Case report

Fatal pulmonary scedosporiosis

Letal verlaufende pulmonale Scedosporiose

R. Horré,[1] B. Jovanić,[1] G. Marklein,[1] G. Schumacher,[1] N. Friedrichs,[2] T. Neuhaus,[3] G. S. de Hoog,[1,4] W. H. J. Becker,[1,4] S. M. Choi,[1,4] and K. P. Schaal[1]

[1]Institute for Medical Microbiology and Immunology, [2]Institute for Pathology, [3]Clinic and Policlinic for Internal Medicine, University of Bonn, Bonn, Germany and [4]Centraalbureau voor Schimmelcultures, Utrecht, The Netherlands

Summary

We report on a case of scedosporiosis in a 72-year-old German woman. Her disease started with a purulent ulceration of unknown course at her left foot. Soon after onset of oral antibacterial therapy she needed in-hospital treatment because of an acute pneumonia. The infection progressed despite the application of different antibiotics. Microscopic examination of tracheal fluid revealed fungal hyphae and therefore treatment with itraconazole was initiated. However, the patient developed renal failure, required mechanical ventilation and finally died in treatment-resistant septic shock. Post-mortem *Scedosporium apiospermum* was cultured from lung tissue taken during autopsy. This is the fourth case of human infection caused by *Scedosporium* species diagnosed in our laboratory during the last 4 years.

Zusammenfassung

Wir berichten über eine Scedosporiose bei einer 72-jährigen deutschen Patientin. Zuerst litt sie an einer eitrigen Entzündung unbekannter Ursache an ihrem linken Fuß. Kurz nach Beginn einer oralen Antibiotikatherapie entwickelte sie eine akute Pneumonie. Obwohl die Patientin stationär mit verschiedenen Antibiotika behandelt wurde, verlief die Pneumonie progredient. Bei der mikroskopischen Untersuchung von Trachealsekret wurden Pilzhyphen erkennbar, weshalb eine antimykotische Therapie mit Itraconazol eingeleitet wurde. Im weiteren Verlauf wurde die Patientin renal insuffizient, beatmungspflichtig und starb schließlich im therapierefraktären septischen Schock. Postmortal wurde *Scedosporium apiospermum* aus Lungengewebe angezüchtet, welches bei der Autopsie entnommen wurde. Dies ist der vierte Fall einer humanen *Scedosporium*-Infektion, der in den vergangenen vier Jahren in unserem Labor diagnostiziert wurde.

Key words: *Scedosporium apiospermum*, *Pseudallescheria boydii*, pneumonia.

Schlüsselwörter: *Scedosporium apiospermum*, *Pseudallescheria boydii*, Pneumonie.

Introduction

Scedosporium apiospermum (teleomorph: *Pseudallescheria boydii*) occurs world-wide in agricultural soil,[1] polluted water and sewage.[2] It is also a relatively common agent of infections in humans.[3] Classically, since the twenties of the previous century, the species was known as an agent of mycetoma.[4] The first pulmonary infection by *S. apiospermum* was reported in 1955.[5] In recent years, the prevalent clinical appearance is opportunistic dissemination in immunocompromised patients.[6–11] In these patients, infection of the central nervous system is a common complication of the disease.[6] Pulmonary symptoms are also frequent.[12] Most antifungal drugs

Correspondence: Dr. Regine Horré, Institute for Medical Microbiology and Immunology, University of Bonn, Sigmund-Freud-Str. 25, D-53105 Bonn, Germany. Tel.: +49 228 287 5952. Fax: +49 228 287 4480.
E-mail: regine.horre@gmx.de

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have been shown to be inactive against *Scedosporium* species *in vitro*[13,14] as well as *in vivo*.[15] Effective treatment is achieved with combination therapy only.[16]

Case history

A 72-year-old German woman presented herself at the surgical outpatient department of a hospital in Bonn, Germany, with a purulent ulceration on her left little toe. She had been diagnosed with a low-malignant non-Hodgkin's lymphoma 4 years ago. After seven cycles of chemotherapy (Knospe-scheme) complete remission had been obtained. In addition, the patient suffered from chronic renal insufficiency and steroid-induced diabetes mellitus. One year later, ulcus duodeni et ventriculi were recognized. Furthermore, strumectomy was necessary because of hyperthyreosis; the thyroid function was normal afterwards. Her situation was complicated by a deep venous thrombosis, followed by lung embolism and a chronic obstructive lung disease.

