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CASE REPORT

Invasive Pulmonary Fungal Infection Caused by the Fungus Spiromastix in an Immunosuppressive Patient

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Abstract

Invasive fungal infections (IFIs) are an important cause of morbidity and mortality, especially in patients with hematological malignancies and immunodeficiency. Although Aspergillus mold fungi are the most common cause of IFI in this patient group, it has been reported recently in various publications that rare molds may also be the cause. In this case report, an 80-year-old male patient with a diagnosis of acute myeloid leukemia who received remission induction chemotherapy, followed by liposomal Amphotericin B treatment after posaconazole prophylaxis, developed invasive pulmonary fungal infection with Spiromastix fungus mold and was treated successfully with voriconazole. Until today, two cases in which Spiromastix mold fungus was isolated as a causative agent have been reported in the literature, and our case is the first case reported from Turkey.

Keywords: Antifungal therapy; invasive pulmonary fungal infection; spiromastix spp.

Mold of the genus *Spiromastix*, renamed as *Spiromastigoides* in recent studies, belong to the order Onygenales (Euromycetes, Ascomycota). Although there are various species such as *Spiromastix warcupii, Spiromastix grisea, Spiromastix tentaculata, Spiromastix saturnispora* and *Spiromastix sphaerospora* in this genus, some species have been transferred to other species as a result of phylogenetic analysis. It is estimated that the pathogenicity of this fungus, which is isolated from soil and manure piles in various parts of the world, is low. However, it was stated by the researchers that it should be considered as an infectious agent in humans and animals, and it was emphasized that, in addition to the most common fungal agents, especially in the immunosuppressed patient group, unusually rare molds could also be the infection factor[1-3]. In this report, a case of invasive pulmonary fungal infection with *Spiromastix* mold in an immunosuppressed patient is presented.

Case Report

An 80-year-old male patient, who applied to the Internal Medicine Clinic of Istanbul Medeniyet University Göztepe Training and Research Hospital with complaints of fever

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and malaise that had been going on for three days, had a history of surgery and radiotherapy for prostate cancer six years ago. The patient, whose blood tests revealed WBC: 55400/mm^3 and neutrophil: 330/mm^3, was transferred to the hematology clinic, after the bone marrow biopsy result was compatible with the diagnosis of acute myeloid leukemia (AML.) Remission induction chemotherapy and posaconazole (POS) 3×200 mg/day oral suspension for antifungal prophylaxis were started. The patient, whose fever continued, complained of rectal pain on the 5th day of chemotherapy. Physical examination revealed perianal tenderness and edema. The patient with blood WBC: 100/mm^3, neutrophil: 10/mm^3, CRP: 7.8 mg/dl was treated with meropenem 3×2 gr IV, daptomycin 1×6 mg/kg IV empirically after blood cultures were taken with the diagnosis of perianal cellulitis according to the febrile neutropenia protocol. High-resolution computed tomography (HRCT) was performed in the patient who had a nonspecific nodular lesion in the lateral right lung middle lobe in the posteroanterior (PA) chest X-ray taken during the first admission to the hospital. In HRCT, a small-scale non-specific nodular lesion was observed in the same region, consistent with the PA radiography. Two consecutive galactomannan (GM) tests (Platelia Aspergillus EIA; Bio-Rad, France) were negative. *E. faecium* reproduction was detected in two simultaneous blood cultures taken during the febrile period, and the fever decreased on the 3rd day of antibiotic therapy. On the 10th day of antifungal prophylaxis, dysphagia and diarrhea started. Physical examination revealed candidal plaques in the mouth. POS prophylaxis was discontinued and empirical Liposomal Amphotericin B (LAmB) 1×3mg/kg/day antifungal treatment was started. In the control HRCT of the patient who had fever again on the 12th day of LAmB treatment, a 2.5 cm diameter nodule in the lateral segment of the right lung middle lobe, with an air-crescent appearance in the middle (progression in the existing lesion), and three newly emerged nodules of various sizes in the right lung and pleural effusion, and ground glass densities were observed in both lungs (Fig. 1). During this period, a sputum sample was sent to the microbiology laboratory. Two consecutive GM tests performed at this time were positive (≥0.5 ng/mL) (2.41-1.63). With the prediagnosis of invasive pulmonary aspergillosis (IPA), the patient's LAmB treatment was discontinued and antifungal treatment was continued with 2×4mg/kg/day voriconazole (VOR), after loading 2×6 mg/kg/day. His fever subsided on the second day of VOR treatment. Spiromastix sp. grew in the sputum culture. Antibiotherapy was discontinued when neutropenia improved and perianal cellulitis sign regressed on the 23rd day of chemotherapy. The patient was discharged with VOR 200 mg 2×1/day oral treatment. Antifungal therapy was terminated in the patient whose radiological findings completely regressed in the third month of VOR treatment (Fig. 2). No fungal infection findings were observed in the six-month follow-up after discharge.

