Invasive aspergillosis of the paranasal sinuses, lung and brain

Abstract
A case of invasive aspergillosis (IA) of paranasal sinuses, lung and brain with a fulminant fatal outcome is reported. A 43-year-old man with a history of skin carcinoma of the nasal region and a course of systemic corticosteroids, presented with symptoms of lung infection. Aspergillus fumigatus was cultured from respiratory and nasal samples. Erosion of adjacent bones of the nasal cavity was acknowledged, but no sinus surgery was performed. A computed tomography of the thorax showed thick-walled cavities of different sizes with air and scarce fluid levels in both lungs. Treatment with voriconazole was administered. The patient deteriorated in the ensuing 2 weeks because central nervous system involvement was observed. No aggressive surgical resection was performed and the patient died 2 weeks later. IA was not confirmed by histopathology because no necropsy was performed.

Key words: aspergillosis, fungal infection, lung infection, antifungal agents

Introduction
Invasive aspergillosis is a disease caused by filamentous fungi Aspergillus spp. in critically ill patients. The most common species is Aspergillus fumigatus, less common being Aspergillus flavus and Aspergillus niger. The majority of patients with invasive aspergillosis have an advanced malignant disease and underlying haematological disease, are in states of immunosuppression such as corticosteroids and cytotoxic therapy, after marrow or solid organ transplantation, with prolonged and profound neutropenia (< 100 cells/µl), with neutrophil dysfunction.

Case report
A 43-year-old man, with a history of skin carcinoma of the nasal region, was admitted to the Pneumonology Department from the Ophthalmology Department of the Medical University in Gdańsk in August 2006 to diagnose and treat multiple cavities within both lungs with suspicion of multiple lung abscesses. In March 2006 the patient was diagnosed with sweat gland carcinoma of the skin with extension of the disease to the nasal sinuses and orbits. Nonradical excision was performed, followed by radical teleradiotherapy (60 Gy/30 fr.). After the treatment the right eye was injured — a series of repair surgeries was done. A short period of systemic steroid therapy: dexamethasone 2 mg tid for 21 days was instituted to treat the oedema. This time the patient’s general condition was good. During a stay at the Ophthalmology Department, the first symptoms (nonproductive cough, high fever, dyspnoea) developed. A chest X-ray showed circular opacities (cavities) in both lungs, interpreted as multiple lung abscesses (fig. 1). Physical examination revealed crackles, and laboratory tests revealed: high CRP (298 mg/l), haemoglobin of 11.0 g/dl; white blood cell count of 8400/µl (90% neutrophils), arterial blood gas values were normal. Treatment with ceftazidime $2 \times 1.0$ g was started; next piperacillin/tazobactam $3 \times 4.5$ g IV was administered with no improvement. During bronchoscopy, a small volume of muco-purulent secretion
was sucked, and bronchial washings revealed florid *Aspergillus fumigatus* culture; other bacteria cultures and Mycobacterium tuberculosis microscopic examination were negative. Nasal discharge samples also grew massive *Aspergillus fumigatus*. Numerous subsequent specimens of blood and urine remained sterile. Serology for HIV was negative.

The deteriorating patient, with a high fever, was transferred to the Pneumonology Department.

Chest CT (fig. 2) revealed several-millimetre-thick cavities 3.5–9.5 cm (with minute septa) in both lungs; “white glass” and small nodules in the surroundings were present. Cefepime 2 × 2.0 g and voriconazole 2 × 0.2 g treatment was instituted with temperature normalization and improvement of general patient being. Blood morphology was stable: haemoglobin of 11.0 g/dl; white blood cell count of 10.8/µl (91% neutrophils) and CRP diminished to 15.5 mg/l. After a week’s stay in the ward, the first neurological signs appeared: headaches and progressive weakness of the left limbs.

Brain CT (fig. 3) showed 3 inflammatory tumours in both hemispheres (0.5–4.0 cm large) with oedema in the surroundings. Treatment with mannitol and furosemide was commenced. Despite voriconazole and cefepime (followed by ceftriaxone) treatment, the clinical condition of the patient deteriorated. Fever returned, the cough became intense and CRP levels increased to 60 mg/l and 197 mg/l. The next chest radiograph (fig. 4) showed thick wall cavities in both lungs; some regression alongside with progression of other cavities in comparison with the former radiograph.

Abdominal X-ray, ultrasonography and echocar-
diography did not show abnormalities. Laryngological examination revealed regrowth of the carcinoma in the nasal region.

At the beginning of October the neurological condition worsened: limbs and face automatisms, difficulty in swallowing, emotional lability appeared. Later, a comatose state supervened and soon the patient died. The family refused necropsy.

