavus</i> (biopsy culture)	ND	Fluconazole (4 weeks); AMFB (4 months)+5-FLU (4 months); itraconazole (5 months)	Alive after 36 months
Moling et al., 2002 ²⁹	48/M	Alcohol abuse/ None	Headache, fever, gait instability, apathy (5 months)	Chronic meningitis + ventriculitis + arachnoiditis	L/CSF	WBC 1880/ μ L; glucose 20 mg/ dL	<i>Aspergillus candidus</i> group (CSF culture)	6.7 (s 1.7) (Platelia)	AMFB (1 week); rifampicin (several months); voriconazole (10 days); itraconazole (10 months)	Alive after 24 months
Kowacs et al., 2004 ⁴⁵	26/M	Near drowning/ None	Fever (37.2 °C), mild meningismus (4 weeks)	Chronic meningitis	L/CSF	WBC 165/ μ L (PMNs 69%); glucose 64 mg/ dL; protein 778 mg/L	<i>Aspergillus fumigatus</i> (CSF culture, 3rd attempt)	ND	Fluconazole (12 days); itraconazole + AMFB (44 days)	Death after 56 days
Ismail et al., 2007 ⁴⁶	73/M	None/Diabetes mellitus; pulmonary asbestosis	Headache, left-sided visual loss, scalp tenderness, fatigue (3 weeks)	Hypertrophic pachymeningitis	L/Meningeal biopsy	WBC 0/ μ L; protein 5670 mg/L	<i>Aspergillus flavus</i> (biopsy culture)	ND	Antifungal treatment (NR)	Death 3 months later
Kagawa et al., 2008 ⁴⁷	33/F	Spinal cord mass lesion	Headache, low grade fever (5 months), hydrocephalus	Chronic meningitis	L/Biopsy VA shunt	WBC 1340/ μ L; glucose 8 mg/ dL; protein 1580 mg/L	<i>Aspergillus</i> spp. (VA shunt biopsy)	ND	AMFB (NR); fluconazole (NR)	Alive after 15 years (multiple recurrences)
Chan et al., 2011 ⁴⁸	59/M	Diabetes; impaired renal function	Headache, diplopia, hoarseness (2 months)	Pachymeningitis	L/Dural biopsy	Glucose 102 mg/dL; protein 1270 mg/L	<i>Aspergillus flavus</i> (culture from dural biopsy)	Positive (β -D- glucan + Platelia)	Voriconazole (2 weeks); casprofungin (4 weeks); voriconazole	Alive after 7 months
Kato et al., 2011 ⁴⁹	42/M	None/None	Headache, right nuchal pain, cranial nerve palsies ^{9,10,11,12} (2 months)	Hypertrophic pachymeningitis	L/CSF	WBC 43/ μ L (PMNs 4%); glucose 56 mg/ dL; protein 1000 mg/L	<i>Aspergillus</i> spp. (CSF PCR positive)	β -D-glucan (Fungitell) 164 pg/mL; serum < 5 pg/mL	Voriconazole (8 week); L-AMB + 5-FLU (2 week); fluconazole 8 weeks	Alive after 30 months
Meningoencephalitis										
Goldhammer et al., 1974 ⁵⁰	45/M	None/none	Headache (9 months), blurred vision (3 weeks)	Meningoencephalitis	Pm/Autopsy (disseminated meningoence- phalitis with pituitary abscess and left optic nerve involvement)	ND	<i>Aspergillus</i> spp. (microscopy smear of pituitary abscess + autopsy)	NA	None	Death 4 days postoperatively

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

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Table 1 (continued)