In the microscopic examination of the sputum sample sent to Istanbul Public Hospitals Services Directorate-2, Hospitals Union Central Microbiology Laboratory for examination, in addition to specific hyphal structures, structures forming an appearance similar to pea granules were observed in the preparation stained with Giemza. The clinical specimen was cultured on Sabouraud dextrose agar (SDA; Biomerioux, France), potato dextrose agar (PDA; Oxoid, UK), and brain heart infusion agar (BHIA; BD, Germany) and incubated at 25°C and 35°C. On the 14th day of incubation, hyaline mold growth was observed in SDA with cottony white surface, colorless-pale yellow color on the back (Fig. 3), and macroscopically white-light brown surface, and a light brownish base color in PDA (Fig. 4). In the microscopic examination of the preparation prepared by using lactophenol cotton blue, hyaline arthroconidium structures including ghost ("disjunctor") cells were observed as well as vegetative hyphae (Fig. 4). The mold isolated due to this appearance was sent to the "Westerdijk Fungal Biodiversity Institute, Utrech, Netherlands" fungal diagnosis center for further identification in case of possible coccidioidomycosis. As a result of the phenotypic and genotypic analyzes made here, the mold *Spiromastix spp.* was defined (identification number: CBS 141512).

Discussion

Neutropenia developing during remission induction chemotherapy applied to patients with hematological malignancies such as AML and myelodysplastic syndrome (MDS) is the most important risk factor for the development of invasive fungal infection (IFI)[4,5]. The most frequently detected mold fungi in these patients are *Aspergillus spp., Zygomycetes* species and *Fusarium spp.*; however, it has been stated that molds, which have been rarely isolated recently, may also be the causative agent of IFI[3,6]. In this case, *Spiromastix* mold fungus was isolated from the sputum sample of the patient who developed invasive pulmonary fungal infection under LAmB treatment following remission induction chemotherapy and POS prophylaxis due to AML.

In patients with febrile neutropenia, pulmonary infiltrates may occur during follow-up in 15-25% of patients with fever exceeding 72-96 hours despite empirical antibiotic therapy, and they can be radiologically visualized. While