**Literature review**

Invasive pulmonary aspergillosis (IPA) is the most severe infection of the respiratory tract caused by fungi of the *Aspergillus* family. In 50% of patients, the disease is disseminated, affecting the brain, liver, kidneys and gastrointestinal tract. It is commonly a fatal disease that is seen in immunocompromised patients. Major risk factors for IPA are: haematological malignancy, solid organ and bone marrow transplantation, AIDS, corticosteroid (dose of 0.5 mg/kg/day prednisone for longer than 30 days) and cytotoxic therapy, and prolonged (for more than 3 weeks) and profound neutropenia (< 500/µl) lasting for over 20 days [1, 2].

Rarely, IPA is reported in apparently immunocompetent patients with advanced COPD treated with inhaled steroids, although the infection itself usually follows a short course of systemic corticosteroids [3–5]. There have been isolated cases of atypical pathogen pneumonias with respiratory insufficiency and fatal outcome because of concomitant fungal infection. Invasive aspergillosis of paranasal sinuses is a chronic disease, which is complicated by intraorbital or intracranial extension. Almost 60% of patients have an unfavourable outcome: no response to treatment, frequent relapses or death [6]. The treatment consists of complete
surgical evacuation (debridement) of fungi masses (performed 4 times on average in every patient) combined with antifungal therapy for many months [7]. 10–15% of IPA patients develop brain aspergillosis [8]. Mortality rate in immunocompromised hosts is very high reaching 95%, and in immunocompetent hosts — 40–65% [8]. The most common CNS aspergillosis is abscess or multiple fungal abscesses, which need to be differentiated from bacterial abscesses, tuberculosis meningitis and brain tumours. Infection reaches the brain directly from the nasal sinuses (esp. maxillary sinusitis) via vascular channels or in blood borne fashion from the lungs or gastrointestinal tract. Aspergillus hyphae invade the arteries and veins producing a necrotizing angiitis, secondary thrombosis and haemorrhage. Hemorrhagic infarcts convert into septic infarcts, evolving to abscesses and cerebritis. Radical surgical debridement can be curative if the extent of resection reaches uninvolved tissue. More often, stereotactic aspiration or drainage relieves mass effect, improves the efficacy of systemic or intraventricular drug treatment, and helps to set a definite diagnosis.

Clinical picture
Patients usually present with respiratory symptoms consistent with bronchopneumonia: fever (especially in patients with neutropenia), haemoptysis, pleuritic chest pain, cough, sputum production and dyspnea. The chest radiograph shows nonspecific changes consistent with bronchopneumonia, single/multiple rounded opacities, pleural-based infiltrates (pulmonary infarctions) and cavititation. Typical chest CT scan findings are multiple nodules, halo sign (zone of low attenuation due to haemorrhage surrounding the pulmonary nodule), the air crescent sign (crescent-shaped lucency secondary to necrosis).

Diagnosis
Mycoses Study Group proposed a working case definition of IPA [9] (tab. 1). The diagnosis of IPA is definite when tissue histopathology shows the hyphae or culture from lung tissue obtained by an invasive procedure such as transbronchial biopsy, percutaneous needle aspiration, or when open-lung biopsy is positive.

Sputum or BAL fluid positive culture is not proof of IPA because colonization of the bronchial tree by Aspergillus species is quite common — sensitivity is low: sputum 8–34%, BAL 45–62% [10]. Methods based on the detection of antifungal antibodies have low sensitivity in patients in a state of immunosuppression, so tests based on identifying fungal antigens or metabolites released into circulation, Aspergillus DNA detection by PCR-based molecular methods, are of great interest and importance. Galactomannan is a polysaccharide cell wall component of the Aspergillus and Penicillium species that is released into the circulation during fungal growth in the tissues. Different assays, starting with latex agglutination, radioimmunoassay, enzyme-linked immunosorbent assay inhibition and double-sandwich enzyme-linked immunosorbent assay, enable the detection of galactomannan at concentrations of 15 ng/ml to as low as 0.5 ng/ml, respectively [11]. Sensitivity in immunocompromised patients is 67–100%, specificity 86–99% [12]. The sensitivity of the test with serum in non-neutropenic patients is low (15–30%), but with BAL fluid it is high — 90% [11]. Another integral component of the cell walls of a number of pathogenic yeasts and filamentous fungi (Aspergillus, Candida, Fusarium and others) is glucan. The sensitivity and specificity of glucan assays are comparable to those of galactomannan [12]. PCR-based molecular methods, which detect Aspergillus DNA in blood or BAL samples, are very promising. Aspergillus may transiently colonize the respiratory tract; 25% of the BAL samples from healthy subjects are positive for Aspergillus by PCR. Blood-based PCR assays have a sensitivity of 79–100% and specificity of 81–93% [12].

