Case Report

Highly effective unconventional management of aspergillosis of the left maxillary sinus in an 11-year-old girl with rhabdomyosarcoma embryonale of the frontal sinus

Jaroslaw Peregud-Pogorzelski, Pawel Wawrykow, Sebastian Wozniak, Anna Zakowska and Andrzej Brodkiewicz

Department of Pediatrics, Pediatric Hematology and Oncology, Pomeranian Medical University, Szczecin, Poland

Invasive fungal infections are common causes of death in children treated for malignancies, and therefore present an important and growing clinical problem. Fungal invasion usually affects immunocompromised patients, but increased incidences are also associated with intensification of antineoplastic therapy and increased numbers of organ and bone marrow transplantsations. Fungal infections in parameningeal and cerebral locations carry high risks of treatment failure. We describe the case of an 11-year-old female patient with rhabdomyosarcoma embryonale of the frontal sinuses with metastases to the neck lymph nodes, treated according to the CWS 2002 protocol for high-risk patients. Left maxillary sinus aspergillosis was diagnosed during chemotherapy following radiotherapy, and 56 days after surgical excision of the tumour. No effect was achieved by use of amphotericin B. Further treatment included intravenous voriconazole at 6 mg per kg body weight every 12 h for 2 weeks, followed by oral voriconazole at 4 mg per kg body weight twice daily for 6 months. Simultaneous excision of necrotic tissues from the nasal cavity, ethmoid bone, maxillary sinus and frontal recess was performed. The sinus was kept open for 3 weeks to allow voriconazole lavage every 12 h for 3 weeks. This unconventional treatment resulted in eradication of sinus aspergillosis and allowed intensive chemotherapy to be continued with no recurrence of aspergillosis.

Introduction

Primary and secondary immunodeficiencies, use of immunosuppressive drugs or broad-spectrum antibiotics, long-term parenteral nutrition, and in-dwelling central catheters all predispose to invasive fungal infections (Hasan & Abuhammour, 2006; Abbasi et al., 1999; Cuccia et al., 2000; Müller et al., 2002). Prolonged neutropenia during antineoplastic therapy, impaired granulocyte function during the course of malignancy, abnormal T-cell immunity in patients after bone marrow transplantation, and procedures performed for the treatment of solid tumours are also risk factors for fungal infections (Hasan & Abuhammour, 2006; Müller et al., 2002; Cesaro et al., 2003). Most of these risk factors are present in children with malignancies. The central nervous system is most frequently involved in bloodstream infections, while respiratory tract involvement results from airborne infections (Hasan & Abuhammour, 2006; Cuccia et al., 2000; Müller et al., 2002). Invasive fungal sinusitis remains an important diagnostic and therapeutic problem associated with high mortality.

We present a case of invasive fungal sinusitis in a child treated for rhabdomyosarcoma embryonale in the frontal sinus and left maxillary sinus. Unconventional management consisted of maxillary sinus surgery with excision of a necrotic mass with septate hyphae, and local and systemic amphotericin and voriconazole treatment. This therapeutic regimen resulted in successful eradication of the infection and allowed continuation of chemotherapy with no infection recurrence.

Case report

An 11-year-old female patient with rhabdomyosarcoma embryonale located in the frontal and left maxillary sinuses and with metastatic disease in the neck lymph nodes was treated according to the Cooperative Weichteilsarkom Studie (CWS) 2002 protocol (ftp://ftp.uke.uni-hamburg.de/pub/temp/CWS-2002P-Oktber03_Korrektur.pdf) for high-risk patients. Adjuvant chemotherapy for 7 weeks was followed by total excision of the tumour within the macroscopic margins of intact tissue. Simultaneous postoperative chemotherapy and radiotherapy were introduced. After completion of radiotherapy and 56 days after sinus surgery, the patient developed fever and mucus and pus discharge from the left
nasal duct, with concomitant left eyelid oedema. Cultures from the nasal duct discharge revealed the presence of filamentous fungi. Magnetic resonance imaging showed the presence of a pathological mass in the left maxillary sinus but no signs of bone destruction adjacent to the brain (Fig. 1). No fungal pulmonary involvement was found. The patient underwent excision of necrotic tissues from the frontal sinus orifice and her left maxillary sinus was opened.

The fever, left eyelid oedema and left nasal discharge resolved after 5 weeks of treatment with amphotericin B at 1 mg per kg body weight. Amphotericin B soluble in sodium deoxycholate was used. However, following the next chemotherapy cycle (16th week of treatment according to the CWS 2002 protocol), her fever recurred, together with left orbit oedema and left eye subconjunctival haemorrhage.

Magnetic resonance imaging again revealed pathological changes within the left maxillary sinus. Systemic and local amphotericin B proved ineffective. Cultures from the discharge from the left nasal cavity revealed *Aspergillus niger*. Because of the overall severe status of the patient, a wide antrostomy of the left maxillary sinus with excision of the fungal mass was performed, and the nasal cavity, ethmoid bone and frontal recess were cleaned. Histopathological studies of masses removed from the sinus revealed the presence of hyphae resembling *Aspergillus* sp. The galactomannan and *Candida* mannan antigens proved to be negative.