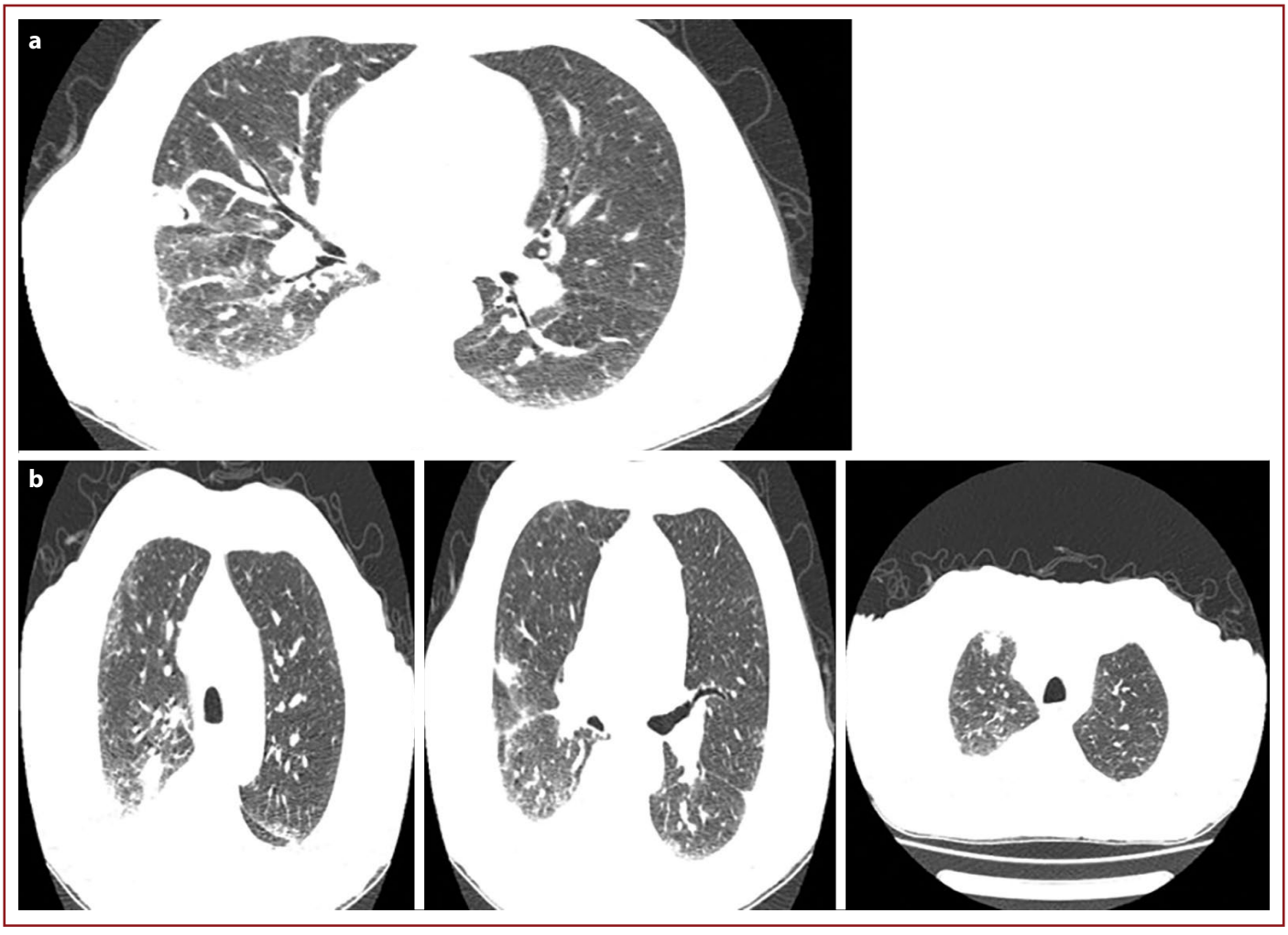

Figure 1. (a) Nodule with a diameter of 2.5 cm in the lateral segment of the right lung middle lobe with an air crescent appearance in the middle (progression in the existing lesion), **(b)** Three different newly emerging nodules and pleural effusions in various sizes in the right lung, and ground-glass densities in both lungs at various locations.

pulmonary infiltrates can be detected at low rates with conventional x-ray radiography in this patient group, this rate rises up to 50% in CTs examined simultaneously. Therefore, HRCT is preferred in the follow-up of fungal infections. In HRCT, especially halo sign and air-crescent findings give important clues in terms of IPA and other fungal agents. However, both radiological images can be detected in non-infectious conditions as well as in fungal and non-fungal infections[7-9]. In our case, a nonspecific nodular lesion was detected in the lateral side of the middle lobe of the right lung in the PA chest X-ray taken during the first admission, and a small-scale non-specific nodular lesion was observed in the same region in HRCT, consistent with the PA chest X-ray. It was unclear how long this lesion had existed since the patient's previous chest radiographs were not available. In the later HRCT of the patient, a 2.5 cm diameter nodule in the lateral segment of the right lung middle lobe, with an

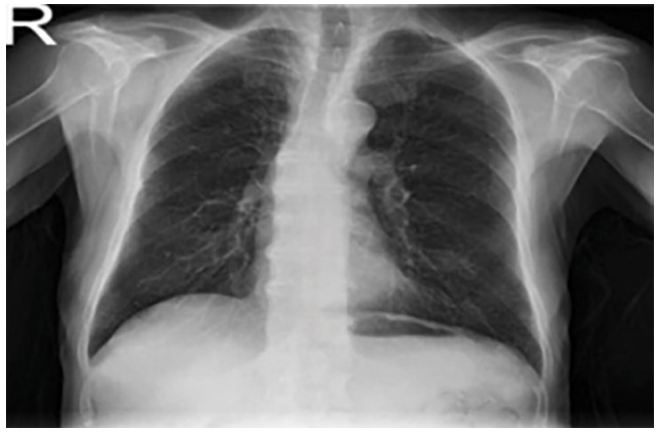

Figure 2. X-ray appearance in the third month of voriconazole treatment.

air-crescent appearance in the middle (progression in the existing lesion), and three newly emerged nodules of vari-

Figure 3. *Spiromastix* sp. growth after 14 days of incubation at 25°C in SDA.

SDA: Sabouraud dextrose agar.

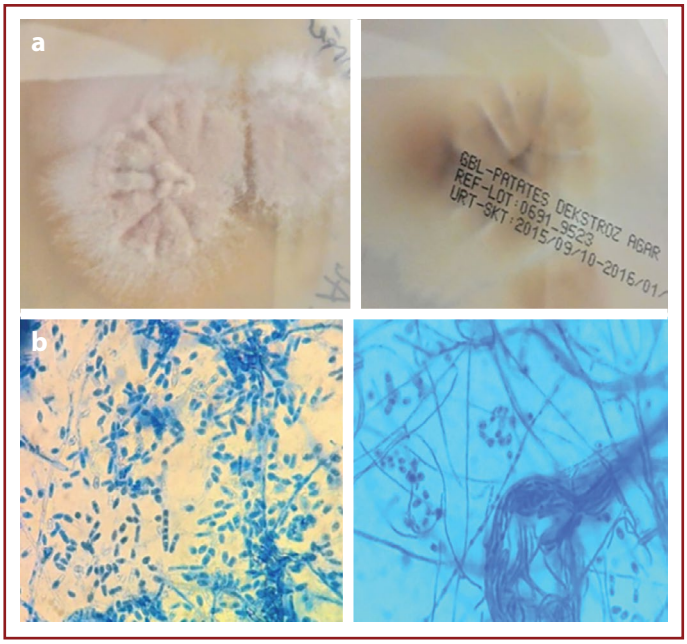

Figure 4. *Spiromastix* sp. **(a)** Macroscopic view in PDA after 14 days of incubation at 25°C, **(b)** Microscopic view of arthroconidium structures.

