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Fatal Community-Acquired Peritonitis Due to Invasive Necrotizing Intestinal Mucormycosis: Case Report and Review of the Literature

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Abstract

We report here a rare case of fatal rapidly progressive necrotizing gastrointestinal mucormycosis due to *Mucor circinelloides f. circinelloides* in the setting of community-acquired peritonitis, in an immunocompromised adult patient. Diagnosis was established by direct examination of peritoneal fluid showing hyphae consistent with mucormycosis confirmed by the culture.

Keywords: Invasive fungal infection, mucormycosis peritonitis

Main Points

- Think of a mucormycosis in case of atypical peritonitis, especially in immunocompromised patient.
- The clinical picture can be misleading initially.
- Medicosurgical treatment is needed.

Case Presentation

A 67-year-old woman with a history of rhizomelic pseudopolyarthritis disease, treated with long-term corticosteroids since 2012 at the daily dose of 5 mg per day, was referred to the emergency department for acute abdominal pain and intestinal occlusion. On admission (day 0), baseline C-reactive protein was 20 mg L^{-1}, 6200 μL WBC, and liver and kidney functions were normal (urea 5.3 mg dL^{-1}, creatinemia 0.70 mg dL^{-1}, AST 17 IU L^{-1}, ALT 15 IU L^{-1} and GGT 19 IU L^{-1}). On day 1, her clinical status deteriorated with acute respiratory failure and haemodynamic instability requiring admission to the intensive care unit. On arrival, rapidly progressive neurologic disorder and Glasgow coma scale (GCS) < 8 required intubation in addition of persistent haemodynamic instability despite high dose of norepinephrine. Biological biomarkers showed high lactic acidemia, renal failure and massive hepatic cytolysis. A computed tomography (CT)-scan showed sigmoidal perforation prompting surgery. Extemporaneous examination of the peritoneal cavity found generalised stercoral peritonitis with an aspect of "green peritoneum" over the whole peritoneal surface. The surgical procedure consisted in a sigmoidectomy without restoration of continuity, small bowel resection, lavage and laparostomy. Intravenous antibiotics (piperacillin-tazobactam, metronidazole and amikacin), fluconazole and hydrocortisone supplementation were promptly initiated. Upon surgery, patient's clinical status further deteriorated with multiple organ failure associating acute respiratory distress syndrome, haemodynamic dysfunction requiring high doses of norepinephrine infusion and renal

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replacement therapy. A second surgical exploration performed on day 2 revealed massive necrosis of the epiploon, therefore omentum resection along with pleural drainage was performed. At day 4, fungal culture from peritoneal fluid recovered from the first surgery became positive with Mucorales, which prompted the initiation of liposomal amphotericin B (L-AmB, 5 mg kg^{-1} a day from the start). The third surgical look at day 4 found multiple necrotizing areas across the digestive tract. Fourth look at day 6 led to abdominal wall closure without resection. All intraoperative peritoneal fluid samples yielded colonies of *Mucorales* identified by mass spectrometry as *Mucor circinelloides* confirmed then *as Mucor circinelloides f. circinelloides* using PCR sequencing targeting the D1/D2 region of the large subunit of ribosomal DNA. Furthermore, specific Mucorale PCR performed on whole blood was positive on day 7 (positive target: *Mucor/Rhizopus*). The diagnosis of rapidly progressive invasive mucormycosis resulted in increasing the dose of L-AmB at 10 mg kg^{-1} and the addition of isavuconazole (200 mg as loading dose then 200 mg per 8 h as a rescue combination therapy). Bacteriological findings revealed faecal flora including *Escherichia coli*, *Streptococcus* spp., *Enterococcus faecalis*, *gallinarum* and *faecium*, leading to the addition of intravenous vancomycin. Upon sedation interruption, the patient showed no sign of awakening, except opening of the eyes to pain stimulation. A neck and head CT-scan showed a posterior pharyngeal abscess, fusing along the intubation tube, with osteolysis of nasal turbinate, ischemic plaques under cortical left frontal and cortico-subcortical parieto-occipito-temporal right and left parietal regions. Electroencephalogram showed a slowing brain activity and no grapho-epileptogenic element. MRI found bifocal ischemic recent lesions probably of septic origin or due to vasculitis associated with right temporo-parietal haemorrhagic lesions. Considering the lack of clinical improvement, several clinician-family conferences about prognosis were realised, and a strategy of care withdrawal was decided.

