Cerebral aspergillosis carries a mortality rate close to 100%, especially in immunocompromised patients. We describe 3 patients who contracted cerebral aspergillosis after neurosurgery, 2 of whom survived after exhaustive surgical treatment and medical treatment with high doses of amphotericin B (once liposomal), 5-fluorocytosine and itraconazole. We review the few non-fatal cases of cerebral aspergillosis reported. We consider that surgical excision must be complete and repeated if necessary, always in combination with medical treatment.

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INTRODUCTION

Aspergillosis remains one of the most difficult infections to treat, especially in immunocompromised patients. Mortality rates range from 75% to 100%, despite therapy with amphotericin B in many cases (1, 2). Cerebral aspergillosis carries a mortality rate close to 100%, and diagnosis is often made post-mortem (1–4). Nosocomial transmission has been documented (5).

Very few non-fatal cases of cerebral aspergillosis have been reported. We describe 3 patients who contracted cerebral aspergillosis after neurosurgery, 2 of whom survived.

CASE REPORT

Patient 1

A 17-year-old girl was transferred to our intensive care unit because of stiffness of the neck and fever. 15 months previously she had undergone surgical treatment for an ependymoma of the left parietofrontorolandic region and had received prednisone 20 mg/day for a month. 14 months later she underwent complete excision of a recurrence. The ventricle was opened and cerebrospinal fluid (CSF) was ejected. The wound was closed and a drain inserted. The postoperative course was complicated by CSF leakage around the dura mater. Histological examination showed the mass to be a dermoid (3).

On arrival in our unit the girl was febrile (40°C) but alert. She had a right pyramidal syndrome and hemiparesis as sequelae of the tumour. The scar was clean. Laboratory results were as follows: WBC 8,900/μl, Hb 87 g/l, platelets 289,000/μl, CSF 1,900 cells/μl (97% neutrophils), RBC 1/μl, protein content 1.1 g/l, and sugar content 2 mmol/l. Direct examination and bacterial culture of CSF were negative. Two scalp punctures were also negative.

We began empirical antistaphylococcal chemotherapy. The scar became inflamed and an intracerebral abscess developed on the side of the craniotomy. She was reoperated 3 weeks after initial surgery. Bone was removed and revealed abundant, turbid liquid. The area was highly inflamed. Direct examination of surgical specimens and CSF was negative, but Aspergillus fumigatus grew on culture. Histological examination showed an inflammatory granuloma. Aspergillus antigen was never detected in CSF. Treatment was started with amphotericin B 1 mg/kg daily and 5-fluorocytosine (5-FC) 7.5 g daily. 5-FC was stopped 5 days later because of thrombocytopenia. After an initial clinical and CSF improvement her local and meningeal status deteriorated. A brain scan showed right ventriculitis and an abscess at the site of previous surgery. An Ommaya cistern was inserted, without extensive surgery cleaning. The amphotericin dose was raised to 1.5 mg/kg, itraconazole 600 mg/day was added (serum level 388 mg/l, CSF level 0), and injections of amphotericin B (0.5 mg every 48 h) were made into the cistern. After a brief improvement her clinical and neurological status again worsened. She developed a neurological deficit, coma and severe sepsis. Over the subsequent 6 weeks she underwent 6 operations for drainage of a cyst, insertion of a new cistern, and external ventricular derivation because of intracranial hypertension and hydrocephalus. She received a total amphotericin B dose of 2 g over 72 days, and itraconazole for 30 days. She died from intraventricular haemorrhage in the intensive care unit 96 days after onset of the illness.

Patient 2

A 68-year-old man with bladder cancer (PT1 stage) underwent endoscopic tumour excision and radiotherapy (50 Gy to the bladder). 17 months later he developed left hemiparesis with altered mentation and signs of intracranial hypertension. The computerized tomography (CT) scan revealed a right occipital lesion, with spontaneous hyperdensity and contrast enhancement, oedema and a mass effect. He underwent total surgical removal with opening of the dura mater. Histological examination showed the mass to be a metastasis of the bladder cancer. He received 21 Gy to the brain, and prednisone 40 mg/day was started.

Five months later, a CT scan performed because of hallucinations and disorientation showed an extradural empyema and 3 right parieto-occipital abscesses. Over the previous 48 h a purulent fluid had discharges from the scar, without fever. Neurological examination showed a left homonymous lateral hemianopsia. The empyema, abscesses and bone flap were removed. The surgical findings were pus behind the scalp, a dura mater covered with bleeding granulations and a raised CSF pressure behind the dura mater. Aspergillus fumigatus was found by direct examination and culture in the extradural and intracerebral pus. In vitro antimicrobial susceptibility was as follows: 5-FC, resistant; amphotericin B and nystatine, sensitive; miconazole and ketoconazole, intermed-
ately resistant (6). Amphotericin B in lipid emulsion (Intralipide 20%, 1.5 mg/kg daily) and 5-FC (7.5 g/day) were started and the patient was transferred to our unit.

