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CASE REPORT

Fatal mycotic aneurysm caused by *Pseudallescheria boydii* after near drowning

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Abstract *Pseudallescheria boydii* is a rare cause of mycotic infection. Factors predisposing to systemic infection include traumas, immunosuppression, and near drowning. We report a case of multiple aneurysms caused by this hyalohyphomycete, occurred after near drowning. The car driven by a 53-year-old woman plunged into a canal in The Netherlands. After a 20-min-long submersion, the woman was rescued. At hospital, a severe aspiration of muddy water and a mycotic pneumonia were diagnosed. Despite the immediate prescription of a long-term antimycotic therapy and the initial good response, the patient died 4 months later. The autopsy showed a mycotic aneurysm of the abdominal aorta and multiple ruptured mycotic aneurysms of the circle of Willis with fatal subarachnoid bleeding.

Keywords *Pseudallescheria boydii* · Mycotic aneurysms · Near drowning

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Introduction

Near drowning with delayed death after successful treatment of early complications results from prolonged cardiorespiratory failure, hypoxic encephalopathy, or infections [1–4]. Early and aggressive antibiotic treatment is the therapy of choice after near drowning; mycotic infections after aspiration should be considered as well. Infection by *Pseudallescheria boydii* after submersion has been rarely reported [5]. This hyalohyphomycete is found in soil, sewage, and stagnant water [6]. The mycetoma of the lower limbs, also known as "Madura foot", is the most common infection caused by this fungus [6]. Focal infections, e.g., sinusitis, otitis externa, parotitis, osteomyelitis, endocarditis as well as systemic infections have been reported in few cases [7–9]. Near drowning can cause immunosuppression [6] thus facilitating the dissemination of focal infections. We report the clinical course of a 53-year-old woman who died because of subarachnoid bleeding from ruptured mycotic aneurysms 4 month after a near-drowning episode.

Case report

On November 6, a car driven by a 53-year-old woman plunged into a canal (The Netherlands). The canal contained freshwater, the temperature being approximately 5°C. The car was immediately submerged and the woman was rescued only 20 min later. At resuscitation, there occurred severe aspiration of mud and water, severe hypothermia (28°C), and asystolia. Resuscitation was finally successful. During the next 6 weeks, which is until 23rd of December, she was treated against severe complications: respiratory therapy until November 16. Early bronchopneumonia was successfully

treated with antibiotics. Following bronchoalveolar lavage (December 1), *Candida albicans*, *Burkholderia cepacia*, and *P. boydii* were cultured. Therapy with itraconazole was started on December 11 and continued for approximately 10 weeks (2×200 mg/day).

Computed tomography (CT) performed on December 10 revealed, among others, interstitial affection of the lungs and nephrocalcinosis. With the antimycotic therapy, the patient recovered well. During 16th to 23 rd of December, she complained about headaches and neck pains, especially after periods of rest which were attributed to LC 4–5 cervical syndrome (whiplash). The patient was discharged on the 23rd of December. The antimycotic therapy was continued at home. From the beginning of February, she suffered from nausea and gastric pains. She was therefore readmitted to a hospital on the 11th of February. She had hyponatremia (128 mmol/l) and hypocalcemia (3.3 mmol/l). The antimycotic therapy was discontinued. Abdominal sonography was inconspicuous. A symptomatic therapy was given. She was discharge on 18th of February. She was readmitted to gastroenterology on February 25 with recurrent nausea, vomiting, and vertigo. In addition to still existing hyponatremia, she developed a hyperfibrinogenemia, i.e., 908 mg/dl (reference up to 350 mg/dl). All other lab parameters were normal. Abdominal sonography showed a 1.8-cm-long aneurysm of the abdominal aorta (not seen on the CT of December and on the ultrasound of mid-February).

