Letter

Breakthrough zygomycosis following empirical caspofungin treatment: report of two patients with leukemia and literature review

Pierre Sujobert,1 Nicolas Boissel,1 Anne Bergeron,2 Patricia Ribaud,3 Herve Dombret,1 Olivier Lortholary,4,5 Emmanuel Raffoux1

1 Service clinique des maladies du sang, Hôpital Saint Louis, AP-HP, Paris, France
2 Service de pneumologie, Université Paris 7, UFR Denis Diderot, Hôpital Saint Louis, AP-HP, Paris, France
3 Service d'Hématologie-Greffe, Hôpital Saint-Louis, AP-HP, Paris, France
4 Université Paris 5 René Descartes, Service des Maladies Infectieuses et Tropicales, Centre d'Infectiologie Necker-Pasteur, Hôpital Necker-Enfants Malades, AP-HP, Paris, France
5 Institut Pasteur, Unité de Régulation des Infections Rétrovirales, Paris, France

Corresponding Author & Address:
Emmanuel Raffoux
Service clinique des maladies du sang, Hôpital Saint Louis, 1 avenue Claude Vellefaux, 75010 Paris, France
Email: emmanuel.raffoux@sls.aphp.fr

Published: 2nd September, 2010 Accepted: 2nd September, 2010
Received: 16th July, 2010 Revised: 17th August, 2010

Open Journal of Hematology, 2010, 1-3

©Raffoux et al.; licensee Ross Science Publishers
ROSS Open Access articles will be distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided that the original work will always be cited properly.

Keywords: echinocandin, caspofungin, breakthrough zygomycosis

ABSTRACT

Breakthrough zygomycosis are increasingly reported life-threatening complications among patients with hematological malignancies, especially since the use of broad spectrum antifungal treatments like voriconazole. We report two cases of breakthrough zygomycosis after caspofungin exposure, with a review of literature.

INTRODUCTION

Zygomycetes infections are increasingly reported life-threatening complications occurring in immunocompromised patients (mostly with hematological malignancies) or in diabetic patients [1]. In allogeneic hematopoietic stem cell transplants recipients, limited data have shown that prolonged voriconazole treatment has been associated with an increase in incidence of zygomycosis [2-5]. We report two cases of pulmonary zygomycosis diagnosed in patients treated empirically with caspofungin, another widely used broad spectrum antifungal treatment with a literature review.

CASE REPORTS

Patient n°1

A 40-years-old man was hospitalized for relapsing acute myeloid leukemia four years after...
allogeneic transplantation from a sibling donor. A second complete remission was attained with gemtuzumab ozogamycin and cytosine arabinoside. While he was neutropenic (absolute neutrophil count < 100/μl), he became febrile at day 3, and caspofungin was begun at day 8 as empirical antifungal therapy for unexplained persistent fever under piperacillin-tazobactam. He finally became apyretic at day 11 when antibiotics were switched for the association of ceftazidime and vancomycin. At day 15, although he was still under caspofungin therapy, he was febrile again with dry cough and wheezing. The CT-scan of the chest revealed diffuse bronchiolar micronodules with ground-glass opacities. Caspofungin was pursued and antibiotics were empirically switched for imipenem, but the patient never became apyretic, even after bone marrow recovery. At day 48, antibiotics and caspofungin were delayed to exclude drug-induced fever, but no change was noted. A new CT-scan showed the same images, and a diagnostic bronchoalveolar lavage fluid examination was normal. The tracheobronchial aspiration sample was negative on direct examination, but the culture showed one colony of Aspergillus fumigatus, which prompted us to initiate a treatment with voriconazole even if repeated serum galactomannan assays were negative (0.07 GMI). After the first consolidation course with the same chemotherapy regimen, he had unexplained neutropenic fever with dry cough again. No further exploration was made, and the patient improved after bone marrow recovery. At day 11 of the second consolidation course, he was in respiratory distress, with febrile dry cough, diffuse coarse crackles and wheezing. There were diffuse nodular lesions on the CT-scan of the chest and the tracheobronchial fibroscopy found white lesions in the right main stem bronchus. Histological examination of transbronchial biopsy and bronchoalveolar lavage demonstrated numerous broad, non septate, right angled filamentous hyphae. The culture of the transbronchial biopsy allowed the identification of Absidia corymbifera, with the natural in vitro resistance to voriconazole and caspofungin (CMI ≥8µg/ml). Voriconazole was switched (after a 60 days treatment) for high dose liposomal amphotericin B (10 mg/kg/d) but the patient died of massive hemoptysis 15 days later.

