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Failure of Deferasirox, an Iron Chelator Agent, Combined with Antifungals in a Case of Severe Zygomycosis▽

Zygomycosis, an increasingly prevalent systemic fungal disease, mostly occurs in immunocompromised patients (6, 8). First-line therapeutic strategy includes surgery and lipid amphotericin B (2, 8). New iron chelators have recently been reported to be successful experimentally (3) and in a patient with refractory zygomycosis (5, 7). We report a case of abdominal zygomycosis which was refractory to a combination of antifungals, major surgery, and deferasirox, a recently approved iron chelator.

An 18-year-old leukemic woman presented a febrile neutropenia and abdominal pain after a first course of chemotherapy. Ultrasound showed a small liver abscess. All bacterial and fungal samples remained negative. Despite broad-spectrum antibacterials, peritonitis signs led to an emergency laparotomy that revealed an inflammatory parietal infiltration of the right colon. A peritoneal lavage and a liver biopsy were performed. Cultures of peritoneal samples remained negative. The microscopic liver examination revealed zygomycosis. A synergistic combination of liposomal amphotericin B (10 mg/kg of body weight/day) and caspofungin was started (9). Two weeks later, in the context of fever, posaconazole was added. Blood cell count was restored slowly, and fever resolved. One week later, after a clinical improvement, she was admitted to the intensive care unit for severe sepsis. A computed tomography (CT) scan revealed a right alveolar syndrome, multiple liver abscesses (Fig. 1a), and a large infiltration of the colon wall. A bronchoalveolar lavage and biopsy ruled out pulmonary zygomycosis. A new surgical intervention consisted of a right colectomy and a liver necrosectomy. Histopathology confirmed an extensive zygomycosis. Deferasirox (25 mg/kg/day) was added. One week later, peritonitis signs reappeared. The third surgical examination was combined with a right thoracotomy because of diaphragm necrosis extending to the lung. Diaphragm samples showed necrosis. Three weeks later, abdominal lesions of zygomycosis increased (Fig. 1b) and motivated a surgical debridement because of a complete liver necrosis. Major bleeding occurred during the hepatic dissection, and a right hepatectomy was required. In the postoperative setting, the patient died of multiple organ failure.

The mortality of disseminated zygomycosis may reach 100% (8). Hepatic lesions are often considered as bowel fungal metastases by dissemination to the liver via portal venous circulation (4, 8). Through their marked angiotropism, zygomycetes create thrombosis, infarction, and bleeding (4, 8, 10). Because of the severity of this case, a combination of caspofungin, high-dose liposomal amphotericin B, and posaconazole therapy was initiated (9). Zygomycetes require iron storage for growth and pathogenicity (1). An iron chelator like deferoxamine acts as a xenosiderophore for zygomycetes, supplying previously unavailable iron (1). In contrast, other drugs such as deferiprone and deferasirox, the first orally bioavailable iron chelator, induce iron starvation for zygomycetes (1, 3, 5). Deferasirox decreases tissue fungal burden synergistically with liposomal amphotericin B (4). Deferasirox is also known to enhance the host inflammatory response to zygomycetes (3). We added deferasirox therapy 3 weeks after the diagnosis and for 1 month. But several potential factors may explain the deferasirox failure here: its poor bioavailability in the context of abdominal surgery or its lack of efficacy against the isolate encountered. In disseminated zygomycosis, further studies clarifying the role of iron chelators are thereby mandatory (3, 5).

REFERENCES

1. **Boelaert, J. R., M. Locht, J. Van Cutsem, V. Kerrels, and A. Cantinieaux.** 1993. Mucormycosis during deferoxamine therapy is a siderophore-mediated infection. In vitro and in vivo animal studies. J. Clin. Investig. **91:**1979–1986.