On brain where CT was performed on the 1st of March, there occurred enhancements surrounding the brain ventricles, a hydrocephalus, and signs of local pressure. One day later, there occurred double vision. She was then transferred to neurosurgery on March 3. Subsequent CT showed stenosis of the middle cerebral artery and accumulation of cerebral liquor. Therapies were by dexamethasone and a ventricular drainage. The liquor showed an increase of cells (500/μl) and proteins (800 μg/μl) suggesting chronic inflammation but no signs of stiff neck.

During the following days, there occurred an increase of the white blood cells and the C-reactive protein. On March 18, the woman suffered from a severe subarachnoid bleeding from a hitherto unknown aneurysm of the posterior cerebral artery. She died on March 22.

Autopsy findings

Multiple fungal aneurysms were found in the circle of Willis (Fig. 1) affecting the posterior cerebral arteries, the posterior communicating arteries, and the bifurcations of the left internal carotid artery. Rupture of an aneurysm of the left posterior communicating artery (diameter 0.8 cm) had caused a subarachnoid bleeding at the brain base, extending in a subdural bleeding surrounding the medulla oblongata and the cerebellum and a hematocephalus. An aneurysm of the abdominal aorta was localized below the origins of the renal arteries and was characterized by abscess of the aortic wall, ulceration, and parietal thrombosis. Postprimary tuberculosis was found with a scar of the apical region of the right upper lobe as well as a vomica (diameter 1 cm) in the subapical region of the same lobe.

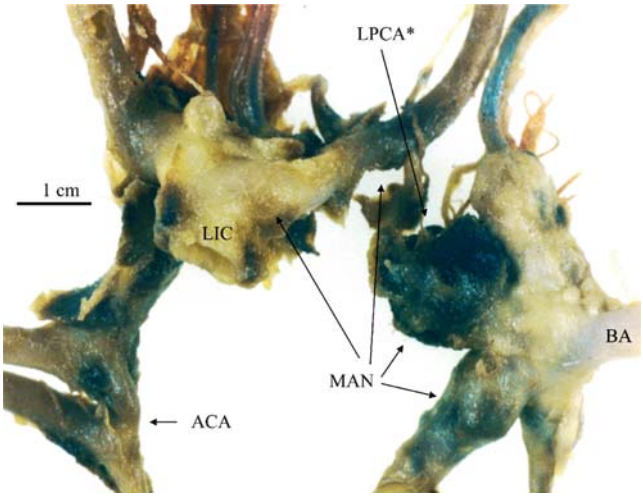

Fig. 1 Multiple mycotic aneurysms (*MAN*) of the Circle of Willis with rupture of the left posterior communicating artery (*LPCA**). Note the granular surface of the vessels. *BA* basilar artery, *LIC* left internal carotid, *ACA* anterior communicating artery

Histological investigation

Both macroscopically affected and unaffected arteries were investigated (Figs. 2, 3, and 4). The less affected were the iliac arteries; here, microfocal incipient necrosis of the media alternating with layer necrosis either acellular as with diffuse cellular infiltration was detected. Very early steps seem to involve the stellate muscles which are immediately followed by different types of elastic lamina destruction: swelling, fragmentation, and dissolution. In the carotid arteries, the inner media shows destruction and dissolution of the elastic membrane while the outer media show destruction of the stellate muscles with incipient destruction of the elastic membrane. Advanced wall necrosis is present in the aneurysmatic arteries: dissolution of the wall structures loss of the intima, necrosis and fading of the structural elements (muscle, elastic membrane), wall dissections, fibrin insudation, and thrombosis.

Microbiology

After early detection of *P. boydii*, this pathogen could no longer be demonstrated in subsequent clinical specimens.

