Severe invasive pulmonary zygomycosis by *Rhizomucor pusillus* and concomitant severe bacterial endocarditis in acute promyelocytic leukaemia

Zigomicosi polmonare invasiva da *Rhizomucor pusillus* e concomitante endocardite batterica in paziente con leucemia promielocitica acuta

Roberta Rocconi¹, Sandra Mazzucato², Claudio Farina³, Stefano Grandesso²

¹UOC Haematology, Ospedale dell’Angelo, Venezia-Mestre, Italy; ²UOSD Microbiology, Clinical Pathology Department, Ospedale dell’Angelo, Venezia-Mestre, Italy; ³UOC Microbiology and Virology, AO “Papa Giovanni XXIII”, Bergamo, Italy

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**INTRODUCTION**

The prevalence and incidence of opportunistic mycoses have increased over the past fifteen years, particularly in a specific subset of patients, like those treated with intensive chemotherapy regimens for acute leukaemias and those treated with bone marrow transplantation [1, 2]. In both these cases there is a deep immunosuppression that favours opportunistic infections. Lungs are the most affected site of involvement in *Rhizomucor pusillus* infection, particularly in haematological patients. The infection evolves rapidly, more so if diagnosis and treatment are delayed; the overall mortality rate for *Rhizomucor* infections is about 50%. We report here the case of a patient with severe pulmonary infection caused by *Rhizomucor pusillus* associated with a bacterial endocarditis in a woman diagnosed with acute promyelocytic leukaemia.

**CASE REPORT**

A 58-year-old woman was admitted to the Haematology Division of the Hospital dell’Angelo on February 2009 for pancytopenia discovered on routine blood tests. Ten years before she had undergone left quadrantectomy followed by local radiotherapy for breast carcinoma, and four years before she had suffered from acute myocardial infarction treated by coronary stenting.

Bone marrow examination, immunophenotyping and PCR revealed acute promyelocytic leukaemia with t(15;17) PML/RARα; ecocardiography revealed normal EF and moderate mitral valve insufficiency.

We started induction chemotherapy with all-transretinoic acid plus idarubicin associated with levofloxacin and fluconazole prophylaxes. During the 12-day aplasia following induction therapy the patient experienced grade 3 gastrointestinal toxicity and grade 4 oral mucositis. After haematological recovery, fever with severe acute respiratory distress syndrome occurred; pulmonary CT scan showed acute pneumonia with heart enlargement (Figure 1).

The patient was admitted to ICU where blood and bronchoalveolar lavage (BAL) cultures were performed and found positive for *Enterococcus faecalis* and *Pseudomonas aeruginosa*; also transesophageal echocardiography was performed and showed probable endocarditis with severe aortic and mitral valve insufficiency and congestive heart failure.
Specific antibiotic and antifungal therapy with voriconazole 4 mg/kg iv were administered. The thoracic CT scan performed one week later showed a pseudo-nodular right lung lesion (6 cm of diameter) with central cavitation, and smaller multiple nodular lesions in the left lung; a second BAL culture was performed and found positive for *Enterococcus faecalis* and *Rhizomucor pusillus* (Figure 2). Voriconazole therapy was interrupted and liposomal amphotericin B therapy at the dose of 5 mg/kg was started. Thoracic CT scan control performed after one more week revealed progressive lung lesion impairment. Severe acute bleeding from endotracheal tube occurred and tracheotomy was necessary; the following blood cultures were negative and progressive clinical improvement occurred.

When the patient came back to our Division after 48 days in ICU, sputum cultures were performed and found positive for *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterococcus faecium*, *Hafnia alvei* and *Candida tropicalis*. Acute left pneumothorax occurred after a few days, which was completely resolved by inserting a drainage. We then started consolidation therapy with all-transretinoic acid for only 15 days. Thoracic control CT scan revealed good response with residual bilateral lung lesions of about 1.5 cm of diameter (Figure 3); liposomal amphotericin B therapy was stopped due to moderate renal failure, and posaconazole 800 mg/day therapy was started and given for 3 months.

In the meantime, together with the thoracic surgeon and the infectious disease specialist, we agreed on the need of surgical intervention, therefore in June 2009 the patient underwent superior and inferior right lobar pulmonary resection. Histological finding was negative.

