Case Report

Fatal post-traumatic zygomycosis in an immunocompetent young patient

Marina Kontogiorgi,¹ Ioannis Floros,¹ Apostolos Koroneos,¹ Chrysanthi Vamvouka,² Olga Paniara,³ Charis Roussos¹ and Christina Routsis¹

Correspondence
Christina Routsis,
croutsis@hotmail.com

¹Critical Care Department, Medical School of Athens University, Evangelismos Hospital, Athens, Greece

²Department of Pathology, Evangelismos Hospital, Athens, Greece

³Department of Clinical Microbiology, Evangelismos Hospital, Athens, Greece

Received 8 October 2006

Accepted 5 March 2007

Zygomycosis, a relatively uncommon infection, usually occurs among immunocompromised individuals. It has been reported only rarely in trauma patients. A fatal case is reported of pulmonary and rapidly progressive cutaneous zygomycosis in a young, otherwise healthy farmer, with multiple bone fractures, wounds and soft tissue injuries after an accident with an agricultural machine in the field. *Rhizopus* spp. was isolated from both cultures of bronchial washings and wound samples. The diagnosis was confirmed by histopathological examination of tissue specimens from a large wound. Despite systemic antifungal therapy and surgical debridement, the patient's condition deteriorated and he died from refractory septic shock.

Introduction

Zygomycosis, an opportunistic invasive infection caused by fungi of the class *Zygomycetes*, specifically orders *Mucorales* and *Entomophthorales*, is an uncommon disease, mainly confined to patients with haematological malignancy, organ transplantation, uncontrolled diabetes mellitus or other circumstances resulting in immunosuppression (Ribes *et al.*, 2000; Walsh *et al.*, 2004). Although the frequency of zygomycosis has been increasing over the past 10 years, there are only a few reports of this infection in immunocompetent patients. We report a fatal case of zygomycosis due to *Rhizopus* spp, causing necrotizing fasciitis in a young, otherwise healthy, trauma patient with multiple bone fractures and soft tissue injuries.

Case report

A 25-year-old, previously healthy male farmer was transferred to our hospital after he had been crushed by an agricultural tractor, when it was overturned while working in the fields. The emergency department evaluation revealed multiple open fractures of the right thighbone and the tibia, right hand (supracondylar humerus and ulna fractures), first-degree burns and multiple lacerations, abrasions and contusions throughout his body, and a large open wound in the right thigh. All wounds were contaminated with soil and organic material. Head and chest radiological examinations, including

computed tomography (CT) scans, were normal. Stabilization of bone fractures was performed in an emergency surgery, followed by wound debridement.

Postoperatively the patient was admitted to the intensive care unit and was mechanically ventilated, he was haemodynamically stable, and sedated with 2–4 mg propofol $\text{kg}^{-1} \text{h}^{-1}$ and 0.1–0.5 μg remifentanyl $\text{kg}^{-1} \text{min}^{-1}$. Arterial blood gas analysis on a fraction of inspired O_2 (FiO_2) of 0.4 showed pO_2 174 mmHg, pCO_2 33 mmHg and pH 7.41. The main laboratory findings were: 9.6 g haemoglobin dl^{-1} , 5500 white blood cells ml^{-1} , 100 000 platelets ml^{-1} , 27 786 U creatine kinase l^{-1} , 22 U glutamic oxaloacetic transaminase l^{-1} and 25 U glutamic pyruvic transaminase l^{-1} . The patient received empirical antibiotic therapy, including 5.2 g ticarcillin/clavulanic acid every 8 h, 600 mg clindamycin every 6 h and 400 mg ciprofloxacin every 12 h. On day 3 in the intensive care unit a chest X-ray showed atelectasis of the right upper lobe (Fig. 1) and a marked hypoxemia was noted; pO_2 was 60 mmHg and pCO_2 44 mmHg at FiO_2 0.1. Atelectasis was resolved by fibre-optic bronchoscopy, which revealed purulent material in the corresponding bronchus. Culture of the bronchial washings, on Sabouraud dextrose agar, yielded fungus. Microscopic examination of growth, using lactophenol cotton blue, revealed the presence of nonseptate broad hyphae with nondichotomous, irregular branching, at right angles, and well developed rhizoids, indicative of *Rhizopus* spp. In addition, *Candida* spp. and a few colonies of Gram-negative bacteria were cultured. Liposomal amphotericin B (4 mg kg^{-1} per day) was immediately started. However, the patient's clinical

Abbreviation: CT, computed tomography.

Fig. 1. Chest X-ray showing atelectasis of the right upper lobe of the lung.

condition gradually deteriorated with fever up to 39 °C and hypoxemia. Chest X-ray and CT scan revealed the reappearance of atelectasis, bilateral pleural effusion and diffuse pulmonary infiltrates. A second bronchoscopy disclosed again purulent secretions and haemorrhagic mucosa with oedema in both main and subsegmental bronchi. Again, the bronchoalveolar lavage fluid culture revealed *Rhizopus* spp., *Aspergillus* spp. and Gram-negative bacteria. The dose of liposomal amphotericin B was increased to 8 mg kg⁻¹ per day.

