

**CASE REPORT**

## **Acute invasive rhinosinusitis case caused by *Aspergillus flavus* in two patients prediagnosed with mucormycosis**

Müge Aslan<sup>1</sup>, Yasemin Öz<sup>2</sup>, Özcan Bor<sup>3</sup>, Eren Gündüz<sup>4</sup>, Filiz Akşit<sup>5</sup>

<sup>1</sup> Microbiology Laboratory, Yozgat State Hospital, Yozgat, Turkey

<sup>2</sup> Department of Microbiology, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey

<sup>3</sup> Department of Child Health and Disease, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey

<sup>4</sup> Department of Hematology, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey

<sup>5</sup> Retired lecturer, Eskişehir, Turkey

### **ABSTRACT**

Acute invasive rhinosinusitis caused by *Aspergillus* spp. may lead to invasive disease and mortality, especially in immunocompromised individuals. In this report, two invasive fungal rhinosinusitis cases in an immune compromised patient have been presented that were pre-diagnosed with mucormycosis, but with a positive culture for *Aspergillus flavus*. Twenty-four years old male patient with aplastic anemia and seven years old patient with acute lymphoblastic leukemia; facial pain, edema, and necrotic lesions developed in both cases. Tissue samples were obtained from lesions through the nose by biopsy for definitive diagnosis. Septate fungal hyphae observed on the microscopic examination of the specimen, and *A. flavus* was isolated in the culture in both cases. Surgical debridement could not be performed because of patients' general conditions. Despite antifungal therapy and treatments, patients died. Delay in diagnosis and treatment may lead to high mortality rates. These cases emphasize the importance of diagnosis with culture. *J Microbiol Infect Dis* 2015;5(3): 137-141

**Key words:** Acute invasive fungal rhinosinusitis, *Aspergillus flavus*, diagnosis.

## **Mukormikoz öntanıli iki olguda *Aspergillus flavus*'un neden olduğu akut invaziv rinosinüzit enfeksiyonu**

### **ÖZET**

*Aspergillus* türlerinin neden olduğu akut invaziv fungal rinosinüzit; immünsüprese hastalarda mortaliteye yol açabilir.

Rinoserebral mukormikoza klinik olarak benzediğinden mukormikoz ön tanısı almış ancak kültürde etken olarak *Aspergillus flavus* üretilmiş iki invaziv fungal rinosinüzit olgusu bu raporda sunulmuştur. Aplastik anemi tanısıyla takip edilen 24 yaşındaki erkek hasta ve akut lenfoblastik lösemi tanısıyla izlenen yedi yaşındaki kız çocuğunda yüzde ağrı, ödem, ve burun çevresinde nekrotik lezyonlar mevcuttu. Antifungal tedaviye rağmen burunda nekroz gelişti. Tanı amacıyla burundaki lezyondan alınan biyopsi örneğinin mikroskopik incelemesinde septalı hifler görüldü ve kültürde iki olguda da *A. flavus* izole edildi. İki olgumuzda da gerekli tedaviler yapılmış olup cerrahi debridman hastaların genel durum bozukluğu nedeniyle yapılamadı ve antifungal tedaviye rağmen hastalar kaybedildi. İnvaziv fungal enfeksiyonlarda erken tanı ve tedavi hayati önem taşımaktadır. Bu olgular, fungal enfeksiyonların tanısında ve tedaviyi doğru şekilde yönlendirebilmede kültürün önemini vurgulaması açısından önemlidir.