Discussion

Mucormycosis is a rare and often-fatal invasive fungal infection (IFI) caused by fungi of the *Mucorales* order, an ubiquitous environmental mould found in decaying organic substrates. In a review of 929 reported cases of confirmed mucormycosis, 47% were attributed to the genus *Rhizopus*, 18% to *Mucor*, 7% to *Cunninghamella* and 4% to *Rhizomucor*.[1] Mucormycosis frequency is increasing in France, and the use of molecular diagnostic tools has led to optimise the diagnosis, which may partly explain the recent rise in incidence.

Mucormycosis is opportunistic necrotizing infections mostly associated with intrinsic host immune deficiency such as neutropenia, corticosteroids, haematological malignancy and solid organ or haematopoietic stem cell transplant. Other risk factors are diabetes mellitus, direct inoculation through traumatic injuries (soil-contaminated wounds) and in critically-ill burned patients with extensive soft-tissue damages. Tissular localisations may be rhino-orbital, cerebral, pulmonary, cutaneous, disseminated, gastrointestinal or miscellaneous. Cerebral invasion by Mucorales has an extremely poor survival.[2] Gastrointestinal mucormycosis is difficult to assess due to nonspecific clinical symptoms or signs and poor level/degree of suspicion.[3] Gastro-intestinal mucormycosis generally occurs after ingestion of contaminated food. Peritonitis is rarely described, and its occurrence has been mostly associated with continuous ambulatory peritoneal dialysis.[4] An unusual case of peritonitis due to *Mucor* complicated with invasion of the colon, an intestinal perforation in the setting of corticosteroids and azathioprine treatment, has been described previously.[5] Another case of total gastric necrosis with spontaneous perforation due to mucormycosis has been reported in the setting of heroin abuse, diabetes mellitus, hypertension and chronic kidney disease treated by dialysis.[6] At the tissular level, angio-IFIs induce massive necrotizing vasculitis. Thromboembolic dissemination of fungi leads to obstruction of vessels due to the ability of fungi to adhere to endothelium. Direct vascular invasion causes angionecrosis and contributes to dissemination. A review of 200 cases of gastrointestinal mucormycosis in apparently immunocompetent hosts has been recently published, showing that 50.6% of the cases were recorded in Asia.[3] All cause mortality rate was estimated to be 54% and reached up to 96% in the case of disseminated disease. The infection commonly affected the intestine (64.2%) followed by stomach (33%); *Rhizopus* species were the predominant (67.5%) etiological agents.[3]

Diagnosis of invasive mucormycosis may be clinically challenging, and direct examination and then culture remain the gold standard. The detection of DNA in blood may be related to the invasiveness of the fungus, as intravascular invasion is one of its main characteristics. A persistent positive qPCR after treatment initiation was associated with death, as described previously.[7] Despite the angioinvasive nature of *Mucorales*, blood cultures are very rarely positive.

Treatment options for invasive mucormycosis are limited. There have been no prospective randomised trials to define the optimal antifungal therapy. Surgery is strongly recommended and increase survival rates associated with treatment initiation. The recommended treatment is first-line L-AmB (at least 3-5 mg kg^{-1} per day).[8] The combination of medical and surgical treatments led to decreased mortality compared with antifungal therapy alone.[1,2,8] High-dose L-AmB 10 mg kg^{-1} of liposomal amphotericin B is recommended in the case of rhino-sino-orbito-cerebral involvement.[8] Caspofungin and L-AmB combination was shown to have a synergistic effect in diabetic ketoacidosis mice with mycormycosis on the account of the degradation of cell wall beta-glucan cross linking by caspofungin, which strengthens polyene entry into cells.[9] In the literature, there are several case reports of favourable outcome in patients, with mucormycosis, treated

with combination polyene–echinocandins.[10,11] Posaconazole is recommended as alternative and salvage therapy.[8] Combination antifungal therapy with L-AmB and posaconazole can also be considered for salvage therapy of mucormycosis.[12] Isavuconazole may be an effective treatment option for disseminated mucormycosis in patients who have been found unresponsive to other therapies, especially in combination treatment as the VITAL study showed isavuconazole activity against mucormycosis with efficacy similar to amphotericin B with good tolerance.[13] A successful combination therapy with L-AmB, caspofungin and isavuconazole has been recently described in a 7-year-old child treated for acute lymphocytic leukaemia complicated by disseminated mucormycosis during induction chemotherapy.[14] Controlled randomised trials are required to optimally address the issue of disseminated mucormycosis. Successful adjunctive combination immunotherapy has been reported with the use of interferon-γ and nivolumab.[15]

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