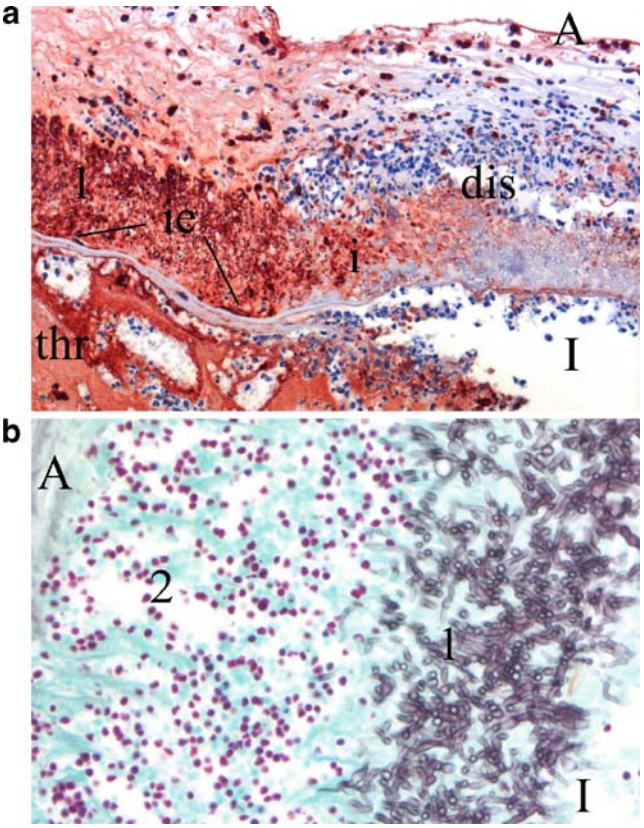

Fig. 2 Basilar artery. *A* adventitia, *I* intima, *ie* internal elastic lamina. **a** Fibronectin ×200; subtotal necroses of the vessel wall with detachment of the intima (*I*), splicing and partial fragmentation of the internal elastic lamina (*iel*), formation of a fibrin rich thrombus (*thr*), fibrin exudation (*1*), and wall dissection (*dis*) with surrounding polynuclear infiltration. **b** Grocott–Gomori methenamine silver stain, ×200. *1* hyphae with conidophores and conidia in inner media, *2* polynuclear infiltration in outer media

Three blood-culture bottles were plated on different agars but showing no growth. After death, *P. boydii* could be easily cultured from heart blood and from aortic tissue. *E* test (AB-Biodisk, Solna, Sweden) showed a minimum inhibitory concentration of itraconazole of about 16 μg/ml.

Discussion

From the first reported case of *P. boydii*-induced encephalitis in a submersion victim [10] and from the subsequent cases [11–14], it is obvious that aspiration of polluted water can be a predisposition of this uncommon mycosis. If molds are detected in this group of patients, they should not be regarded as contaminants. It has been suggested that near-drowning-related hypoxia and frequently used corticoid therapy can cause fatal immune modulation permitting fungal invasion. Also, the irritation of the cellular immunity due to the near drowning could be one factor easing infection of the host. The latent periods between the event and clinical manifestation of *P. boydii* vary considerably and periods of 4–5 months have been reported [15]. In our case, the fungi could have persisted in a vomica over the time of antimycotic therapy and after its termination, they could have spread via the bloodstream and infect the arteries. The only way of eradication would have been surgical removement of this focus [16], but it was not visible in thorax radiography. In this case, it is more likely that the early infection of the arteries took already place during therapy, i.e., prior to the symptoms headache and neck pain that were starting in the sixth week. Then, the question arises whether the antimycotic therapy had been

