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CASE REPORT

Disseminated *Rhizopus microsporus* infection in a patient on oral corticosteroid treatment: a case report

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ABSTRACT

A 71-year-old male with mild steroid-induced hyperglycaemia was diagnosed with a lethal invasive *Rhizopus microsporus* infection.
Disseminated zygomycosis is a rare entity and is most frequently found in neutropenic patients with haematological malignancies, post-transplants or in patients on deferoxamine therapy. Infection is characterised by tissue infarction and necrosis due to angioinvasive hyphae. Culture of *Zygomycetes* is necessary for species determination but histology is a must to prove the infection. Ante-mortem diagnosis and culture is challenging and therefore mortality approaches 100%. Apart from amphotericine B, most anti-fungals have no activity against *Zygomycetes* but posaconazole might offer new possibilities as a first-line agent. Timely diagnosis, rapid surgery of infected tissue, correction of underlying disorders and correct anti-fungal therapy might be life-saving. Due to the increasing use of potent immunosuppression, stem cell and organ transplants and possibly selection for *Zygomycetes* by prior treatment with broad-spectrum antifungal therapy, the incidence of zygomycosis is rising. Therefore, clinicians might encounter an increasing number of zygomycosis cases in the near future.

KEYWORDS

Corticosteroids, disseminated zygomycosis, non-neutropenic, *Rhizopus microsporus* var. *microsporus*

INTRODUCTION

Very few cases of zygomycosis in adults due to *Rhizopus microsporus*, a fungus belonging to the class of *Zygomycetes*, have been reported in English literature.[1-6] Disseminated zygomycosis caused by *Rhizopus microsporus* var. *microsporus* has only been reported once.[6] Disseminated zygomycosis is almost exclusively diagnosed in patients with major risk factors for development of zygomycosis such as neutropenia, (post) transplantation, haematological malignancies, diabetic keto-acidosis and corticosteroid treatment.[7,8]
We present a case of disseminated *Rhizopus microsporus* infection in a non-neutropenic patient with corticosteroid therapy and mild steroid-induced hyperglycaemia.

CASE REPORT

A 71-year-old male presented to the emergency department with acute, non-colic like, abdominal pain in the lower right quadrant. There was no history of fever, but he was complaining of shortness of breath on exertion for three weeks without chest pain, cough or sputum production. There were no complaints of nausea or vomiting and his defecation and urinary patterns were unremarkable.
He had been treated with 90 mg/day oral prednisolone therapy for idiopathic thrombocytopenic purpura (ITP) for two months. Further medical history was uneventful.
On physical examination the body temperature was 37.4°C, blood pressure 170/88 mmHg, pulse rate 108/min, pulse oxymetry 99% SaO_2 (room air) and respiratory rate was 18 breaths/min. Lung and heart sounds were normal. Abdominal examination showed right flank and lower quadrant pain without rebound tenderness or guarding. No masses or lymphomas were noted. Genital inspection and

rectal examination were unremarkable. Both shins showed brownish discoloured petechiae.

Laboratory findings were as follows (normal reference values in parentheses): haemoglobin 7.8 mmol/l (8.5 to 11.0), mean corpuscular volume 90 fl (80 to 100), white cell count 5.4 x 10^9/l (4.0 to 11.0) with 76% segments and 21% lymphocytes and no bands in the differentiation, platelets 23 x 10^9/l (150 to 400), C-reactive protein 100 mg/l (<5), glucose 10.2 mmol/l (4.0 to 9.0), and creatinine 66 µmol/l (60 to 110). Serum electrolytes and liver biochemistry were normal. Urinalysis: >100 erythrocytes (0 to 5) and no leucocytes/visual field; no protein or casts were noted but glucosuria without ketonuria was present.

Abdominal ultrasound and plain X-ray taken on the day of first presentation were normal and patient was admitted for observation of the abdominal pain, mild steroid-induced hyperglycaemia and haematuria due to thrombocytopenia (*figure 1*). The next day an IV-contrast enhanced abdominal CT was made which showed no abnormalities except for irregular enhancement of the upper zone of the right kidney, suspect for a cyst. Cystoscopy and urine cytology were normal and haematuria receded spontaneously. Infection parameters rose (day 3) and a chest X-ray revealed a large opacity in the left lung. In contrast, a chest X-ray taken three months prior to presentation showed no abnormalities.

Pneumonia and/or a possible malignancy of the lung was suspected and oral moxifloxacin was started and prednisolone dosage was tapered (day 3).

A contrast-enhanced CT thorax showed an opacity in the left lung and an additional mass in the right apex (day 4). Blood, sputum and urine cultures for bacteria and fungi remained sterile (*figure 2*).