Additionally, at the same time compartment syndrome developed in the right leg, where the large open wound was, requiring fasciotomy (Fig. 2). Wound samples culture showed multiple pathogen growth, including *Rhizopus* spp., *Aspergillus* spp., *Enterococcus faecalis* and Gram-negative bacteria. Debridement was carried out once or twice daily. Despite the multiple surgical debridements and antibiotic treatment against the pathogens isolated, the wound gradually deteriorated. The wound margins turned

Fig. 2. View of the patient's large infected wound in the right thigh with necrotic margins; a fasciotomy incision is visible on the outer side of the thigh.

violaceous, and the skin and subcutaneous tissue became necrotic. Histopathological examination of excised tissue specimens showed extensive necrosis and invasion of the vessels, and the presence of broad aseptate hyphae with right-angle branching, consistent with the morphology of *Zygomycetes* (Fig. 3). A human immunodeficiency test was negative. Despite the supportive care, surgical debridements, and antibiotic and antifungal treatment, the patient's condition deteriorated, and he died from refractory septic shock on the 19th day post-trauma.

Discussion

Zygomycosis typically occurs in patients with leukaemia, solid organ or bone marrow transplants, diabetes mellitus, neutropenia or who are undergoing treatment with steroids. *Zygomycetes*, especially *Mucorales*, are widespread in nature, subsisting on decaying vegetation and diverse organic materials. The most common route of transmission is inhalation of spores from the environment. For this reason rhinocerebral and pulmonary zygomycosis are the usual types of this infection in immunocompromised patients, followed by gastrointestinal, cutaneous and disseminated infection (Ribes *et al.*, 2000; Walsh *et al.*, 2004).

Although *Mucorales* show minimal intrinsic pathogenicity towards immunocompetent persons, they can initiate

Fig. 3. Inflammatory infiltration of the muscle by mucor. Cells were stained with haematoxylin and eosin, and visualized at ×10 (a) and ×400 (b) magnification.

aggressive and fulminant infections under certain clinical conditions (Ribes *et al.*, 2000; Walsh *et al.*, 2004). *Rhizopus*, *Mucor*, *Rhizomucor*, *Absidia* and *Apophysomyces* are the most commonly encountered genera. In particular, cutaneous involvement was the presented pattern in 176/929 patients (19 %) in a review of all English language reports of zygomycosis. Penetrating trauma was reported for 60/176 (34 %) of these patients (Roden *et al.*, 2005). A direct entry of environmental fungi through superficial wounds at the time of the accident has been implicated.

The severity of cutaneous zygomycosis in otherwise healthy trauma patients with open wounds, ranges from contamination to extensive necrotizing fasciitis (Patino *et al.*, 1991; Cocanour *et al.*, 1992; Kordy *et al.*, 2004; Tang & Wang, 1998; Adam *et al.*, 1994; Johnson *et al.*, 1987; Song *et al.*, 1999; Andresen *et al.*, 2005). Reported cases include 8 patients with severe necrotizing fasciitis due to zygomycosis after a volcanic eruption in Colombia (Patino *et al.*, 1991), a collective series of 11 trauma patients with cutaneous involvement of diverse severity (Cocanour *et al.*, 1992) and other isolated reports. An additional case of zygomycosis, caused by *Apophysomyces elegans*, in a previously healthy patient, who developed necrotic and disseminated soft-tissue lesions after traumatic injury as a result of the tsunami that ravaged the Indian Ocean has been recently reported (Andresen *et al.*, 2005).

Pulmonary mucormycosis is very rare in the absence of an underlying illness (Lee *et al.*, 1999; Butala *et al.*, 1995; van Dam *et al.*, 2005). Isolated pulmonary mucormycosis, due to *Rhizopus* spp., in a previous healthy, young trauma patient with multiple injuries has been recently reported (Aboutanos *et al.*, 2003). It was suggested that he became prone to this infection, since the protective role of the pulmonary macrophages and neutrophils were compromised in the setting of pulmonary contusion that he had. The patient in the present case did not have signs of lung contusion in the chest X-ray and the CT scan on admission. However, the contribution of the relative immunosuppression that the multiple trauma brings about, and the direct contamination of the wounds with soil rich in organic material, may explain in part the fungal infection.

Lung tissue biopsy is necessary for the definitive diagnosis of pulmonary zygomycosis. Such an intervention was not done in our patient; therefore, there is no direct evidence of the pulmonary fungal infection. However, it could be considered that our patient, as a farmer, may have already had the upper respiratory track colonized by *Rhizopus* spp. before the accident. Since non-septate hyphae were found in both bronchial washings and bronchoalveolar lavage fluid cultures, fungal infection was highly likely.

In all mentioned studies of either cutaneous or pulmonary zygomycosis, the best outcome was obtained when the diagnosis was made early, aggressive surgical debridement was used and high doses of amphotericin B were given. Nonsurvivors usually had rapidly progressive infection, whereas survivors had minor disease. In our patient the

disseminated severe infection probably contributed to his fatal outcome.

In conclusion, rapidly progressive zygomycosis can occur in otherwise healthy individuals following trauma. A high level of clinical suspicion is important in any trauma patient, especially in the presence of open wounds and soft tissue injuries contaminated with soil, even in the absence of immunosuppression. Early recognition is essential in order to control this uncommon infection by combined surgical and medical therapy.

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