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SHORT COMMUNICATION

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Secondary prophylaxis of invasive fungal infections with combination antifungal therapy and G-CSF-mobilized granulocyte transfusions in three children with hematological malignancies

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Abstract Fungal infections represent a life-threatening complication for patients receiving chemotherapy or undergoing hematopoietic stem cell transplantation. Historically, antifungal monotherapy is associated with a poor outcome. We treated three children with hematological malignancies and proven fungal infections (one cerebral mold infection, one disseminated *Candida* infection, one nasopharyngeal mucor infection) with combination antifungal therapy plus granulocyte-colony-stimulation-factor-mobilized granulocyte transfusions as secondary prophylaxis during subsequent neutropenic episodes. With this approach, the fungal infection was effectively treated, and the anticancer therapy was completed without major delay. All children survived the fungal infection and the underlying malignancy. These experiences illustrate the feasibility of this approach using more than one antifungal agent together with immunetherapy in high-risk patients.

Keywords Fungal infection · Childhood · Cancer · Combination therapy · Granulocyte transfusion

Introduction

Patients contracting fungal infections in the early phase of chemotherapeutic treatment for hematological malignancies require treatment for a life-threatening infection in the presence of persistent and long-term neutropenia [6, 13]. Frequently, discontinuation of chemotherapy is required to effectively treat the fungal infection, and this discontinuation carries the risk of ineffective anticancer therapy [8].

In 2002 and 2003, three children with proven invasive fungal infections were treated at our institution using an antifungal combination therapy and granulocyte-colony-stimulation-factor-mobilized (G-CSF-mobilized) granulocyte transfusions (GTX) as secondary prophylaxis during neutropenia. Using this strategy, all children survived the antitumor therapy, including one hematopoietic stem cell transplantation (HCT), and the fungal infections.

Patients

Patient 1 This 5-year-old boy was admitted for acute lymphoblastic leukemia (ALL) in relapse. After the initiation of chemotherapy (dexamethasone, 6-mercaptopurine, vincristine, high-dose methotrexate) in Macedonia, he was transferred to our clinic for further treatment. The child was in a poor general condition and febrile. An elevated C-reactive protein level (218 mg/l) was noted. Despite broad-spectrum antibiotic treatment and therapy with fluconazole (5 mg/kg bodyweight), the clinical situation worsened during the last 2 weeks. Multiple hypodense

lesions in the liver and spleen (Fig. 1) were detected ultrasonographically. Blood cultures remained sterile, but via ultrasound-guided fine-needle aspiration, a *Candida albicans* infection was diagnosed in of one of the lesions. Due to the poor clinical situation of the patient, we initiated antifungal therapy with liposomal amphotericin B (3 mg/kg/day). There was no clinical improvement after 3 days of therapy; therefore, caspofungin (50 mg/m^2) was added to the treatment schedule, and antileukemic chemotherapy was initiated. During four subsequent episodes with profound neutropenia after chemotherapy (according to the German ALL-relapse protocol) the boy received a total of 15 GTX. One month later, the lesions in the liver and spleen were reduced in number and size, and the antifungal regimen was changed to itraconazole (5 mg/kg/day orally) for 1 month. While on itraconazole with subtherapeutic serum levels, the patient developed probable *Candida* meningitis (headache, fever, pleocytosis, focal lesions on cranial magnetic resonance tomography; the cultures remained sterile). After changing to the intravenous formulation of itraconazole and adding flucytosine to the treatment schedule, a transient amelioration was seen, but only therapy with caspofungin, (50 mg/m^2), fluconazole (20 mg/kg/day), and liposomal amphotericin B (2 mg/kg/day) resulted in the normalization of the CSF findings and defervescence (voriconazole treatment was given in this context initially, but discontinued after 2 days due to mental disturbances). In total, the boy received a combination of antifungal treatment together with GTX for 11 months during profound neutropenia (absolute neutrophil count (ANC) <500/μl) while completing the chemotherapy. Unfortunately, he died due to an acute liver failure on the basis of a chronic hepatitis B infection contracted in Macedonia 10 months after his completion of the chemotherapy protocol.