**Anahtar kelimeler:** Akut invaziv fungal rinosinüzit, *Aspergillus flavus*, tanı

### **INTRODUCTION**

Invasive fungal rhinosinusitis, being the infiltration of the mucosa of the nasal cavity and paranasal sinuses by fungal pathogens, a subtype of which is encountered less often and having a mortal course

with a rapid progression, is referred to as acute invasive fungal rhinosinusitis (AIFR). AIFR may metastasize to the orbit or the cavernous sinus and cerebral parenchyma via the vasculature in immunosuppressed patients, presenting with progressive a course. The allergic grounds and mucosal

**Correspondence:** Müge Aslan, Yozgat State Hospital, Microbiology Laboratory, Yozgat, Turkey  
Email: drmucu@hotmail.com

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thickening look seem to be the main predisposing factors in these patients. Long term antibiotherapy, steroid use, chronic bacterial sinusitis, presence of diseases such as uncontrolled diabetes mellitus, haematological malignancies with suppression or collapse of the immune system, patients receiving chemotherapy subsequent to bone marrow transplantation or aplastic anemia also constitute an important place in the risk group.<sup>1-7</sup>

The most frequently determined agents are *Aspergillus* spp. and the fungi in *Mucorales* species. It may abruptly result in death by virtue of vascular invasion by the pathogen and the resultant thrombotic ischemia. It is postulated to have a mortality rate in a range between 50-80%.

Here, two invasive fungal rhinosinusitis cases have been presented that were prediagnosed with mucormycosis, but with a positive culture for *A. flavus*, because it clinically resembles rhinocerebral mucormycosis in which ischemia and necrosis remain at the forefront as a result of angio-invasion, which is clinically more precise within *Mucorales* members.

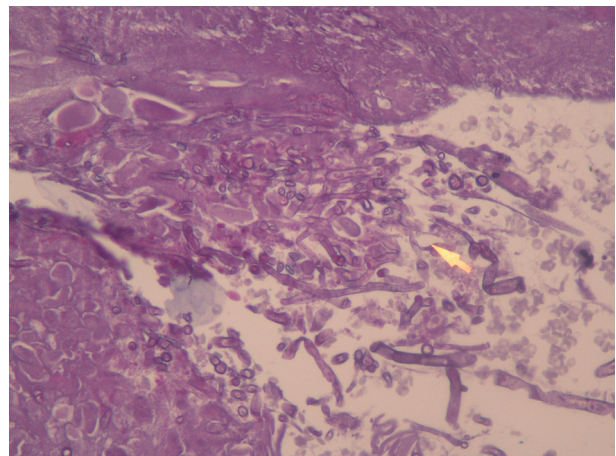
### CASE 1

With an onset on the 37th day of hospitalization of a 24-year-old male patient with febrile neutropenia followed-up at the Haematology clinic diagnosed with aplastic anemia, swelling and hyperemia developed on the left side of his face with concomitant epistaxis on 30th day. In the laboratory examination of the patient, the white blood cell count was determined as 13.1 K/uL (4.4-11.3); Hb, 8.9 g/dl (12.3-15.3); platelets, 607 K/uL (150-450); fasting blood glucose, 284 mg/dl (70-115); urea 72 mg/dl (10-50); creatinine 1.68 mg/dl (0.6-1.3), erythrocyte sedimentation rate, 87mm/h (0-12); and CRP, 16 mg/L (0-5). He received Piperacillin/Tazobactam and amikacin ten days followed by imipenem and teicoplanin. 200 mg oral Voriconazole initiated on 40th hospitalization day; but changed it to i.v liposomal Amphotericin B 300mg/day; because of fever persistence and soft tissue density suggestive of fungal infection was observed in the left maxillary sinus on the paranasal magnetic resonance imaging (MRI) examination and on day 48 (Figure 1). Ubiquitous crusts through the nasal passage, black skin lesions and nasal necrosis developed despite antifungal therapy. Taking into consideration the mucormycosis, biopsy was conducted on the lesion with the purpose of definitive diagnosis and subsequently, the treatment was switched to posaconazole (4 x 200 mg/oral form) on 60th hospitalization