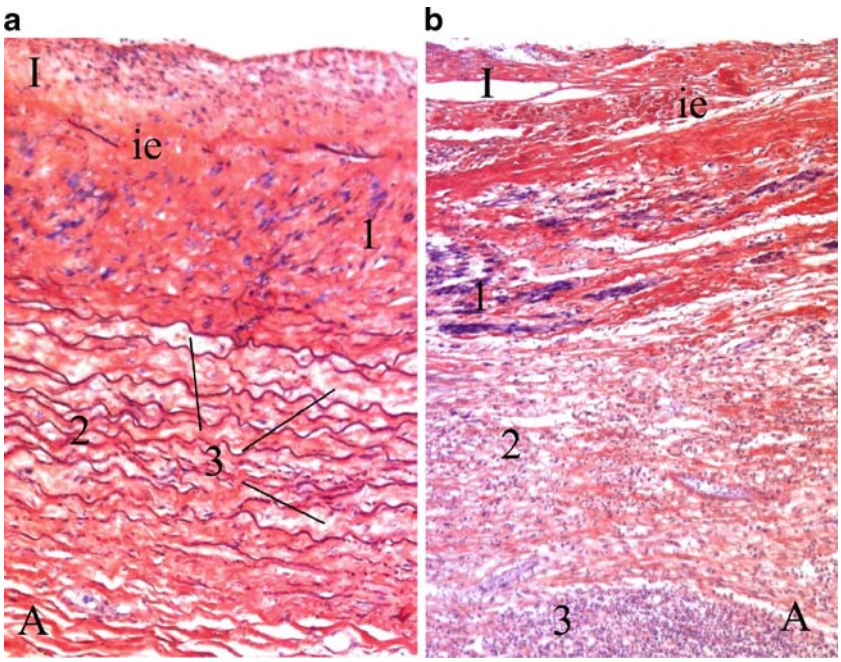

Fig. 3 Artery walls, PTAH. *A* adventitia, *I* intima, *ie* internal elastic lamina. **a** Common carotid artery, ×200. Subtotal necrosis with disappearance of the stellate muscle cells, polynuclear infiltration of the intima, fragmentation, dissolution and fading of the internal elastic lamina (*ie*); swelling, diffusion, and fragmentation of the elastic fibers of the inner media (*1*); intact fiber texture of the outer media (*2*) with microfocal interlaminar edema (*3*). **b** Aorta, ×200; wall necrosis with fading of the internal elastic lamina (*ie*), massive fiber swelling together with fragmentation and metachromasia of the inner media (*1*), fiber diffusion, focal swelling, cellular infiltration of the outer media (*2*), polynuclear infiltration of the adventitia (*3*)