Patient 2 This 3.5-year-old girl received induction chemotherapy for ALL according to the German ALL-Berlin–Frankfurt–Münster protocol (1 week prednisone, followed by dexamethasone, vincristine, daunorubicine, asparaginase, and methotrexate intrathecally). Forty-seven days after initiating chemotherapy she was neutropenic (ANC <500/μl), febrile, and showed asthenia of the lower limbs. Following a generalized seizure, a magnetic resonance imaging scan of the brain revealed a huge abscess formation (Fig. 2), and the girl was transferred to our hospital for further evaluation. The initial culture and histopathological examination of the abscess were uninformative. Empirical treatment consisted of broad-spectrum antibiotic treatment (piperacillin-combactam plus aminoglycoside together with liposomal amphotericin B (3 mg/kg/day), and 4 weeks later, a second biopsy revealed branching hyphae highly suggestive of an *Aspergillus* infection. The culture remained sterile (while on therapy with liposomal amphotericin B, 3 mg/kg/day). During two subsequent neutropenic episodes, she received a total of six GTX and a combination of antifungal treatment with voriconazole (loading 6 mg/kg/day on day 1, afterwards, 4 mg/kg/day) and caspofungin (50 mg/m^2). Currently, there are only minimal residual intracranial lesions. The combination antifungal treatment was continued until she completed the intensive chemotherapy (the total duration was 5 months). Today, the patient receives an oral antileukemic maintenance treatment (methotrexate and mercaptopurine orally); the antifungal treatment consists of voriconazole (2×100 mg/day, orally). Her general neurological performance is normal with only minor residual cerebral dysfunction (weakness of the right hand and limb, minimal walking difficulties, but continuously improving skills).

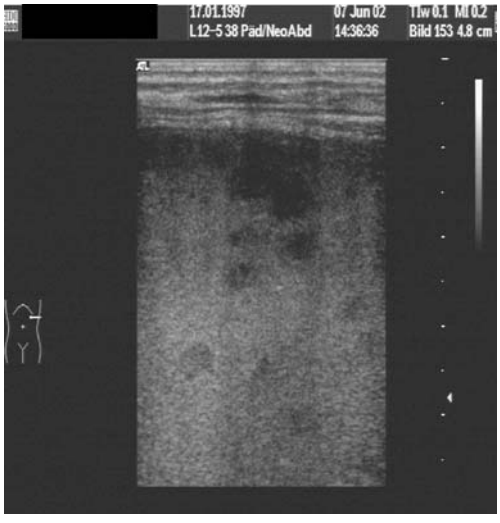

Fig. 1 Ultrasound picture of the spleen in patient 1 showing hypoechogenic lesions. *Candida albicans* was isolated via fine-needle puncture

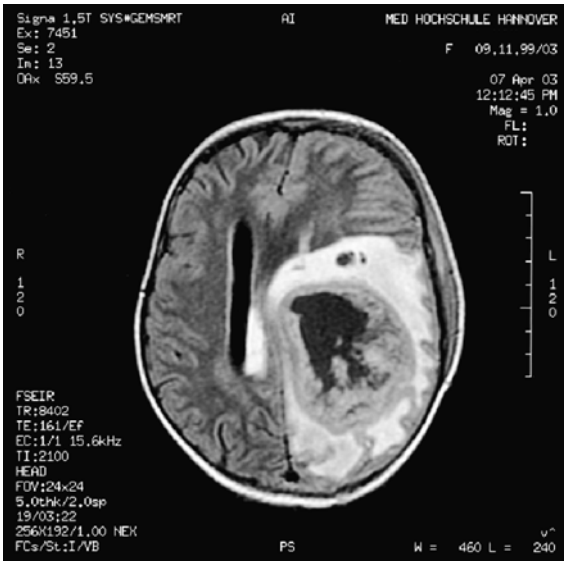

Fig. 2 Magnetic resonance imaging of the brain (axial T2 weighted flair) showing a huge abscess formation in patient 2. Branching hyphae were seen on biopsy

Patient 3 This 16 year old male adolescent received an HCT for a myelodysplastic syndrome 3 years before admission. Later, he was admitted for a secondary acute myeloid leukemia, and received induction chemotherapy (high dose cytarabine) prior to a (projected) second HCT. After 3 weeks with profound neutropenia (ANC <500/μl), the boy developed a necrotic lesion in his palate (Fig. 3). The first biopsy was uninformative, but antifungal treatment including voriconazole (2×4 mg/kg/day, intravenously), liposomal amphotericin B (3 mg/kg/day) and caspofungin (loading 70 mg/day, then 50 mg/day) was initiated empirically. Cultures of the second biopsy 2 weeks later revealed *Absidia corymbifera* (mucor). Then, local therapy with amphotericin B nasal spray and nasal rinses (1 mg/ml in 5% Glucose) was begun several times per day; the therapy with liposomal amphotericin B was continued. Two weeks later, the HCT (matched unrelated donor) was performed. During the neutropenic period before and after HCT, he received a total of 19 GTX until the fungus engrafted. Prior to engraftment after HCT, the C-reactive protein-levels rose to a maximum of 466 mg/l and voriconazole was changed to flucytosine, but was switched back again 2 weeks later because of increasing liver enzymes. After normalization of the thrombocyte count, a surgical debridement was performed. Caspofungin treatment was stopped after 3 months; the liposomal amphotericin B was continued for a total duration of 6 months. Today, 2 years after HCT, the boy is still in ambulatory care, but is not receiving antifungal medication. The necrotic lesion of the palate was surgically debrided again and the soft palate was covered.

