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Short communication: Unsuspected cerebral phaeohyphomycosis presenting as chronic basilar meningitis

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Abstract: A 60-year-old male patient with a chronic basilar meningitis e.c.i. since 20 years presented three months before his death with a worsening of his condition. Under the suspicion of neurosarcoidosis or a cerebral autoimmune vasculitis he was treated with corticosteroids and cyclophosphamide. Autopsy revealed phaeohyphomycosis of the basal leptomeninges. The etiologic agent was not identified.

Key words: cerebral phaeohyphomycosis, basilar leptomeningitis, neurotropic fungus, Fontana-Masson staining.

Introduction

Cerebral phaeohyphomycosis is a rare clinical condition with less than 100 cases described world-wide (Horré & de Hoog, 1999). Headache is a prominent presenting symptom. The most common physical findings of this condition are neurologic symptoms including cranial nerve deficits and seizures (Dixon *et al.*, 1989). We present a patient from The Netherlands with a clinical picture of a chronic progressive meningoencephalitis which ultimately proved fatal. At autopsy a basilar leptomeningitis with ependymitis due to phaeohyphomycosis was discovered.

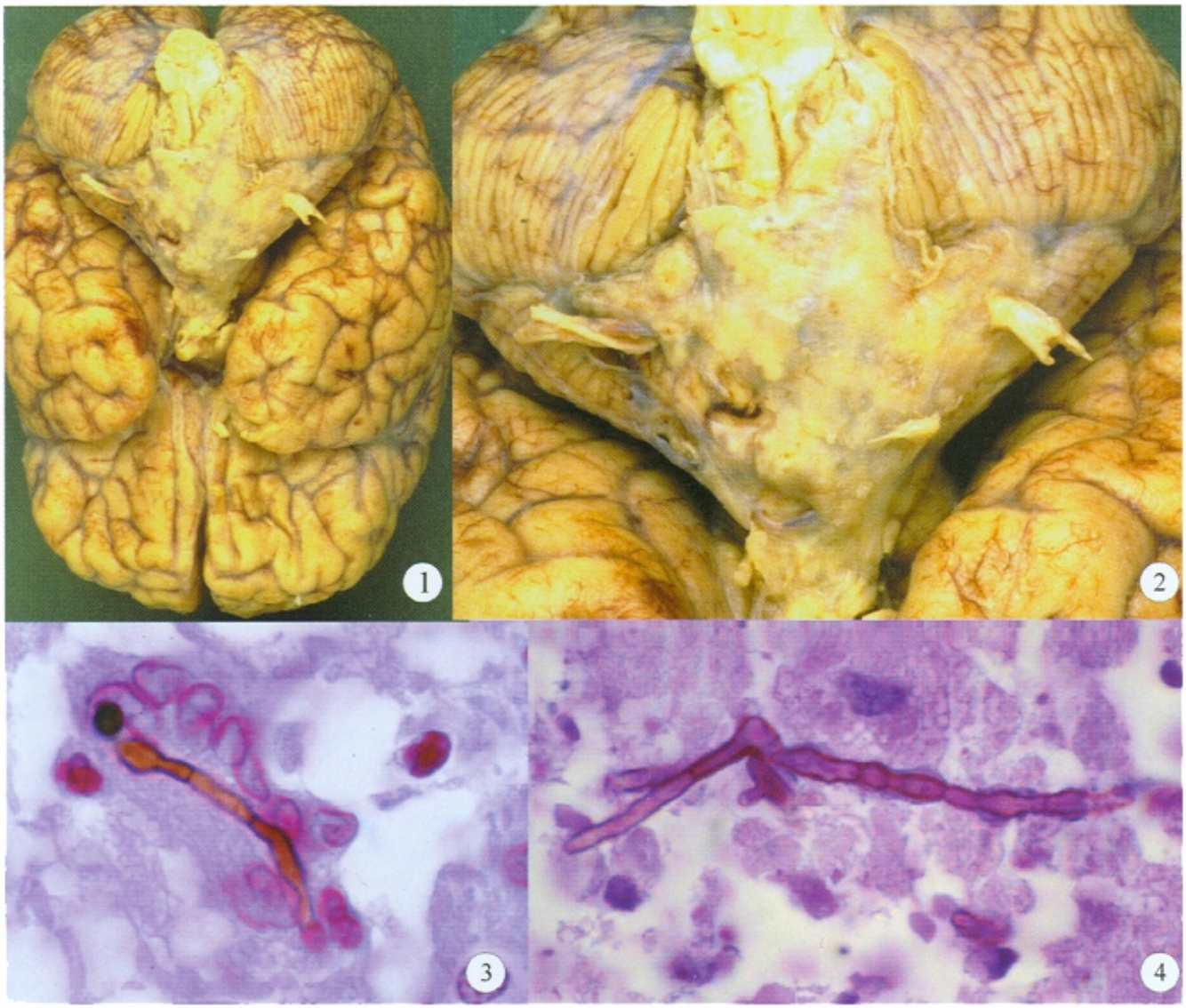
Case report

A 60-year-old male patient (school teacher) presented in July 1997 in a lethargic state with a 4-month history of slowly progressing headache. The medical history indicated an admission in 1975 with meningoencephalitis of unknown origin and granulomatous lesions in lungs and liver. Although cultures for mycobacteria remained negative he received a full course of antituberculous treatment without results. He improved after corticosteroid therapy was initiated. He was admitted six times in 22 years with mostly respiratory complaints for which he received courses of prednisone, anticholinergica and β-2-sympathicomimetica with a good outcome.