Author, year [Reference]	Age/ sex	Risk factor/ Underlying disease	Sign and symptoms (time duration)/ Time from TX		Diagnosis/ methods	CSF characteristics	Aspergillus species	CSF Ag GMN (method)	Antifungal treatment (time duration)	Outcome
				Syndrome						
Cox et al., 1990 ⁵⁷	31/M	None/AIDS	Headache, fever (38.2 °C), confusion, vomiting	Meningoencephalitis	PM/Autopsy (<i>Aspergillus</i> meningitis; mycotic aneurysms; endocarditis; myocarditis)	ND	<i>Aspergillus</i> spp. (autopsy histology)	NA	None	Death after few days
Breneman et al., 1992 ⁵	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	<i>Aspergillus</i> <i>fumigatus</i> (Brain biopsy culture)	NA	AMFB (few days)	Death after few days
Van der Knaap et al., 1993 ⁵⁸	3/M	None/Galactosemia	Fever (40 °C), nuchal rigidity, convulsions, left hemiparesis	Meningoencephalitis	L/CSF positive antigen	Normal	<i>Aspergillus</i> spp.	Positive (NR)	AMFB + 5-FLU (NR)	Improvement
Mikolich et al., 1996 ⁶	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	<i>Aspergillus</i> <i>fumigatus</i> (brain biopsy)	NA	Itraconazole (24 months)	Alive after 4 years
Darras-Joly et al., 1996 ²³	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	<i>Aspergillus</i> <i>fumigatus</i> (surgical culture)	Negative (NR)	AMFB (72 days) + itraconazole (30 days)	Death after 96 days
Schwartz et al., 1997 ⁵⁹	18/M	Chemotherapy/ ALL	Meningism, fever/(92 days post- chemotherapy)	Meningoencephalitis	L/Brain biopsy	WBC 1056/μL (PMNs 96%)	<i>Aspergillus</i> spp. (Brain biopsy)	ND	Itraconazole (4 weeks); voriconazole (6 months)	Death after 6 months
Koh et al., 1998 ⁶⁰	15/F	Chemotherapy/ALL	Flaccid weakness lower extremities, slurred speech, urinary retention	Meningiomeloencephalitis	Pm/Autopsy (Multifocal leptomeningeal exudates; fungal abscess/necrosis in spinal cord)	ND	<i>Aspergillus</i> spp. (autopsy histology)	ND	ND	Death 21 days later
Payot et al., 1999 ⁶¹	29/M	None/AIDS	Headache (3 weeks), nausea (1 week), fever (39 °C), nuchal rigidity	Meningoencephalitis	Pm/Autopsy (<i>Aspergillus</i> purulent basal meningitis + bulbar encephalitis)	WBC 19/μL (PMN 50%); protein 1080 mg/L	<i>Aspergillus</i> spp. (autopsy histology)	ND	None	Death after 7 days
Fasciano et al., 1999 ⁶²	26/M	Steroid treatment/ Chronic asthma	Fever, quadriplegia, areflexia; hydrocephalus (2 weeks)	Meningoencephalitis	L/Brain biopsy/ Autopsy: (Aspergillosis of brain, meninges, cauda equina, lungs, thyroid; bilateral uncal herniation)	WBC 1300/μL (PMNs 98%); glucose 40 mg/ dL; protein 1100 mg/L	<i>Aspergillus</i> <i>fumigatus</i> (brain biopsy)	ND	AMFB iv and intrathecal + 5-FLU (2 weeks)	Death after 6 weeks
Chandra et al., 2000 ⁶³	40/F	None/Ethmoid and sphenoid sinusitis	Headache, fever, vomiting (1 week); left proptosis	Meningoencephalitis	L/Brain biopsy	NR	<i>Aspergillus</i> <i>fumigatus</i> (biopsy)	ND	NR	NR