On admission he was a pyrexia and had a left hemianopia. The CT scan showed a cicatrical lesion. The CSF was normal except for an elevated protein content (0.65 g/l). Tests for Aspergillus antigen remained negative. The WBC count was 4,400/μl, with 750 lymphocytes/μl (CD4+ 36%). The fundi/oculi remained normal. The WBC count was 11,340/μl. Antibiotics were started for suspected meningitis. The other had an ependymoma and had received steroids. The other had a decrease in the papillary oedema and normalization of the CSF (70 cells/μl, 1.7 g protein, normal glycocra). He had been discharged a month after the operation, with mild fever and 100 cells/μl in the CSF.

He was readmitted urgently 2 weeks later to our intensive care unit with fever, confusion and a stiff neck. His temperature was 38.8°C. There were no focal deficits, but he was disoriented and aggressive. The scar was clean. The WBC count was 8,000/μl, and CSF was sterile and contained 700 cells/μl (57% polymorphonuclear cells), 1.5 g/l protein and 33% sugar. Antistaphylococcal chemotherapy had no effect. Because of persistent fever, worsening headache and pain in the right ear he underwent surgery and replacement with new fat. There was a small abscess behind the scar. The removed fat grew Aspergillus fumigatus, while the aponevrosis and glue. A colony of Aspergillus fumigatus grew on cultures of CSF leaking from the scar and was considered spurious. He was discharged a month after the operation, with mild fever and 100 cells/μl in the CSF.

Patient 3

A 29-year-old man with no particular history underwent the removal of a right acoustic neurinoma by the translabyrinthine route, with mastoidectomy and filling of the cavity with fat and fascia lata. Three days later he developed fever (38°C), with severe headache a week later. The CSF contained 830 cells/μl (53% polymorphonuclear cells), 0.83 g/l protein and 2.7 mmol/l glucose (glycemia 8.6 mmol/l); bacteriological tests were negative. The WBC count was 11,340/μl. Antibiotics were started for suspected postoperative staphylococcal meningitis. CSF leakage required external lumbar derivation and further surgery to fill the hole with fat. A colony of Aspergillus fumigatus grew on cultures of CSF leaking from the scar and was considered spurious. He was discharged a month after the operation, with mild fever and 100 cells/μl in the CSF.

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To, intravenous drug users (10). Another mode of invasion is extension from an adjacent area, e.g. the sinuses (11, 12). In our knowledge, 13 cases of cerebral aspergillosis have been reported after neurosurgical procedures (4, 13–23), with only 3 survivors (2 immunocompetent patients and 1 with diabetes mellitus (15, 17, 23).

Two of our patients were immunocompromised. One had an ependymoma and had received steroids. The other had bladder cancer with cerebral metastases, and had undergone local irradiation and steroid therapy. Two cases involved CSF leakage immediately after the first operation and meningismus occurred shortly afterwards, as in a previous report (20). The diagnosis was always made after surgery. In cases 1 and 2 of this report, only extradural or intracerebral pus grew aspergillus fumigatus, while the fat used to fill the mastectomy cavity in case 3 grew A. fumigatus. Although all 3 patients had laboratory evidence of a meningeal reaction, Aspergillus was never cultured from CSF obtained by lumbar puncture.

Two of the patients were cured after medical and surgical treatment. Patient 2 underwent complete removal of the abscess, the empyema and the bone, plus treatment with high-dose amphotericin B (up to a cumulative dose of 5 g) and itraconazole (400 mg/day). Patient 3 also underwent aggressive neurosurgery, with complete removal of infected tissue. AmBisome treatment permitted us to give high amphotericin B doses and, although the CSF concentration was not as high as expected, the efficacy of AmBisome was probably explained in part by a high concentration in the temporal muscle.

Rindgen et al. (24) treated 28 immunocompromised patients with proven invasive aspergillosis with AmBisome and 9 (32%) were cured. In 1 case the AmBisome concentration in the brain was 2.15 mg/kg at autopsy, i.e. 0.09% of the total dose (24). In rat pharmacology studies, Proffitt et al. (25) found that the use of AmBisome (5 mg/kg daily) increased the mean brain concentration of amphotericin B 3-fold in comparison with amphotericin B at 1 mg/kg daily. All 3 patients in this report received itraconazole, although the CSF concentrations were below the detection limit of the assay used. However, itraconazole is highly
lipophilic, with a fat tissue/plasma concentration ratio of 16.9 (26). It is noteworthy that itraconazole and amphotericin B have, at worst, an additive effect (26). The limiting factor in the use of itraconazole is that it cannot be administered parenterally. The value of local therapy (amphotericin B inserted into a cavity catheter) is not clear. In case of failure of parenteral amphotericin B, intrathecal amphotericin B could be a means of obtaining higher local concentrations. However, intrathecal administration may result in headache, delirium, vomiting, paraesthesias, arachnoiditis, radiculopathy, myelopathy, nerve palsies and meningitis (27).

During the months preceding the study period, building demolition work was undertaken opposite the hospital, and this is a known risk factor for aspergillosis (5). Camarata et al. (28) have reviewed 13 patients who have been successfully treated. Six of them were immunocompromised, and all but 3 underwent exhaustive surgical treatment. One underwent aspiration and drainage of the lesion. Medical treatment included amphotericin B in every case. We consider that post-neurosurgical meningitis should raise the possibility of cerebral aspergillosis. Surgical excision must be complete and repeated if necessary. Medical treatment consists of amphotericin B, with or without 5-FC and itraconazole. Intrathecal amphotericin B injections may be envisaged.

REFERENCES


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