PDA: Potato dextrose agar.

ous sizes in the right lung and pleural effusion, and ground glass densities were observed in both lungs (Fig.1).

GM is a serological test found in the cell wall of especially Aspergillus genus and some other hyaline mold fungi (*Fusarium, Penicillium, Paecilomyces*) and used especially in the diagnosis and treatment follow-up of invasive aspergillosis (IA). Although the application area of the GM test is the diagnosis of IA, it has been reported in the publications that it cross-reacts with rare mold fungi[10,11]. In this case, GM values, which were negative at the beginning, were found to be positive (≥0.5 ng/mL) (2.41-1.63) two times consecutively in the following periods, and became negative again after VOR treatment. This elevation in the GM test was thought to be due to *Spiromastix* infection.

Antifungal prophylaxis is strongly recommended during remission induction therapy of AML/MDS patients. Studies have shown that prophylaxis with POS reduces mortality in this patient group, and the use of 600 mg/day during chemotherapy has become a standard practice[12]. However, an infection that develops four days later or more following the use of antifungal medication that was started primarily is considered a breakthrough infection. Although *Aspergillus* and *Candida* species are the leading agents in the infections developing in this patient group, the factors may change depending on the antifungal drug administered, the control of the underlying disease, and the local epidemiology, and breakthrough infections caused by other rare agents during the use of antifungals are becoming increasingly important[13-15]. In our case, POS was started prophylactically with chemotherapy, but treatment with LAmB was continued because of the mucositis and diarrhea that developed in the patient. Despite this, the patient's clinic progressed and antifungal therapy was replaced with VOR. Clinical improvement was achieved as a result of this treatment.

Mold fungus of the genus *Spiromastix* has been isolated from soil and manure piles in various regions of the world, such as Africa, Australia, the Middle East and South East Asia[2,16]. Today, in parallel with the developments in the field of molecular mycology, the diagnostic possibilities of such rare molds have increased and they have begun to be defined as infectious agents in humans and animals from clinical samples[17]. This mold fungus was first isolated from biopsy material taken from intervertebral discs during discospondylopathy in a German wolfhound and was defined as *Spiromastix* genus according to its morphological features and molecular analysis results[2]. For the first time in humans, it has been reported by Stchigel et al.[1] that the molecular and phenotypic analyzes of the mold isolated from lung biopsy material was *Spiromastigoides asexualis*. Our case is also the first case reported from our country.

In the microscopic examination of the mold fungus isolated from the patient, a possible coccidioidomycosis infection was initially suspected due to hyaline arthroconidium (Fig. 2) structures, and the case was evaluated in terms of

coccidioidomycosis, which has become a more common and important infection factor with the increasing international travels[18]. In general, the transmission route of endemic mycoses is by inhalation of infectious conidia after environmental and soil contact. Most of the time, infections are silent in immunocompetent individuals, while re-activation of the disease can be observed when the individual lives in an area where the fungus is not endemic and the immune system is suppressed[19]. For this reason, questioning patients with immunodeficiency in terms of short and long-term residence and travel places will guide the differential diagnosis of endemic mycoses, which have latent periods ranging from a few weeks to several years, as a possible factor[18,20,21]. When the travel history of our case was investigated, they stated that they had traveled all over the countries of North Africa, the Middle East and Southern Europe with a caravan during the summer months for about forty years, and sometimes they were in very dusty environments. The fact that the *Spiromastix* genus mold was also detected in the soils of this region suggested that the patient may have encountered this agent during travels, and it was concluded that the travel history should be questioned in the diagnosis.

As a result, the effectiveness of the antifungal agent applied in immunosuppressive patients should be closely monitored, and care should be taken in terms of breakthrough infections (developing under treatment) caused by rare molds that show primary or secondary resistance to the drug used. In addition, it should be kept in mind that IFI may be caused by common factors as well as other rare molds in patients in the risk group today, and laboratory results should be evaluated together with clinical and radiological imaging methods.

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Informed Consent: Written informed consent was obtained from the patients' family for the publication of the case report and the accompanying images.

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Conflict of Interest: None declared.

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