Therapy
The outcome of therapy is dependent on recovery of the underlying host defence defect, such as the resolution of neutropenia or the tapering of...
immunosuppression therapy, intensive antifungal therapy for many weeks, sometimes surgical resection in cases of massive haemoptysis or residual localized pulmonary lesions in patients with continuing immunosuppression.

Usually antifungal therapy lasts 10–12 weeks; 4–6 weeks from when the disease is clinically/radiologically resolved.

The most widely used drugs in the treatment of IPA are amphotericin and azoles. In definite IPA, the drug of first choice is voriconazole [13] in possible amphotericin (voriconazole is not effective in Zygomycetes infection, which can mimic Aspergillus infection). In the treatment of brain aspergillosis, voriconazole results were better than amphotericin [14]. In table 2, the dosing and response rates of different medication therapy are shown.

Usually monotherapy is employed; the use of combination therapy has not been shown to be more effective. Although in resistant cases, a salvage therapy consists of amphotericin or voriconazole plus caspofungin [20].

### Discussion

The presented case study shows a patient who succumbed to paranasal sinuses and lung aspergillosis, followed by brain aspergillosis, with a fatal outcome. There were no typical risk factors of invasive aspergillosis development: long-standing, high-degree immunosuppression, widespread neoplastic disease, neutropenia, HIV infection or chronic lung disease (esp. COPD). Encountered risk factors were: corticosteroid therapy after ophthalmic repair surgeries in the dose 6 mg/day of dexamethasone (equal to 40 mg prednisone) for 21 days, radiotherapy and locally advanced skin cancer of the nasal region with extension to paranasal sinuses. The steroid dose was equal to 0.5 mg/kg/day prednisone, but the therapy course was shorter than 30 days, when the risk of infection increases substantially. Paranasal sinus necrotic tissue (debris) was a good medium to grow Aspergillus. According to the authors, the main reason for Aspergillus lung infection was massive, persistent inhalation of fungi conidia, and to a lesser degree blood borne dissemination.

Fast developing symptoms and antibiotic response after subsequent therapy, despite negative culture results of sputum and bronchial washings, suggested bacterial infection. Radiological studies and fungal cultures pointed to Aspergillus co-infection. On chest CT scans there were signs seen in the fungal infection: thick-wall cavities (nontypical for bacterial infections), with “white glass” and small nodules in the surroundings. It lacked the crescent sign — very specific for fungal infection. An explanation is the fast evolution of nodules into cavities because of the intense immunological response. The diagnosis of IPA was a probable one, according to the Mycoses Study Group [9]: culture of bronchial washings and nasal discharge yielded a florid growth. During bronchoscopy no bronchial specimens were taken. After a partial radiological response and much better patient condition during voriconazole treatment, it was supposed that diagnosis of IPA was very probable and a decision about resignation from other confirming studies (bronchial samples, serology and metabolites assays, PCR studies) was undertaken. Invasive aspergillosis of paranasal sinuses and lungs was treated with voriconazole, which is the drug of first choice in culture positive infections.

### Table 2. Efficacy of invasive aspergillosis treatment

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>% response rate</th>
<th>References</th>
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<tbody>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>1–1.5 mg/kg/day IV</td>
<td>33–54</td>
<td>[15]</td>
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<tr>
<td>Amphotericin B cholesteryl sulphate</td>
<td>3–4 mg/kg/day</td>
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<tr>
<td>Amphotericin B lipid complex</td>
<td>5 mg/kg/day</td>
<td>42–67</td>
<td>[16]</td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>5 mg/kg/day</td>
<td>30–60</td>
<td>[17]</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>6 mg/kg IV twice daily on day 1, then 4 mg/kg IV twice daily for at least 7 days, then 200 mg PO twice daily</td>
<td>53</td>
<td>[13]</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>200 mg IV twice daily for 2 days, then 200 mg IV once daily for 12 days or 200 mg PO 3 times daily for 3 days, followed by 200 mg PO twice daily</td>
<td>39–66</td>
<td>[18]</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>70 mg IV once, then 50 mg IV once daily in cases of IPA unresponsive to other antifungal therapies</td>
<td>41</td>
<td>[19]</td>
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sinus debridement was performed because of difficult local conditions after the first surgery and radiotherapy. This influenced the success of pharmacological treatment and perpetuated the inoculation of spores from the paranasal sinuses.

Diagnosis of brain aspergillosis was also not straightforward. CT scan suggested multiple brain abscesses — not proving bacterial or fungal aetiology. No biopsy was done because of bad patient condition and unfavourable prognosis. Wide spectrum antibacterial and antifungal drugs were continued to treat both conditions.

References