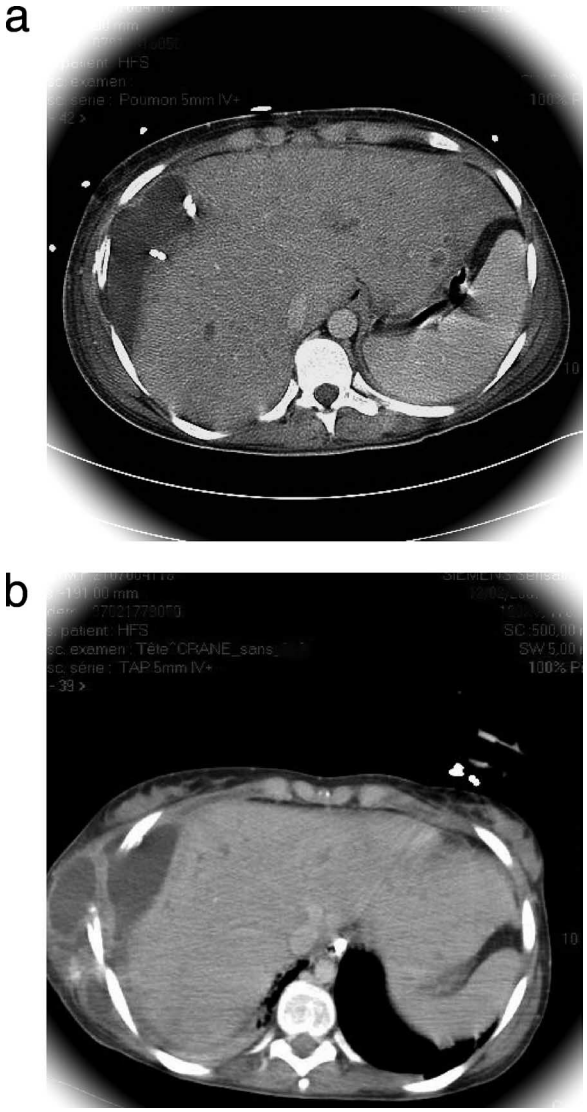

FIG. 1. (a) Abdominal CT scan: multiple hypodense lesions and a large liver abscess related to zygomycosis. (b) Three weeks after deferasirox therapy onset, abdominal CT scan showed an increase of the liver lesions with a subcutaneous involvement.

2. **Dannaoui, E., J. Meletiadis, J. W. Mouton, J. F. G. M. Meis, P. E. Verweij, and the Eurofund Network.** 2003. In vitro susceptibilities of zygomycetes to conventional and new antifungals. J. Antimicrob. Chemother. **51:**45–52.
3. **Ibrahim, A., T. Gerbermariam, Y. Fu, L. Lin, M. Husseiny, and S. French.** 2007. The iron chelator deferasirox protects mice from mucormycosis through iron starvation. J. Clin. Investig. **117:**2649–2657.
4. **Ibrahim, A. S., B. Spellberg, V. Avanessian, Y. Fu, and J. E. Edwards.** 2005. *Rhizopus oryzae* adheres to, is phagocytosed by, and damages endothelial cells in vitro. Infect. Immun. **73:**778–783.
5. **Ibrahim, A. S., J. E. Edwards, Jr., Y. Fu, and B. Spellberg.** 2006. Deferiprone iron chelation as a novel therapy for experimental mucormycosis. J. Antimicrob. Chemother. **58:**1070–1073.
6. **Marty, F. M., L. A. Cosimi, and L. R. Baden.** 2004. Breakthrough zygomycosis after voriconazole treatment in recipients of hematopoietic stem-cell transplants. N. Engl. J. Med. **26:**350–352.
7. **Reed, C., A. Ibrahim, J. E. Edwards, I. Walot, and B. Spellberg.** 2006. Deferasirox, an iron chelator agent, as salvage therapy for rhinocerebral mucormycosis. Antimicrob. Agents Chemother. **50:**3968–3969.
8. **Spellberg, B., J. Edwards, and A. Ibrahim.** 2005. Novel perspectives on mucormycosis: pathophysiology, presentation and management. Clin. Microbiol. Rev. **18:**556–569.
9. **Spellberg, B., Y. Fu, J. E. Edwards, Jr., and A. S. Ibrahim.** 2005. Combination therapy with amphotericin B lipid complex and caspofungin acetate of disseminated zygomycosis in diabetic ketoacidotic mice. Antimicrob. Agents Chemother. **49:**830–832.
10. **Zeller, V., and O. Lortholary.** 2004. Vasculitis secondary to fungal infections. Presse Med. **33:**1385–1388.

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