Physical examination on admission showed a cachectic and drowsy patient with a temperature of 38.7°C, an irregular pulse of 76 and a blood pressure of 115/75 mm Hg. The patient had a right central facial paresis. The deep tendon reflexes were brisk on the right side and a positive Babinski sign was apparent on the right.

Laboratory investigations showed a peripheral white blood cell count of 13.7 × 10^9/L with 89% neutrophilic granulocytes, a sedimentation rate in the first hour of 25 mm, a CRP of 119 mg/L and a serum glucose of 10.6 mmol/L. Kidney and liver functions were normal. Cerebrospinal fluid (CSF) showed 96 white cells/mm^3 of which 96% were lymphocytes. The total protein was 10,350 mg/L and glucose was 2.8 mmol/L. Staining and culture for bacteria, fungi and mycobacteria was negative. A cryptococcal latex antigen test was repeatedly negative. Tuberculin skin testing was negative. A PCR for *Mycobacterium tuberculosis* on CSF (Roche, Mijdrecht, The Netherlands) was negative. An immunological work-up revealed no clues to the diagnosis. CT and MRI scans with and without contrast revealed no mass lesions of the brain. There were signs of ischemic lesions in the left side of the brainstem.

Because of the apparent basilar meningitis, treatment was started for tuberculous meningitis. Several attempts were made to detect *M. tuberculosis* in CSF without positive results. Therefore, under the suspicion of neurosarcoidosis or a cerebral auto-immune vasculitis, therapy with 60 mg prednisone daily was initiated



Plates 1, 2. Macroscopy of the brain showing a yellow discolouration of the leptomeninges indicating a basilar meningitis.
Plate 3. Brown coloured hyphae inside a multinucleated giant cell. Fontana-Masson staining. ×400.
Plate 4. Hyphae in necrotic area. PAS staining. ×400.

although no laboratory findings consistent with sarcoidosis were positive. There was no improvement in his condition. He developed seizures and respiratory insufficiency for which he was intubated. Repeated radiological investigations gave no clue to the cause of his disease. Finally cyclophosphamide was added to the regimen. He developed a leukopenia and died of a septic shock two months after admission.

At autopsy, macroscopic examination of the brain (weight 1140 g, normal 1200-1400 g) revealed severe fibrous thickening with yellow discolouration of the basal leptomeninges (Plate 1, 2) and of the choroid plexus in the fourth ventricle. Microscopically, these structures showed a marked polymorphonuclear and lymphohistiocytic infiltrate, dispersed areas of necrosis, and occasional granulomata in a background of fibrosis. Within scattered multinucleated giant cells (Plate 3) and in the necrotic areas (Plate 4) hyphae were easily found in the Hematoxylin & Eosin, Periodic Acid-Schiff and Fontana-Masson staining. The brown-pigmented hyphae exhibited distinct septation with occasional branching and intercalary swollen cells. Additionally, microscopical examination revealed a subtle granular ependymitis in the lateral ventricles with dispersed multinucleated giant cells and hyphae. Brain abscesses and acid-fast bacilli were absent. The basilar artery and smaller vessels in the basal leptomeninges showed moderate to severe concentric fibrosis of the intima. However, vasculitis or infiltration of fungal hyphae in the vessel walls was not noted. The brain stem, cerebellum and basal parts of the cerebrum (including the basal ganglia) contained dispersed small foci of old-

er and more recent ischemic necrosis with variable accumulation of lipid phagocytes. In the lungs, small, non-necrotic granulomas with multinucleated giant cells without fungal elements were seen. Because the brain was already immersed in formalin attempts to isolate the fungus in culture failed as did attempts to amplify fungal DNA in the affected area with broad range primers.

Discussion

Cerebral phaeohyphomycosis is a rare, usually fatal infection. Although histopathology is unreliable to identify a specific dematiaceous hyphomycete we suspect that our case might have been caused by a *Cladophialophora* species, because of the anatomical location of the lesion and the ubiquitous distribution of this species (Horré & de Hoog, 1999). Our patient had no travel history to regions such as the Middle East or East Asia were other neurotropic members of the family *Herpotrichiellaceae,* the species *Ramichloridium mackenziei* Campbell & Al-Hedaithy and *Exophiala dermatitidis* (Kano) de Hoog are most prevalent (Horré & de Hoog, 1999). This is the first reported case from The Netherlands, although previous cases might not have been documented due to absence of autopsy data or misdiagnosis of histopathology. The typical brown melanized hyphae can be difficult to detect in histological sections at an early stage of infection and could be confused with hyaline hyphomycetes. Application of the Fontana-Masson melanin stain reveals dematiaceous fungi and should be performed and examined routinely when hyphae are found in tissues of the central nervous system. The clinical symptoms and signs of infection are largely non-specific and, when there are mass lesions, include headache and papilledema and localized neurological deficits.

Reminiscent of our case is the patient described by Bennett *et al.* (1973) and three other cases reviewed in that report in which only diffuse basilar meningitis was present without brain abscesses. This might also be related to the chronicity of clinical signs. Patients with a chronic meningitis as the only manifestation of cerebral phaeo-hyphomycosis might have a longer protracted illness. The course of disease ranged from a few weeks (Dixon *et al.*, 1989) to as long as five years (Sandhyamani *et al.*, 1981). Cerebral phaeo-hyphomycosis has been diagnosed during life only when surgical intervention was performed. Cultures of CSF are generally negative. When meninges were involved the outcome of all patients described to date is dismal. Our patient had complaints and signs of basilar meningitis for more than twenty years. We can only speculate to the cause, but it seems unlikely that the initial symptoms are attributable to the phaeohyphomycotic infection. A more plausible explanation would be that the treatment with corticosteroids and in a later stage with cyclophosphamide predisposed him to development of the infection.

Acknowledgement

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