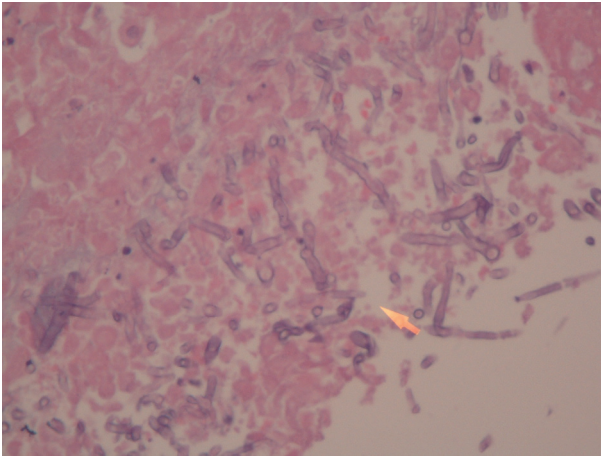
day. Structures with septate hyphae were observed on the microscopic examination of the biopsy specimen (Figure 2-3). *Aspergillus flavus* was isolated from the culture of this specimen (Figure 4). The results of in vitro antifungal susceptibility with E test method were found to be 6.00, 1.00, 4.00 µg/mL for amphotericin B, voriconazole and itraconazole, respectively. With regard to this case, GM antigen was detected positive consecutively two times (0.58 and 0.62 indexes) on 65 and 69th day; which was performed within the varying intervals of hospitalization. Surgical debridement could not be performed due to the patient's general condition, and he died on the 75th day of hospitalization.



**Figure 1.** Brain magnetic resonance imaging (T1-weighted, transversal view) shows a soft tissue density in the left maxillary sinus.



**Figure 2.** Fungal hyphae in the chronically inflamed stroma and the lumens of small diameter vessels on the histopathological examination carried out by PAS staining (x400).



**Figure 3.** Fungal hyphae on the necrotic background on the histopathological examination carried out by H & E staining (x400).



**Figure 4.** Three-day *A. flavus* colonies in SDA

## CASE 2

In a 7-year-old patient followed-up in the pediatric haematology clinic, diagnosed with refractory and relapsing acute lymphoblastic leukemia (ALL), in the period of febrile neutropenia, a necrotic lesion appeared that was suggestive of mucormycosis on the right side of the nose in addition to swelling of the right eye and edema on the right side of her face. She received Piperacillin/Tazobactam and amikacin fourteen days followed by an imipenem. The results of paranasal and orbital MRI carried out for the diagnosis were consistent with fungal infection. Liposomal amphotericin B (5 mg/kg intravenously daily)

treatment was initiated on 45th day, but surgical debridement could not be performed because the patient's general condition was impaired. Suggestive of the prediagnosis of mucormycosis, a tissue sample was obtained from the lesion through the nose by biopsy for the purpose of the definitive diagnosis. Septate fungal hyphae were observed on the microscopic examination of the specimen and *A. flavus* was isolated in the culture on 57<sup>th</sup> day. The results of in vitro antifungal susceptibility test with E test were found to be 0.047, 0.25 and 0.047 µg/mL for amphotericin B, voriconazole and itraconazole, respectively. GM positivity detected one time with 0.52. The patient died on the 62th day of the infection in spite of the chemotherapy, broad spectrum antibacterial and antifungal therapy.

## DISCUSSION

Intensive and prolonged term use of modern chemotherapeutics in haematological malignancies during the recent years has ensured successful results in primary disease. On the other hand, long term neutropenia, which is induced by chemotherapy, increases the incidence of invasive fungal infections in these patients. The majority of the cases with acute fulminant sinusitis presented in the literature are comprised of patients with haematological malignancies. One of our patients was followed-up with the diagnosis of aplastic anemia, and the latter had ALL. When nasal cavity and paranasal sinuses are affected by invasive fungal infections, first, mucosal paling depending on ischemia and subsequently, gray discoloration and black crusts will be observed depending on the necrosis. The commonly encountered symptoms are fever (44%), nasal ulceration and black necrotic tissue in the nose (38%), periorbital and facial edema (34%), vision disorders (30%), headache (25%), and facial pain (22%). While headache was present in one of the cases on presentation, proptosis, fever, nausea and periorbital cellulitis developed during the following days. Facial pain, edema, vision disorders and necrotic lesions were present in both cases.