Figure 1. *Thorax*

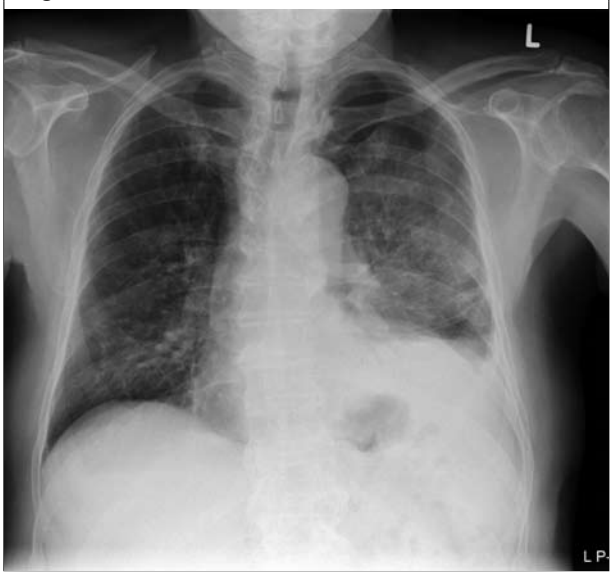
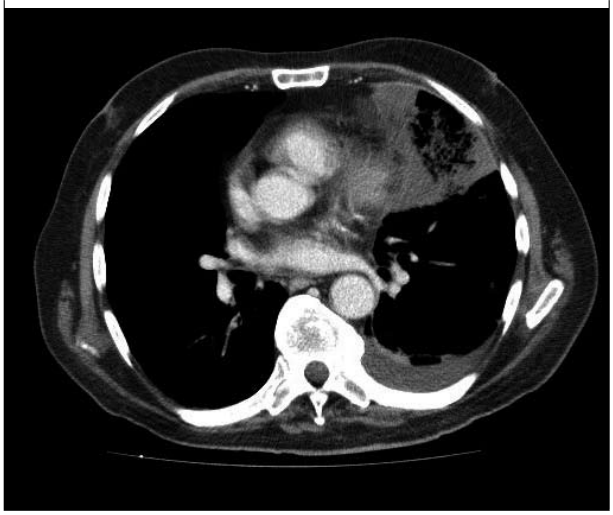


Figure 2. *CT-scan*



Bronchoscopy and broncho-alveolar lavage (BAL) were performed on the 10th day of admission demonstrating a purulent haemorrhagic area in the left upper lobe. Lung biopsy was abandoned because of the patient's low platelets. Lavage analysis demonstrated an inflammatory process, no malignant cells, no *Pneumocystis jiroveci* and no acid-fast bacilli. Culture grew pharyngeal flora including *Candida albicans*. Oral glimepiride was started for mild hyperglycaemia and antibiotics were changed into ciprofloxacin and amoxicillin intravenously. Oral itraconazol 300 mg twice a day was added empirically for systemic mycosis and prednisolone therapy was stopped (day 14).

After 24 days of hospital admission a high-resolution CT thorax showed progression of pulmonary lesions but no halo-sign. The right kidney now demonstrated evidence of infarction. By this time, the glimepride had been stopped and glucose levels remained within the normal range. Invasive aspergillosis and changing antifungal therapy into voriconazole was considered after further deterioration of the patient's clinical state. However, in absence of further diagnostic procedures and normal aspergillus antigen test (Galactomannan), itraconazole therapy was continued.

On the 31st day the patient became febrile, developed respiratory failure and was transferred to the ICU of a tertiary care hospital. The patient died one day after open lung biopsy.

Post-mortem histological examination showed broad, irregular branched, aseptate hyphae in the left lung, and right kidney. Cultures of this material grew *Rhizopus microsporus*.

DISCUSSION

Zygomycosis is the third most common invasive fungal infection after candidiasis and aspergillosis.[9] The incidence of zygomycosis is rising due to multiple factors including

the increasing use of potent immunosuppression, stem cell and organ transplants and possibly selection for *Zygomycetes* by prior treatment with broad-spectrum antifungal therapy, which has no activity against *Zygomycetes*.[10] *Rhizopus*, together with *Mucor, Rhizomucor, Absidia, Apophysomyces, Cunninghamella* and *Saksenaea* are placed in the order of *Mucorales*, class of *Zygomycetes*. The common term zygomycosis is used for infections caused by any of these fungi. The organisms are ubiquitous spore-forming saprophytes growing in decaying organic matter. Inhalation or percutaneous introduction of spores causes infection almost exclusively in patients with underlying immuno-compromising conditions. Diabetes mellitus and/or keto-acidosis, neutropenia, haematological malignancies, deferoxamine therapy, IV drug use, local burn wounds or trauma, severe malnutrition and solid organ transplantation are known risk factors for invasive zygomycosis.[7,8]

Infection is characterised by tissue infarction and necrosis due to angioinvasive hyphae. Once established, the disease is rapidly progressive and often fatal.

Six clinical syndromes caused by *Zygomycetes* are recognised: rhino-orbital-cerebral, pulmonary, cutaneous, disseminated, gastrointestinal and miscellaneous forms.