Patient n°2

A 30-years-old woman was hospitalized because of T-cell acute lymphoblastic leukemia with mediastinal involvement. After a seven-day corticosteroid prephase, she received remission induction chemotherapy with prednisolone, daunorubicin, L-asparaginase, vincristine and cyclophosphamide. She was neutropenic from day 15 until day 35. She received caspofungin from day 22 to day 37 as empirical treatment for unexplained persistent fever under broad spectrum antibiotics. All the blood cultures were negative, as were sequential serum galactomannan index measures. The thoracic CT-scan was normal. After completion of the induction course, she was in complete remission and received the two first consolidation courses (cyclophosphamide, etoposide and methotrexate on day 43 and cytosine arabinoside and L-asparaginase on day 59), without any clinical symptoms. She was neutropenic on day 60, and started complaining about cough with purulent expectoration. On day 61, she was admitted in the intensive care unit because of an Escherichia coli septic shock. The total body CT-scan showed an atelectasy of the apical segment of the left inferior lobe, and a concomitant left maxillary sinusitis. The tracheobronchic fibroscopy found a complete obstruction of the apical bronchus of the left inferior lobe by a white necrotic formation. Histological examination revealed multiple irregularly shaped hyphae consistent with Zygomycetes, but the culture was negative. No evidence of fungal infection was found neither in multiple transbronchial nor in transparietal biopsies performed in the same area. The surgical biopsy of the maxillary sinus was negative too. The septic shock resolved after two days, and she was treated with high dose liposomal amphotericin B (10mg/kg/d). After thirty days of treatment, the lesion was aspirated during a bronchoscopy, and a secondary prophylaxis was begun with posaconazole. Twenty months later, the patient is still alive with no evidence of zygomycete infection.

DISCUSSION

Zygomycetes are emerging fungi that cause dramatic invasive infections in immune-compromised patients, usually associated with a high mortality rate. We report two cases of
pulmonary zygomycosis in neutropenic patients who were previously treated with caspofungin as empirical therapy.

To our knowledge, six other cases have been described as case reports [6-10] including one under empirical micafungin treatment [11]. The main clinical features of these cases are summarized in Table 1. In absence of consensual diagnostic criteria of breakthrough zygomycosis, the delay between broad spectrum antifungal treatment and zygomycosis diagnosis may challenge the concept of an association between these two conditions. In three published cases, the time interval between echinocandin initiation and zygomycosis diagnosis was very short (less than fifteen days) [7, 9, 11]. In such cases, one might ask whether it is a real zygomycosis breakthrough under caspofungin, or only a failure of caspofungin in zygomycosis treatment. In both our cases, there was a longer time interval between the discontinuation of caspofungin and zygomycosis diagnosis, especially for patient 1. However, he presented similar symptoms at the beginning (day 15) while he was under caspofungin, and when the diagnosis was formally made three months later. Moreover, the same nodules increasing with time were seen on repeated CT-scans of the chest. The isolation of one colony of Aspergillus fumigatus only in the tracheobronchial aspiration culture with negative serum galactomannan assays must be considered as contamination or colonization. Together, this clinical course and imaging data argue for an early beginning of zygomycosis infection under caspofungin therapy, with stabilization of the infection in non neutropenic periods.

Breakthrough zygomycosis under antifungal treatment have been already well described with voriconazole. In 2004, four reports from transplant centers have described an increase in incidence in zygomycosis in patients given prolonged prophylactic voriconazole [2-5]. The authors suggested that voriconazole may also have exerted selective pressure for growth of zygomycetes, which are naturally resistant to voriconazole. Moreover, recent in vivo data suggest that voriconazole exposure may enhance zygomycosis virulence, as proven for Rhizopus oryzae [12]. These reports highlighted the potential risks of empirical or prophylactic broad spectrum antifungal therapy, which may favor the emergence of the more resistant or more virulent fungi, a fact that has also been reported recently in solid organ transplantation patients [13].

Could caspofungin, another broad spectrum widely used antifungal agent, exert a selective pressure that promotes zygomycetes growth? A recently published prospective case-control study in solid organ transplant recipients argues for this hypothesis, as caspofungin exposure was independently associated with the subsequent occurrence of zygomycosis [13]. Such a selective pressure is theoretically conceivable if caspofungin has no or limited action on zygomycete. In fact, based on unimpressive in vitro activity, this agent has long been considered to be ineffective against zygomycetes. However, this idea has been recently challenged by in vitro and in vivo data. First, Rhizopus oryzae, the organism most frequently involved in zygomycosis at least in the United States, express the enzyme 1,3-β-D-Glucan Synthase, which is the target of caspofungin [14]. Second, caspofungin treatment in association with lipid complex of amphotericin B was showed to have clear although modest activity at relatively high concentration in a mouse model of disseminated Rhizopus oryzae infection, both as a curative or prophylactic therapy [15]. Third, the same authors have shown in a limited retrospective study the potential benefit of the addition of caspofungin to polyene in 41 patients with rhino-orbital-cerebral mucormycosis [16]. However, one report has shown disappointing results with this association [17]. Without a prospective randomized study evaluating the combination of caspofungin and polyene therapies, we are still unable to appreciate the potential clinical activity of caspofungin against zygomycetes. So the hypothesis that caspofungin may exert selective pressure for growth of zygomycetes cannot be ruled out.