Viscoli et al., 2002 ⁶⁴	NR	BMT/Acute lymphoblastic leukemia	Fever, neurological deficit, seizures/5 days post-BMT	Meningoencephalitis	Pm/Autopsy (diffuse meningeal and parenchymal infiltration)	NR	<i>Aspergillus</i> spp. (meningeal and parenchymal)	578 (s 25.7) (Platelia)	NR	Death
Wang et al., 2003 ⁶⁵	39/M	Steroid treatment/SARS	Tentorial herniation	Meningoencephalitis	Pm/Autopsy: (<i>Aspergillus</i> meningitis; multiple brain abscess containing aspergillus; disseminated aspergillosis heart, kidney, spleen, pancreas, adrenal glands)	ND	<i>Aspergillus</i> spp. (autopsy histology and culture)	ND	None	Death
Roberts et al., 2004 ⁶⁶	71/F	None/Sinusitis	Fever (38.3 °C), severe headache, diplopia, confusion (5 weeks)	Meningoencephalitis	Pm/Autopsy (<i>Aspergillus</i> granulomatous meningitis; thrombosis of basilar artery)	WBC 286/μL (PMNs 38%); glucose 23 mg/dL (s 99); protein 850 mg/L	<i>Aspergillus</i> spp. (autopsy histology)	ND	None	Death after 10 days
Botturi et al., 2006 ⁶⁷	59/F	Steroid treatment/Sphenoid sinusitis/	Headache, diplopia; bilateral 6th nerve palsy (5 weeks)	Meningoencephalitis	L/Brain biopsy	WBC 920/μL (PMNs 96%); glucose 0 mg/dL; protein 180 mg/L	<i>Aspergillus</i> spp. (biopsy)	ND	AMFB (8 weeks); voriconazole (6 months)	Alive after 23 months
Gabelmann et al., 2007 ⁶⁸	43/F	Chemotherapy/AML; sinusitis	NR	Meningoencephalitis	Pm/Autopsy	NR	<i>Aspergillus</i> spp. (autopsy histology)	ND	NR	Death after 41 days
Van de Beek et al., 2008 ³⁶	62/F	Kidney-pancreas transplant/End stage disease	Headache (6 months), altered consciousness	Meningoencephalitis	L/Autopsy (cerebral aspergillosis)	WBC 286/μL (PMNs 90%); glucose 27 mg/dL; protein 830 mg/L	<i>Aspergillus</i> spp. (autopsy histology)	2.72 (s 0.06) (Platelia)	ABLC	Death after 12 days
Spinal arachnoiditis										
Bryan et al., 1980 ⁶⁹	26/M	IVDA (heroin)/None	Headache, nausea, vomiting (weeks), low back pain; hydrocephalus	Spinal arachnoiditis	L/Lumbar biopsy (lesion L3-5)	WBC 1857/μL (PMNs 43%); glucose 6 mg/dL; protein 5170 mg/L	<i>Aspergillus flavus</i> (immunofluorescence on biopsy) (CSF)	NA	AMFB + rifampicin (10 weeks)	Alive after 14 months
Stein et al., 1982 ⁷⁰	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	WBC 62/μL (PMNs 30%); glucose 70 (105) mg/dL; protein 350 mg/L	<i>Aspergillus terreus</i> (2 CSF cultures) ^f	NA	AMFB (NR)	Death 26 days after laminectomy
Van de Wyngaert et al., 1986 ⁷¹	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	<i>Aspergillus fumigatus</i> (CSF) precipitin	NA	AMFB (3 months) + rifampin (10 days)+ 5-FLU (3 months)	Alive after 229 days

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Table 1 (continued)

Author, year [Reference]	Age/ sex	Risk factor/ Underlying disease	Sign and symptoms (time duration)/ Time from TX		Diagnosis/ methods	CSF characteristics	Aspergillus species	CSF Ag GMN (method)	Antifungal treatment (time duration)	Outcome
				Syndrome						
Endo et al., 2001 ⁷²	55/M	Neurosurgery/ Pituitary adenoma	Diplopia, retro-orbital pain (1 year), loss of vision/9 years	Arachnoiditis; subdural abscess	L/Abscess aspiration	NR	<i>Aspergillus fumigatus</i> (abscess culture)	ND	AMFB + fluconazole (4 weeks)	Death after 1 month
Genzen et al., 2009 ⁷³	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	<i>Aspergillus terreus</i> (biopsy culture)	ND (s 0.47)	Voriconazole (78 days); voriconazole + caspofungin (54 days); AMFB (6 days); ABLC (50 days)	Alive after 9 months
Ventriculitis										
Morrow et al., 1983 ⁴	36/M	IVDA (heroin)/None	Fever, generalized seizures, nuchal rigidity (1 day)	Ventriculitis	Pm/Autopsy (ventriculitis & hydrocephalus)	WBC 549/μL (PMNs 27%); glucose 29 (s 90) mg/dl; protein 1200 mg/L	<i>Aspergillus flavus</i> (serology) ^h	NA	None	Death after 40 days
Hummel et al., 2006 ⁷⁴	4/F	Chemotherapy/ALL	NR	Ventriculitis & multiple abscess	L/CSF (Ommaya reservoir)	NR	<i>Aspergillus fumigatus</i> (PCR CSF)	Positive (Platelia)	Voriconazole + caspofungin (5 weeks); intraventricular AMFB (4 weeks); voriconazole (2 months)	Alive after 3 months
Sutton et al., 2009 ⁷⁵	18/M	Lung transplant/ End stage pulmonary disease	Headache, seizure, low grade fever, altered mental status	Ventriculitis	Pm/Autopsy (necrotizing granulomatous inflammation of meninges)	WBC 1100/μL (PMN 79%); glucose 41 mg/ dL (s 122); protein 1090 mg/L	<i>Aspergillus granulosus</i> (autopsy culture)	ND	Voriconazole then ABLC and posaconazole	Death after 87 days
Antachopoulos et al., 2011 ⁷⁶	5/F	VP shunt	Fever (40 °C), tonic/ clonic seizures	Ventriculitis	L/VP	WBC 400/μL (Neutrophil predomi- nance); glucose 25 mg/ dL (s 110 mg/ dL); protein 1000 mg/L	<i>Aspergillus fumigatus</i> (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; 5FLU = 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*.