This case represents a non-neutropenic, immuno-compromised patient on oral corticosteroid therapy with mild, steroid-induced hyperglycaemia who developed a disseminated *Rhizopus microsporus* infection, proven by histological analysis at autopsy. Although diabetes mellitus is a major risk factor for rhinocerebral disease, disseminated zygomycosis is a rare entity and is most frequently found in neutropenic patients with haematological malignancies, post-transplants or in patients on deferoxamine therapy.[11,12] In a large series, *Rhizopus* species accounted for 218 of 465 (47%) patients but *R. microsporus* has only been isolated from 11 of 465 (2%) patients.[12]

R. microsporus is a thermophilic zygomycete with a worldwide distribution, and is saprophytic, living in soil, air and decaying matter and growing well on substrates such as fruits, cereals and bread. Among the four known varieties, only *R. microsporus* var. *microsporus* and *R. microsporus* var. *rhizopodiformis* have been reported to cause infections in humans.[3]

So far only five cases of *R. microsporus* var. *microsporus* have been reported in English literature of which only one disseminated case.[1-5,6]

As this case illustrates, ante-mortem diagnosis of disseminated zygomycosis is a challenge and many patients are often co-infected with other pathogens. Typically, zygomycosis is only considered after precious time has been lost unsuccessfully treating suspected bacterial or other fungal infections with broad-spectrum antibiotics. Due to easy inhalation of spores, pulmonary zygomycosis and rhino-orbital forms of zygomycosis are common; as in this case, the airway was probably the primary site of infection. Negative culture and analysis of bronchalveolar lavage fluids do not safely exclude zygomycosis.[13] Radiological findings such as halo-signs, consolidation and necrosis on (high-resolution) CT scans might support diagnosis but are not specific for zygomycosis.[14] As a result, mortality is high, approaching 100% in disseminated cases.[12] Culture of *Zygomycetes* is necessary for species determination but histology is necessary to prove the infection.

Therefore we stress the importance of tissue biopsy for histological confirmation of zygomycosis. Although at-risk patients might have thrombocytopenia or other conditions making biopsy complicated, timely histological confirmation of zygomycosis could be life-saving. Exogenous transfusion of platelets and tissue biopsy earlier in the course of this case might have provided earlier recognition of the causative pathogen followed by the appropriate treatment.

Furthermore, the immuno-compromised patient population is significant and growing in size as chemotherapy, potent immunosuppressive therapy and transplant procedures are increasing.[15] Therefore, clinicians might start encountering cases of zygomycosis more frequently in the near future.

As noted earlier incidence of zygomycosis is rising. An additive cause might be empirical treatment of at-risk patients with voriconazole causing selection of nonsusceptible fungi such as *Zygomycetes*. Decreased incidences of aspergillosis together with breakthrough cases of zygomycosis are reported in literature. In the same study Kontoyiannis and co-workers marked voriconazole therapy as an independent risk factor for zygomycosis.[16]

For treatment of zygomycosis, amphotericin B in the highest tolerable dose is still the drug of choice together with resection of infected tissue and correction of underlying risk factors. In this case, immunosuppressive therapy was tapered and mild hyperglycaemia treated. Typically, due to the post-mortem diagnosis the patient had not been treated with surgery and treatment with antifungal therapy directed against *Zygomycetes*.

Triazoles, such as itraconazole, fluconazole and voriconazole, have little activity against *Zygomycetes* and therefore are ineffective for empirical treatment when zygomycosis is suspected. However, posaconazole, a new broad-spectrum triazole, has proven successful as salvage therapy in treatment of breakthrough zygomycosis.[17] Furthermore, Peel *et al*. have recently reported a case of disseminated zygomycosis due to *R. microsporus* var. *microsporus* successfully treated with posaconazole as first-line therapy.[6]

In vitro susceptibility testing showed superior activity for a wide range of fungi including *Zygomycetes* for posaconazole compared with fluconazole, itraconazole and voriconazole.[18] Interestingly, the different species of *Rhizopus* show different susceptibilities in murine models to posaconazole where *R. microporus* var. *rhizopodiformis* is susceptible at higher minimal inhibitory concentrations

and *R. oryzae* is non-susceptible. *R. microsporus* var. *microsporus* susceptibility to posaconazole has not been tested yet.[19] Considering this together with difficulties in appropriate dosage for amphotericin B due to toxic side effects, there might be a new place for posaconazole as first-line therapy for zygomycosis.[20]

CONCLUSION

We present a case of disseminated *R. microsporus* infection in a non-neutropenic patient with mild, steroid-induced hyperglycaemia. Timely diagnosis of invasive zygomycosis, preferably by culture and histological confirmation together with surgery and correction of underlying conditions, is a prerequisite for successful treatment. Posaconazole might offer new possibilities for first-line therapy against zygomycosis although amphotericin B remains the cornerstone of antifungal therapy.

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