Remarkable case of early *Aspergillus* endophthalmitis

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**ABSTRACT**

**Background:** This case demonstrates the early stage of *Aspergillus* endophthalmitis and is the second ultrastructural study of endogenous *Aspergillus* endophthalmitis. It is the first description of phagocytosis of *Aspergillus* fungi by retinal pigment epithelium (RPE).

**Methods:** A case report and detailed light- and electron microscopic findings are presented.

**Results:** Histopathological examination of serial sections of the affected right eye displayed a spread of *Aspergillus fumigatus* fungi along two separate paths: via the retinal and choroidal vessels. The retinal and choroidal lesions were not contiguous. The organisms penetrated blood vessel walls, Bruch’s membrane and the internal limiting membrane, but not the RPE layer. A curious accumulation of the *Aspergillus* fungi was present on the internal aspect of Bruch’s membrane, where the RPE acted as a barrier and the subretinal space was not invaded. Phagocytosis of fungi by the RPE was observed. No inflammatory cells were present between Bruch’s membrane and the RPE.

**Conclusions:** This report describes a remarkable barrier function, possible local immunosuppression and phagocytosis by the RPE cells in a case of early *Aspergillus* endophthalmitis.

**Key words:** *Aspergillus*, Bruch’s membrane, electron microscopy, phagocytosis, RPE.

*Aspergillus* fungi are ubiquitous organisms that can, for example, be found in soil or water. They were first described by the Florentine botanist Micheli, in 1729, who named the organisms *Aspergillus* (= rough head) because of the microscopic shape of the spore-bearing structure.1

Endogenous *Aspergillus* endophthalmitis is a rare event. About 40 well-documented cases have been reported in the literature, 25 of which were examined histologically.2

This is the second ultrastructural study of *Aspergillus* endophthalmitis with involvement of the posterior pole3 and the first report about phagocytosis of *Aspergillus* fungi by retinal pigment epithelium (RPE) cells. Two other ultrastructural studies have been reported on cases with *Aspergillus* keratitis.4,5

**CASE REPORT**

A 47-year-old female with presumed autoimmune necrotizing hepatitis was transferred for liver transplantation to the Johns Hopkins Hospital in Baltimore, USA, in January 1997. Despite high-dose steroid therapy with 60–80 mg prednisone per day, she deteriorated rapidly due to progressive liver failure. The patient had a low white blood cell count of 2800 WBC/mm³. In the last 2 weeks she received fluconazole and broad spectrum antibiotics because of signs of septic spread, originating from *Aspergillus fumigatus* pneumonia. Two weeks before her death, she complained of blurred vision OD; an eye examination could not be performed, however, because the patient collapsed shortly before. The patient died in February 1997. An autopsy revealed disseminated *Aspergillus* infection affecting the lungs, heart, kidneys, oesophagus, stomach, small bowel and brain. In most areas of the infection, infarction with haemorrhages and necrosis were present. The lungs were remarkable for *Aspergillus* fungi invading through the visceral pleura. In the brain, *Aspergillus* organisms were found only within blood vessels, suggesting a very recent dissemination in this organ.

**PATHOLOGICAL FINDINGS**

Gross examination of the right eye revealed yellowish discoloration and thickening of the posterior pole, including the macular area (Fig. 1). Flame-shaped haemorrhages were present at the optic nerve head and temporally along the great blood vessels (Fig. 1). The remainder of the eye appeared unremarkable.

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Microscopic examination of 6-µm-thick serial sections through the eye showed an intense inflammatory cell infiltrate in the submacular choroid composed mostly of myeloperoxidase-positive neutrophils. No lymphocytes or macrophages were detected using immunostaining for CD3, CD20 and KP1. Numerous large septate branching hyphae that stained with PAS and Gomori’s methenamine-silver stain were present in the choroid, the walls of choroidal blood vessels and occasionally within Bruch’s membrane. Some choroidal vessels were thrombosed. A curious accumulation of parallel orientated hyphae with up to five layers was conspicuous on the inner aspect of Bruch’s membrane (Fig. 2, 3). The overlying RPE was intact. Ultrastructurally, phagocytized Aspergillus fungi were present in several RPE cells (Fig. 4). Fungi were found neither in the subretinal space nor in the deep retinal layers. In the retina only the ganglion cell and nerve fibre layers were affected. Dichotomous branching of the fungi at 45 degree angles was frequently observed (Fig. 5). Mild invasion of some large superficial retinal vessels (Fig. 5) and of the central retinal vein at the optic nerve head was present, with Aspergillus hyphae also in the surrounding tissue and the overlying vitreous (Fig. 5). In these areas there was also some haemorrhage in the nerve fibre layer under the internal limiting membrane (Fig. 5). Ultrastructurally, Aspergillus fungi were present within the internal limiting membrane as well (Fig. 6). The fungi displayed a thick cellular wall with a typical electron-transparent layer of chitin (Figs 3, 4, 6).