After surgery, she started maintenance therapy with purinethol 75 mg po and methotrexate 20 mg im for two years. Mitral valve substitution was not necessary. The patient is still very good, maintaining complete haematological and molecular remission after a five-year follow-up.
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**Microbiological diagnosis**

The samples of left and right broncho-alveolar fluid were cultured in Columbia Blood Agar, McConkey agar, Mannitol Salt Agar, Sabouraud Dextrose agar with chloramphenicol (all in aerobic atmosphere at 37°C), Chocolate Agar with PolyVitex (in 5% carbon dioxide for 48 hours at 37°C, bioMérieux, Mercy L’Etoile, France). After 30 hours, colonies grew in both samples in Sabouraud Dextrose agar with chloramphenicol, in Columbia Blood agar and Chocolate agar with PolyVitex. They appeared cotton-candy like in texture. From the front, the colour was initially white, turning to grey as time passed (Figure 4). The reverse was pale. The microscopy morphology showed non septate broad hyphae, rudimentary rhizoids (few in number, located on stolons between sporangiophores, at the base of sporangiophores), sporangiophores (irregularly branched), sporangia (about 50 µm in diameter, round, always with a septum below it), and sporangiospores (small, unicellular, round). Columellae was prominent and pyriform in shape (Figure 5). The isolate matched with a *Rhizomucor pusillus* (Lindt) Schipper strain in all essential characteristics.

The same result was obtained on other left and right BAL samples collected five days after, confirming the pathogenic role of isolate.

**Susceptibility testing**

Susceptibility test was made according to CLSI guideline using broth dilution antifungal susceptibility testing (YeastOne, Trek Diagnostics Systems, Cleveland, OH) that showed: amphotericin B 0.12 µg/mL, voriconazole 4 µg/mL, itraconazole 0.25 µg/mL, and posaconazole 0.12 µg/mL (3).

**DISCUSSION**

The incidence of opportunistic mycoses, especially pulmonary invasive mycoses, has increased over the past fifteen years, due to several factors, like the longer survival of immunocompromised patients and advances in laboratory techniques. *Rhizomucor* is the most common genus causing human *Mucorales* infections in immunocompromised patients, even if it is often associated with animal diseases [4-6].

Haematological malignancies, in particular acute leukaemias, and stem cells transplantation (causing prolonged and profound neutropenia), are the most common underlying predisposing conditions in patients with *R. pusillus* infections, representing about 70% of the cases, with a mortality rate of about 50% [7].

Isolates of *Rhizomucor* spp. can be found worldwide; it commonly contaminates air, soil, water and organic matter [8, 9]. Conidia can easily be airborne and reach the pulmonary alveoli because of their small size (Ribes); they have been isolated from indoor air in hospitals worldwide [2, 10-13].
As far as pathogenicity is concerned, *R. pusillus* is very aggressive due to its angioinvasivity causing thrombosis, haemorrhage and tissue infarction, and a consequent high risk of disseminated infection, particularly on CNS sites [8].

In our specific case, the patient showed a large pulmonary lesion with cavitation, followed by a severe acute bleeding from pulmonary airways. We cannot demonstrate that concomitant acute bacteriological endocarditis was also caused by *R. pusillus* since we know that cardiovascular system infections are very rare, and that the specific diagnosis (of any site) requires biopsy with histopathological identification and culture. *Rhizomucor pusillus*, like all *Mucorales*, is inherently resistant to fluconazole and voriconazole, so patients need to be treated with amphotericin B, sometimes for a few months. We can use alternative antifungal therapy with posaconazole if amphotericin B therapy is contraindicated or if toxicity occurs. Surgical resection has also been necessary in our case because of the persistence of residual pulmonary lesions.

The combination of antifungal specific therapy and surgery improves outcome, particularly in patients with a very aggressive disease; this approach is strongly recommended if large necrotic lesions are present [14, 15].

There are no specific and certain recommendations about primary or secondary prophylaxis for these infections.

Keywords: *Rhizomucor pusillus*, opportunistic infection, bacterial endocarditis.

### SUMMARY

We describe a severe pulmonary invasive zygomycosis sustained by *Rhizomucor pusillus* and concomitant bacterial endocarditis in a woman diagnosed with acute promyelocytic leukaemia.

### REFERENCES