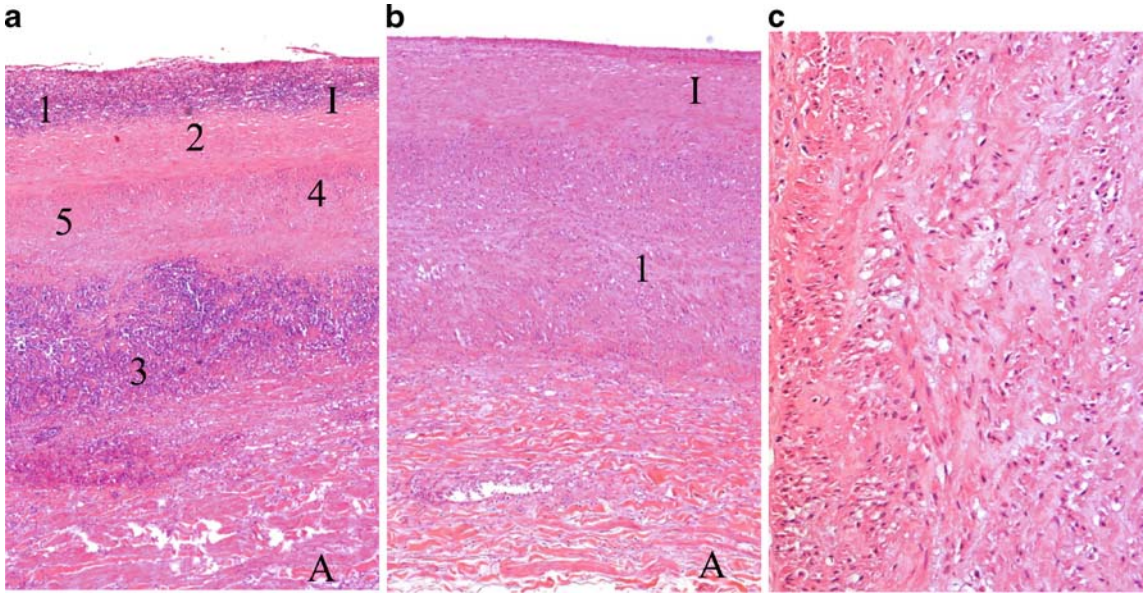

Fig. 4 Iliac artery. H&E. *A* adventitia, *I* intima. **a** ×40, dense infiltration of inner intima and outer media (*1*, *3*), acellular necrosis of outer intima (*2*), and focal necrosis of the media (*5*), incipient necrosis of inner media with fading of stellate muscle cells (*4*). **b** Same section as **a** but approximately 0.5 cm distant; swelling of intimal structures. Outer media (*1*) with multiple cell-depleted homogeneous microfoci. **c** Detail of zone 1 of Fig. 4b, ×200: interlaminar microfocus, edematous, and cell depleted with disintegration of the stellate muscles and microcysts. Incipient microfocal wall necrosis

insufficient. The fungus is often resistant against amphotericin B and 5-fluorocytosine [6] which are the preferred drugs for treatment of systemic fungal infection. Imidazole derivatives are considered highly efficient against pseudallescheriasis and itraconazole is considered to be as effective as other azoles [17]. Itraconazole was given until February in a normal dose (2×200 mg). Oral intake can be insecure [18, 19] but the check of serum levels in February showed them to be in therapeutical range. The susceptibility testing of the fungus postmortem for itraconazole (16 μg/ml) showed that the mold can be resistant against this drug.

The central nervous system is characteristically infected by pseudallescheriasis appearing as a neutrophilic meningitis or brain abscesses after near drowning [5, 9–11, 15, 20–22]. The varied morphology in our case suggests a protracted course possibly based on the influence of the antifungal therapy. After 2 months, the antimycotic therapy was stopped and the symptoms of spreading and invasion progressed.

A particular tropism for the cerebral vessels is typical of aspergillosis of the central nervous system [23]; aspergilli produce elastases and digest the elastic fibers of the artery facilitating the hyphal growth and compromising the integrity of the wall with aneurysm formation and eventual rupture [24, 25]. Hyphae can also proliferate into the lumen determining obstruction and ischemia downstream [26]. The involvement of the cerebral vessels with aneurismatic dilatation is rare in cases of *P. boydii* infection: Only four cases were observed until 2007 [27]. Unfortunately, no histological investigation of the involved vessels was performed [13, 14, 28, 29]. In the present case, all arteries investigated were affected. The types and the extent of damage were extremely variegated, even in one artery at two sites with a distance of 0.5 cm. One had the impression to see different stages of the disease which could reflect relapses, the first step being a multiplicity of micronecrosis with early myocyte necrosis and disintegration of the elastic fibers. These foci seem to merge and give the picture of a homogeneous acellular necrosis of a vessel wall layer. This is only secondarily infiltrated by inflammatory cells. At the very early stage, there obviously exists elastic fiber swelling which is then followed by dissociation, fragmentation, dissolution, and fading. In the latest stages, it comes to ectasia and formation of aneurysm. The vessel wall shows dissection, fibrin exudation, and massive expansion of networks of hyphae together with spores. The vessel wall destruction is associated with thrombus formation. We suppose that in the early stage of the disease, the mold is embolized into the vasa vasorum or enters into the artery from the endothelium. These two ways of invasion could therefore stand for two types of affection: outer media reflecting the vasa vasorum, inner media, and intima reflecting the intimal invasion.

In conclusion, fungal infection and dissemination should be considered in every near-drowning event; a protracted course with inconspicuous interval is possible and if the fungus is detected, a susceptibility testing should verify the effectivity of the antimycotic therapy. From the medicolegal point of view, this case shows an insidious clinical course at

the beginning of which there is a traffic accident. The longer the interval between initial factor and its consequences, the more difficult is the identification of the causal chain. For these reasons if at autopsy a lethal subarachnoid bleeding [30] is associated to multiple aneurysms, the forensic pathologist should consider the type of complication described here, even if there exist no direct hints from the previous history.

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