To conclude, this report show that zygomycosis can develop in neutropenic patients having recently received caspofungin treatment. Physicians should be aware of the risk of breakthrough resistant fungi infections in patients under caspofungin therapy. This report emphasizes the vigilance regarding the risk of breakthrough infections, so that they can receive the appropriate antifungal therapy.

<table>
<thead>
<tr>
<th>Ref / year</th>
<th>Sex/ age (year)</th>
<th>Underlying condition</th>
<th>Type of echinocandin</th>
<th>Other antifungal drugs associated</th>
<th>Time interval between echinocandin initiation and zygomycosis diagnosis</th>
<th>Site of zygomycosis infection</th>
<th>Species identification</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>M, 40</td>
<td>Post allogeneic SCT relapsed acute myeloid leukemia</td>
<td>Empirical caspofungin</td>
<td>voriconazole</td>
<td>3 months</td>
<td>lung</td>
<td>Lichtheimia corymbifer</td>
<td>liposomal amphotericin B</td>
<td>Deceased 15 days after diagnosis. Cause of death : hemoptysis</td>
</tr>
<tr>
<td>Patient 2</td>
<td>F, 30</td>
<td>acute lymphoblastic leukemia</td>
<td>Empirical caspofungin</td>
<td>no</td>
<td>38 days</td>
<td>lung</td>
<td>no identification</td>
<td>liposomal amphotericin B</td>
<td>complete remission (follow up 20 months)</td>
</tr>
<tr>
<td>(6) 2004</td>
<td>M, 61</td>
<td>allogeneic SCT</td>
<td>Preemptive caspofungin</td>
<td>no</td>
<td>6 months</td>
<td>lung</td>
<td>Rhizomucor sp.</td>
<td>aerosolized amphotericin B</td>
<td>complete remission (follow up 5 months)</td>
</tr>
<tr>
<td>(7) 2004</td>
<td>F, 52</td>
<td>Immunochemotherapy for post transplant high grade lymphoma</td>
<td>Empirical caspofungin</td>
<td>voriconazole</td>
<td>15 days</td>
<td>disseminated</td>
<td>Rhizopus oryzae</td>
<td>liposomal amphotericin B</td>
<td>Deceased 4 days after diagnosis. Cause of death : zygomycosis</td>
</tr>
<tr>
<td>(8) 2005</td>
<td>F, 16</td>
<td>allogeneic SCT</td>
<td>Curative caspofungin for Candida krusei infection</td>
<td>no</td>
<td>27 days</td>
<td>lung and sinus</td>
<td>Mucor sp.</td>
<td>liposomal amphotericin B</td>
<td>Deceased 1 month after diagnosis. Cause of death : Pseudo-monas aeruginosa septic shock</td>
</tr>
<tr>
<td>(9) 2007</td>
<td>M, 26</td>
<td>acute lymphoblastic leukemia</td>
<td>Empirical caspofungin</td>
<td>no</td>
<td>14 days</td>
<td>lung</td>
<td>Mucor sp.</td>
<td>first line : liposomal amphotericin B Second line : association of liposomal amphotericin B and posaconazole</td>
<td>dissemination under amphotericin B. Complete remission with posaconazole</td>
</tr>
<tr>
<td>(10) 2009</td>
<td>F, 32</td>
<td>liver transplantation</td>
<td>Prophylactic caspofungin for Candida albicans colonization</td>
<td>no</td>
<td>26 days</td>
<td>rhinocerebral</td>
<td>Rhizopus sp.</td>
<td>liposomal amphotericin B</td>
<td>deceased 1 day after diagnosis. Cause of death : septic shock with multiorgan failure</td>
</tr>
</tbody>
</table>
ACKNOWLEDGEMENTS
PS and ER collected the clinical data. PS, OL and ER performed the review of literature and wrote the paper. PS, NB, AB, PR, HD and ER were in charge of the reported patients. OL is a member of speaker’s bureau of Pfizer, Astellas, Merck Sharp & Dohme, Gilead Sciences, Schering Plough and consultant for Astellas. The other authors reported no potential conflicts of interest.

REFERENCES