She could not recall any kind of trauma of the toe. The wound showed purulent discharge and radiography revealed an osteolytic lesion. *Staphylococcus aureus* and *Enterococcus* sp. were cultured from a wound swab. The patient refused in-hospital treatment and therefore an oral antibiotic therapy was started with flucloxacillin *per os* (p.o.) at a dosage of 3×500 mg day^{-1}). Three days later, the inflammatory process had progressed and in-hospital treatment became necessary. An intravenous antibiotic therapy was started with ampicillin/sulbactam (3×3 g day^{-1}) for 10 days. Although X-ray films showed no change of the lesion, the woman was discharged without pain but with still persisting inflammatory symptoms. The treatment was continued orally. Four days later, she consulted another hospital in Bonn because of fever, pneumonia of the right upper lobe with pleural exudation, cardiac dilatation and decompensation. Laboratory parameters showed elevated levels for C-reactive protein (CRP) of 7.3 mg dl^{-1} (0.5 mg dl^{-1}) and creatinine of 4.3 mg dl^{-1} (0.5–1.0 mg dl^{-1}) (normal results are shown in brackets). An intravenous therapy with ceftriaxone was started. One week later, a bronchoalveolar lavage (BAL) was sent for microbiological examination, from which *Klebsiella oxytoca, Enterobacter cloacae* and a *Prevotella* species were cultured. Although the antimicrobial regime was changed to meropenem (500 mg day^{-1}) and fluconazole (100 mg day^{-1}) intravenously (doses reduced because of renal insufficiency) and clarithromycin p.o. (2×250 mg day^{-1}), radiologically the pneumonia showed progression. As the patient then required intensive-care treatment, she was transferred to the Policlinic for Internal Medicine of the University of Bonn, where an antibiotic treatment with piperacillin/tazobactam (2×4.5 g day^{-1}) and ciprofloxacin (2×200 mg day^{-1}) was initiated. However, CRP did not decrease during the following days and X-ray examination now showed multilobular spreading of the pulmonary infiltrates. Therefore another BAL was performed. In this specimen, instead of bacteria, fungal hyphae could be recognized microscopically and a mould was cultured on Sabouraud glucose agar (SGA) after 4 days of incubation at 30 °C. Assuming an *Aspergillus* infection, serum was tested for galactomannan, but was found to be negative.

Antimycotic treatment with itraconazole (200 mg day^{-1}) was initiated. Nonetheless CRP had risen to 12.74 mg dl^{-1} and the patient developed respiratory insufficiency, progressive personality changes, and renal failure caused by sepsis, followed by the need for mechanical ventilation and haemofiltration. One day later, tracheal fluid and yet an other day later, bronchial fluid were obtained and sent for microbiological examination, from which the mould could be recognized again after incubation on SGA for 3 days. The CRP level had then risen to 31.06 mg dl^{-1}. The patient died on the same day in therapy-refractory septic shock. Death occurred at day 45 after the beginning of antimicrobial chemotherapy in the surgical outpatient department. The mould was identified as *Scedosporium apiospermum* (*Pseudallescheria boydii*) in the post-mortem study.

Pathology

An autopsy followed 1 day after death and multiple lung abscesses were seen macroscopically. Three tissue samples of the lungs were obtained. One for rapid histological examination, one for formalin-fixed paraffin-embedded histopathological examination and the last one for microbiological culture. Histological quick staining with periodic acid-Schiff (PAS) revealed numerous fungal hyphae. However, the examination of the embedded material did not show any of these structures neither by staining with PAS nor with Gomori's methenamine silver stain (GMS).

Mycology

In total, three specimens of the lower respiratory tract (two BAL, one lung tissue) were sent for fungal isolation. They were cultured on Columbia-5%-sheep-blood agar (2 days, 37 °C, 10% CO_2), Candi-Select agar (Becton Dickinson, Sparks, MD, USA) (2 days, 37 °C), and SGA (10 days, 30 °C). Fungal growth could be observed macroscopically on SGA after 3–4 days of incubation at 30 °C. The mould was initially whitish-grey, with a brownish-black reverse after 10 days.

Microscopically, conidiation typical for *Scedosporium* was recognized; in one culture plate, a *Graphium* synanamorph[3] was observed. The diagnosis was confirmed as *Pseudallescheria boydii* by sequencing of the rDNA internal transcribed spacer (ITS) domain. The isolate from lung tissue was deposed in the CBS culture collection (Centraalbureau voor Schimmelcultures, Utrecht, The Netherlands) as CBS 110626.

Discussion

Scedosporium spp. are notorious for their opportunistic behaviour. In the case described here, the patient had a long history of corticosteroid therapy, antibiotic treatment, chronic obstructive lung disease and a metabolic disorder. These all are risk factors for the development of a fungal infection and therefore the patient may have been exceptionally susceptible. At the origin of the infection was a lesion of unknown origin with osteolysis at the left foot. Initially, no hyphae were seen in lung biopsy specimens. The absence of fungal elements in GMS-stained tissue shown to be positive for *Scedosporium* by culturing has been noticed before.[17,18] Apparently the fungus produces local foci in the lungs.

Scedosporium apiospermum, the anamorph of *P. boydii*, as well as its close relative, *S. prolificans*, are known to be resistant to a variety of antifungal drugs. Complete cure of infections caused by this species can be achieved by complete resection of the infected tissue and after recovery of the patient's immunity.[19] Meletiadis *et al.*[16] recently discovered *in vitro* synergistic action between itraconazole and terbinafine, which might provide prospects for successful antimycotic therapy. Because of the patient's sudden death, definitive identification of the aetiologic agent came too late to modify the antifungal treatment.

As far as the microbiological diagnosis is concerned, there is a considerable risk of misidentifying scedosporiosis as aspergillosis.[20,21] This is mainly because of the fact, that clinical and radiographic features, antigen test and the histopathological picture are neither specific for scedosporiosis nor for aspergillosis. Correct diagnosis is significant because antifungal monotherapy, which is the common practice against *Aspergillus*, is inadequate for curing *Scedosporium* infections.

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