The use of radiological imaging methods, CT and MRI demonstrate an infiltration, destruction and frequently, invasion to the contiguous tissues. However, these findings may be confounded by other factors such as mucormycosis, vascular diseases, and benign/malignant tumors.<sup>5,8-10</sup> It has been pointed out that the soft tissue lesion filling the sphenoidal sinus and destroying the bone structure and also extending to the nasal cavity and supracellular

cisterna on MRI examinations of our cases may be consistent with fungal infection. Most patients do not have classic findings in the early phase of infection.

With regard to the definitive diagnosis, it is made by observing fungal hyphae in the tissue specimens. Biopsy sampling must be conducted on suspected nasal or oral mucosal lesions. Tissue samples must be received if possible and stains such as hematoxylin and eosin (HE), Gomorimethenamine silver (GMS) and periodic acid-Schiff (PAS) are useful for identifying the fungi. Furthermore, the sample must be cultured in a suitable medium. The diagnosis in our cases was made by reproducing the agent and in one case by observing fungal hyphae histopathologically. In both cases, *A. flavus* was reproduced as the etiologic agent.

It has been reported that studying GM antigen may be helpful for the early diagnosis of invasive fungal infections.<sup>9</sup> In both cases, GM antigen was detected as positive, which was performed within the varying intervals as from the time of hospitalization.

Early and aggressive treatment is required in invasive fungal sinusitis. Since the acute fulminant disease may result in death within days or even hours, debridement of the overall necrotic tissue is recommended right after diagnosis in order to diminish the fungal burden. It is ascertained that amphotericin B (AMB) intravenously and treating the underlying disease is complementary to surgery and bringing the ketoacidosis under control rapidly in patients with diabetes mellitus enhances survival. It has been reported that although amphotericin B treatment of sinusitis by *Aspergillus* spp. in patients with leukemia, there are studies in which alternative antifungal agents are used.<sup>11</sup> In the literature, the survival rates vary depending on the underlying etiology, ante-mortem diagnosis, and treatment.<sup>1,3,6</sup>

In both of our cases, the treatments required for haematological diseases, which were considered predisposing conditions, were applied. Surgical debridement could not be performed due to impairment in the patients' general conditions, and the patients died despite the systemic amphotericin B treatment.

In conclusion, acute invasive fungal rhinosinusitis is a severe infection affecting immunodeficient individuals, and it has a fatal course. The agents are frequently the fungi which are members of the *Aspergillus* and *Mucorales* species. Both fungal agents display similar clinical features. We also pre-diagnosed our cases as mucormycosis with clinical

signs and symptoms. For this reason, microscopy and culture should be performed for the definitive diagnosis. Radiology, direct microscopy, and histopathological examination carried out for fungal infection.

Compared to mucormycosis, which involves non-septate hyphae and right-angle branching, aspergillosis shows septate hyphae with 45 branches. However, other hyalohyphomycetes, for example, *Fusarium*, and *Pseudallescheria boydii*, have similar histological characteristics to *Aspergillus*. Microbiological cultures provide a definitive diagnosis and distinguish other possible fungal pathogens. Not only *Mucorales* spp. are resistant most of antifungal agents but also *Aspergillus* spp. are susceptible some of them. In presented cases, *A. flavus* was isolated from the culture, and antifungal susceptibility test performed. It was most important point of these cases; because of definitive diagnosis and treatment strategy of fungal rhinosinusitis. The nonspecific onset of the infections, rapid and fatal course, and the impairment in the patients' general conditions are the most important reasons for limitation of diagnosis. Symptoms and signs such as nose ulceration, eschar of the nasal mucosa, black necrotic lesions are more specific, but these findings are present only at an advanced stage. When the manifestations of sinusitis are viewed in patients with immunosuppression, fungal sinusitis must be taken into consideration.

These cases are important to emphasize the significance of culture in the definitive diagnosis of fungal infections.

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