The retinal and choroidal lesions were not contiguous.

DISCUSSION

Endogenous Aspergillus endophthalmitis has been rarely described in immunocompetent persons. It has been far more often reported in immunocompromised patients following drug abuse, alcoholism, heart transplantation, lung transplantation, renal transplantation, liver transplantation, leukaemia, tuberculosis and after Goodpasture’s syndrome.

Figure 1. Right eye after removal of the superior cap. Flame-shaped haemorrhages along the blood vessels and at the optic nerve head. Yellowish discoloration of the central choroid.

Figure 2. Intense infiltration of the choroid (C) by neutrophils. Curious accumulation of Aspergillus fumigatus hyphae at the inner aspect of Bruch’s membrane (arrow). The overlying retinal pigment epithelium is intact (R). (PAS, × 240.)

Figure 3. Transmission electron micrograph of Bruch’s membrane displaying Aspergillus fumigatus hyphae (A) along the inner aspect of Bruch’s membrane (B) with overlying retinal pigment epithelial cells (R). Some fungi are invading through Bruch’s membrane from the choroid. Note the thick chitin cell wall of the organisms. (Uranyl acetate and lead citrate, × 3000.)
syndrome treated with steroids. To our knowledge, *Aspergillus* endophthalmitis has not yet been observed in AIDS, however, and *Aspergillus* infection in general is also rare in AIDS. In our case, immunosuppression by high-dose steroids and liver failure were apparently predisposing factors for the infection.

Widespread dissemination of the fungi into multiple organs was present as is typical, the lungs often being the first and most severe site of manifestation. In the eye, *Aspergillus* infection can occur as endogenous endophthalmitis, orbital aspergillosis following sinusitis or keratitis after trauma to the cornea.

Invasion of blood vessels and angiocentric spread, as in our case, are typical for *Aspergillus* infection. From the vessels the fungi can invade across the vessel wall into the surrounding tissue. *Aspergillus* organisms have been reported to pass through anatomical barriers like Bowman’s and Descemet’s membrane, the lens capsule, internal limiting membrane, Bruch’s membrane, pleura, cartilage and even bone. Accordingly, elastases and collagenases have been demonstrated in *Aspergillus*. Typically, the fungi are orientated parallel to membranes, as along Bruch’s membrane in our case. An accumulation and adherence of *Aspergillus* organisms on the inner aspect of Bruch’s membrane has also been reported in other cases with *Aspergillus* endophthalmitis and seems to be a typical feature. Adherence of *Aspergillus* fungi to polystyrene membranes has also been demonstrated experimentally. Remarkably, the fungi had not yet traversed the RPE cell layer into the subretinal space, which has not been described before. We think this is due to the relatively early stage of the eye involvement and demonstrates a remarkable mechanical barrier function of the RPE in early *Aspergillus* infection, probably due to the tight junctions between the RPE cells.
No inflammatory cells were present between Bruch's membrane and the RPE. This might be due to local immunosuppression by RPE cells which has been shown in experimental studies. Phagocytosis of Aspergillus fungi by the RPE might partly take over the role of the cellular defence, as in our case. Phagocytosis of Aspergillus fungi has also been previously described in tracheo-bronchial epithelium and vascular endothelial cells. The capability of phagocytosis by RPE cells has already been reported for rod outer segments or Staphylococcus aureus organisms. Phagocytosis of Aspergillus fungi by macrophages has also been nicely demonstrated in Aspergillus keratitis. Neutrophils, and at more advanced stages macrophages and granulomatous inflammation with multinucleated giant cells, have been described in Aspergillus endophthalmitis. In our case, the inflammatory cells in the choroid, retina and vitreous were exclusively neutrophils.

For treatment of endogenous Aspergillus endophthalmitis, vitrectomy, intravitreal and systemic treatment with amphotericin B are usually recommended. New antifungal drugs are also available. However, treatment with fluconazole was not successful in our case, demonstrating the remarkably aggressive potential of Aspergillus organisms.

REFERENCES