Subsequent treatment consisted of intravenous voriconazole at 6 mg per kg body weight every 12 h for 2 weeks, followed by oral voriconazole 4 mg per kg body weight for 6 months. Additional sinus lavage with voriconazole was performed twice daily for the first 3 weeks. Due to lack of technical support no monitoring of therapeutic levels in blood and cerebrospinal fluid was performed. The patient’s general status improved and her left eye oedema resolved. Control imaging studies (Fig. 2) and left maxillary sinus endoscopy revealed total regression of the fungal changes. No recurrence of fungal infection was observed, despite continuation of intensive chemotherapy.

**Discussion**

Sinus invasion is one of the most frequent manifestations of fungal infection in patients treated for malignancies. Invasive fungal sinusitis is caused by invasion of pathogens through the nasal mucous membrane, followed by dispersion of fungal spores to the ethmoid bone, orbit or palate (Hasan & Abuhammour, 2006; Müller et al., 2002). The central nervous system may be affected in some cases. Airborne infection leads to pulmonary invasion in 70 % of cases, while sinus involvement is seen in 18 % (Abbasi et al., 1999). Invasion by *Aspergillus* species is associated with poor prognosis, and the mortality in these patients ranges from 50 % to almost 100 % with central nervous system invasion (Leroy et al., 2006).

The long-term and oligosymptomatic course of the disease, and the lack of sufficiently sensitive diagnostic methods, mean that fungal infections may remain undiagnosed for a prolonged period. Additional obstacles result from the presence of non-specific signs, including fever, headache, cough, pus discharge from the nasal cavity and pharyngeal pain. Fungal infection within the sinuses often coexists with pulmonary involvement (Hasan & Abuhammour, 2006; Gupta et al., 2006). Less common, but still characteristic features of fungal sinusitis include blocked nose, bleeding or pus discharge from the nares, deformation of facial soft tissues, orbital oedema, endophthalmitis, visual impairment and destruction of bones. The maxillary,
ethmoid and frontal sinuses are most commonly involved in patients younger than 15 years (Abbasi et al., 1999; Gupta et al., 2006).

Of approximately 1000 species of Aspergillus, fewer than 20 are pathogenic in humans. Severe infections of the respiratory tract and sinusitis in children suffering from malignancies are caused by Aspergillus fumigatus and Aspergillus flavus with equal frequencies (Hasan & Abuhammour, 2006; Müller et al., 2002). In contrast, central nervous system invasion with A. niger is rare, and according to Dotis et al. (2007), the cerebral infection rate in paediatric populations is only 1.8%.

Treatment of invasive fungal infections is difficult because of the relatively small choice of antifungal agents and their limited penetration to the affected tissues, especially in the case of parameningeal or cerebral infections (Abbasi et al., 1999). In the present patient, Aspergillus was isolated from the nasal ducts and therapy was initiated with amphotericin B, with transient improvement and resolution of fever, left eyelid oedema and left nasal discharge. However, the subsequent chemotherapy cycle was followed by recurrence of the fungal infection, and treatment with systemic and local amphotericin B proved ineffective. A. niger was identified by microbiological techniques, and magnetic resonance imaging revealed a pathological mass within the frontal, maxillary and ethmoid sinuses. Because of her severe general status, the patient was scheduled for surgical excision of the necrotic masses from the nasal cavity, ethmoid bone, maxillary sinus and frontal recess. Simultaneous antifungal treatment was established with voriconazole, a broad-spectrum antifungal agent covering Candida and Aspergillus aetiologies, representing the species most frequently seen in patients with malignancies. This patient initially received 2 weeks of treatment with intravenous voriconazole twice daily at a dose of 6 mg per kg body weight, followed by oral voriconazole at a dose of 4 mg per kg body weight twice daily for 6 months. Nasal cavity and maxillary sinus lavage was also performed twice daily with voriconazole solution at a dose of 100 mg for the first 3 weeks. Definitive data on the recommended duration of antifungal treatment in similar cases are currently lacking (Abbasi et al., 1999; Kalwak, 2009).

It should be noted that the relatively low sensitivity and specificity of microbiological and serological methods for detecting localized fungal infections means that imaging studies play an important role in the diagnostic process. According to previous reports, imaging findings suggestive of fungal infections are present in approximately 50% of cases. Surgical treatment is applied, not only for invasive fungal sinusitis, but also for pulmonary, articular and central nervous system manifestations of the disease (Hasan & Abuhammour, 2006; Gupta et al., 2003; Sasindran et al., 2008; Thomas et al., 2003). Despite the use of modern surgical techniques, surgery in these patients carries a high (50%) risk of failure. However, surgery may represent the only option for total evacuation of the affected tissues and for acquiring sufficient diagnostic material to confirm the fungal aetiology of the infection (Hasan & Abuhammour, 2006; Leroy et al., 2006).

Concluding remarks

Parameningeal aspergillosis in patients with malignancies treated with chemotherapy still has a poor prognosis, and all available therapeutic options should be considered for the treatment of these infections. Unconventional therapy in the present case included the use of systemic antifungal agents and surgical excision of necrotic tissues from the nasal cavity, ethmoid bone, maxillary sinus and frontal recess. The sinus was kept open for 3 weeks to enable repeated voriconazole lavage. This treatment strategy resulted in the eradication of sinus aspergillosis, whilst allowing continuation of intensive chemotherapy, with no recurrence of aspergillosis.

References