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) ^a	19 (46.3)	46 (49.5)
Meningoencephalitis	10 (19.2)	13 (31.7)	23 (24.7)
Chronic meningitis/pachimeningitis	8 (15.4) ^b	7 (17.1)	15 (16.1)
Spinal arachnoiditis	5 (9.6) ^c	–(0.0)	5 (5.4)
Ventriculitis	2 (3.8)	2 (4.9) ^d	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/ μ L (range)	640 (5–8800)	988 (0–4100)	678 (0–8800)
Neutrophils predominance (\geq 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 \leq 25 mg/dL	16/39 (41.1)	4/17 (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)

^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.

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/ μ L 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 6 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 uncus 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,^{3,8–22,24–49} while meningoencephalitis was diagnosed in about 25% of patients.^{5,6,36,50–68}

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}

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.^{5,10,18–20,25,33–36,40,57,61,66,70} Cranial nerve palsies were reported in 17.6% (15/85) and seizures (11/86) in 12.8% of patients.

The diagnosis of *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%)^{3,6,10,12,13,15,22,23,25–27,29,32,33,39,44,45,47,52,54,56,58,63,69–73,76,78,79} PR as opposed to immunocompromised individuals (39%).^{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 *Aspergillus meningitis* is hampered by the lack of sensitivity as shown by the 31% of positive results observed in our review of published cases.^{3,9,13,22,23,25,26,29,33,35,37,40,45,52–54,56,70} 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 *in vitro* isolation. However, such large volumes are not easy to obtain in clinical practice.⁸⁰ On the other hand, serial lumbar puncture does indeed seem to have a role since in 9 cases, the fungus could be successfully isolated from cerebrospinal fluid only after several attempts.^{3,25,26,29,35,37,40,45}

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%.^{23,25,28,29,34,36,48,49,64,75,76} 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 background reactivity of CSF.^{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.^{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.^{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.^{25,29} PR Finally, it seems that the Platelia GM test works well irrespective of the species of *Aspergillus* involved as shown by the cases described by Verveij, Moling and ourselves in whom *A. fumigatus*, *A. candidus* and *A. flavus* were respectively cultured from the CSF.^{25,29} PR

Our review shows that *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 2001.⁸⁴

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 *Aspergillus meningitis*.⁸⁵ In our present review, that encompasses a long period of time before the introduction of voriconazole (*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.^{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.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.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%.^{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.⁸⁸ An association between poor outcome and voriconazole concentrations has been initially observed by Pascual and coworkers.⁸⁹ In addition Miyakis et al. recently showed an 11-fold increased risk of death among patients with invasive mycoses treated with voriconazole who had an initial trough concentration of less than 0.35 mg/L.⁹⁰ By contrast, several studies and expert opinion suggest that the optimal maximum voriconazole concentrations should not exceed 5.5–5.8 mg/L.^{89,91,92}

Another crucial issue not yet addressed so far is the optimal length of antifungal therapy in patients with *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 *Aspergillus meningitis* who were treated with voriconazole shows very different lengths of treatment, ranging from 8–14 weeks to 5–12 months.^{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 *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.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.⁹⁴ Except one apparently successful case, flucytosine has been used only in association with AMFB and its role in the treatment of aspergillosis remains anecdotal.^{9,95}

In conclusion, our review shows that *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 (*i.e.*, 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.

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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.

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