Regarding hematological data in the three children, we noted a median increase of the leukocyte count to 2,541/μl 1 h after GTX (ranging from 850 to 3,890/μl), and to 1,548/μl (ranging from 744 to 2,700/μl) on the morning after GTX. Using a thrice-per-week schedule for GTX, the median leukocyte count prior to the following GTX was 566/μl. Using acetaminophen and clemastine as premedicants before GTX, adverse events during or shortly after GTX were seen only rarely: In these 3 children receiving 40 GTX, fever and chills were noted during or after five GTX. None of the GTX had to be discontinued due to adverse reactions in this series.

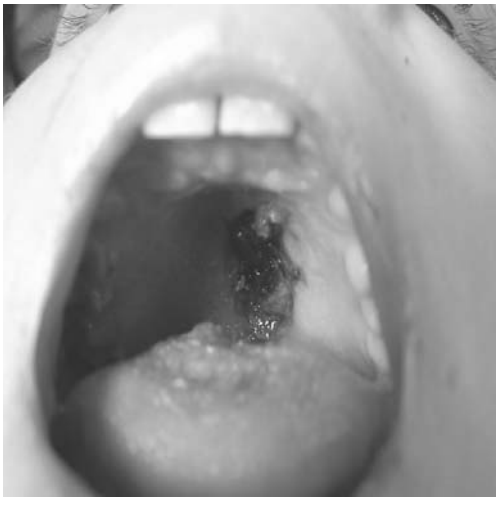

Fig. 3 Necrotic lesion of the palate in patient 3. The biopsy revealed a mucor (*Absidia corymbifera*) infection

Discussion

Combination antimicrobial therapy is the standard of care for many serious infections, e.g., pseudomonas infections and tuberculosis [2]. In fungal infections, the combination of different antifungal agents has been a matter of debate until today, and there is, so far, no evidence of the superiority of combining different antifungal agents over antifungal monotherapy [9, 10, 13]. However, the so-called "gold-standard"—amphotericin B—results only in poor survival rates, especially during an allogeneic HCT [5]. In patients requiring a protracted chemotherapy, delays in anticancer treatment carry the incalculable risk of disease progression or relapse. In addition, in vitro results suggest a synergism between different antifungal agents, and interventional use of hematopoetic growths factors and/or GTX has shown its potential in selected patients [4, 11]. With regard to the prophylactic use of GTX, Kerr et al. performed a case-control study including nine allogeneic HCT recipients at high risk of invasive aspergillosis. According to their data, prophylactic GTX were feasible and resulted in a significant reduction in the period of post-transplant neutropenia. Associated with this reduction in neutropenia was a reduction in the incidence of fever, the number of days of fever, the maximum C-reactive protein levels, and the use of total parenteral nutrition and opiates for mucositis [7]. Interestingly, a combined approach in treating fungal infections (e.g., adding G-CSF to the treatment schedule) must not, by itself, be more expensive than the amphotericin B monotherapy [3], and the costs for GTX at our institution are only as high as the costs for platelet transfusions (e.g., 350€). Our patients confirm previous results and illustrate the feasibility of combining different antifungal agents together with GTX as secondary prophylaxis in patients with "high-risk" fungal infections. Bearing in mind the very unfavorable prognosis of these children based on historical data, we feel that such an approach as presented here is justified in selected patients [1]. Nevertheless, standardized treatment strategies cannot be concluded from such anectdotal case reports, e.g., in patient 1, a very high dosage of fluconazole (20 mg/kg/day) was chosen, although the recommended dosage is only 8 to 12 mg/kg/day. There are convincing clinical data supporting in vitro results that high-dose fluconazole might be more effective than standard or even low dose fluconazole [12]; and therefore, this very high dosage was

used for this patient, with good results and no adverse-effects. Normally, fluconazole is used at our institution at dosages between 8 to 12 mg/kg/day, and the general strategy at our institution regarding treatment of fungal infections is as follows: We start an antifungal monotherapy in uncomplicated candidemia or in pulmonary *Aspergillus* infections in clinically stable patients. After 48 h, we re-evaluate the patient and consider combination antifungal treatment (together with GTX in the neutropenic child) if persistent fever and/or increasing C-reactive protein levels are seen. Regarding *Candida* infections of the central nervous system, the initial treatment consists of fluconazole and flucytosine, which is switched to a fluconazole monotherapy after 2 weeks for a total duration of 4 weeks (unless the patient remains neutropenic). During the time of these case reports, *Aspergillus* infections of the central nervous system were treated using a combination of voriconazole and caspofungin, but due to good results with voriconazole-monotherapy, a single-agent treatment with voriconazole has now become the standard approach. Again, if the re-evaluation after 48 h reveals a disease progression (fever, C-reactive protein level), a combination antifungal treatment will be considered.

To conclude, the authors are aware of the limitations of such case reports and emphasize the need for controlled studies, but with regard to rare infections—as with fungal infections—case reports might add aspects of treatment alternatives in desperate clinical situations.

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