Sir,

Mucormycosis is a rare life-threatening infection caused by fungi of the order Mucorales. Neutropenia and other factors affecting immunity are the most frequent predisposing conditions to mucormycosis. We describe a rare case of mucor necrotizing fasciitis due to dipyrone-induced agranulocytosis. Idiosyncratic drug-induced agranulocytosis is considered a rare but life-threatening adverse event with an approximate incidence ranging from 2.4 to 15.5 cases per million population and a mortality rate about 10%. Early diagnosis and treatment are of paramount importance. Currently, researches must continue to find antifungal alternatives and new combinations of existing drugs. To our knowledge, this is the first report of a perineal necrotizing fasciitis due to Mucor.

A 79-year-old man with hypertension, chronic renal failure, and coelitis presented for a left inguinal hernioplasty. Surgery and the postoperative period developed without incidences, and the patient was discharged from hospital. For pain control, dipyrone (500 mg/day) and paracetamol (1 g/day) po were administered during hospital stay and after discharge.

After 6 days, he was admitted to the emergency department with intense proctalgia, and tachycardia (110 bpm), without other signs or symptoms. In the blood test, a severe neutropenia (10 neutrophiles/μl, 300 leucocytes/μl) was found, in addition to a infectious markers rise (C Reactive Protein 216 mg/L, procalcitonin 13.23 ng/ml) and hyperlactacidaemia (lactate 4.6 mmol/l). Treatment with dipyrone was considered the only cause of severe neutropenia.

The patient subsequently suffered a multiple organ dysfunction that required vasopressor support with norepinephrine and invasive mechanical ventilation after orotracheal intubation. Transabdominal ultrasonography, computed tomography of the abdomen and a colonoscopy were performed, without significant findings. Empiric antibiotic therapy was initiated with intravenous meropenem (3 g/day), tigecycline (100 mg every 12 h) and clindamycin (600 mg/day). Filgastrim (48000 μg/day subcutaneous) was also administered.

An aggressive surgical debridement was achieved after observing a perineal necrotizing fasciitis at surgical exploration. Pseudomonas aeruginosa and Streptococcus agalactiae were found in surgical cultures.

Due to a deteriorating clinical course, surgical debridement was repeated and finally an abdominoperineal amputation was accomplished with a perineal and abdominal Vacuum Assisted Closure (VAC) device implantation.

Notwithstanding, the multiple organ dysfunction did not improve, and the pathologic analysis revealed extensive inflammation and tissue infiltration with hyphae consistent with mucormycosis (figure 1 and 2). Immediate treatment with intravenous liposomal amphotericin B (5 mg/kg/day) was started, and maintained during 21 days.

In the end, the patient underwent a good clinical course, he was weaned from vasopressors and mechanical ventilation, and finally discharged to ward after 56 days of stay in the intensive care unit with normal leucocyte count.

Idiosyncratic drug-induced agranulocytosis is considered a rare but life-threatening adverse event with an approximate incidence ranging from 2.4 to 15.5 cases per million population and a mortality rate about 10%. Current drugs most commonly associated are antibiotics (beta-lactams, cotrimoxazole), antiplatelet agents (ticlopidine), antithyroid drugs, sulfasalazine, antipsychotics (clozapine), antiepileptic drugs (carbamazepine), and nonsteroidal anti-inflammatory drugs (dipyrone). Dipyrone administration is still nowadays a controversial issue, due to this life-threatening complication, but alternative analgesic and antipyretic drugs are not deprived of adverse events. The most common clinical findings are oropharyngeal infections, pneumonia, and gastritis. Up to two-thirds of hospitalized patients present septicemia, severe sepsis or even septic shock. Advanced age (>65 years), bacteremia, shock, renal failure, and a neutrophil count under 0.1 x10⁹/l are markers of poor prognosis. Nevertheless, an ear-

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Severe Mucor necrotizing fasciitis associated to dipyrone-induced agranulocytosis

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ly broad-spectrum antibacterial therapy and hematopoietic growth factor use could reduce the mortality rate up to 5% \(^1\).

Neutropenia and other factors affecting immunity (poorly controlled diabetes mellitus, hematological malignancies with or without stem cell transplantation, prolonged use of corticosteroids, desferoxamine use, iron overload, major trauma, malnourishment, illicit intravenous drug use, neonatal prematurity) are the most frequent predisposing conditions to mucormycosis. In developed countries it is less common, and it is normally associated to diabetes or hematological malignancies after chemotherapy or stem cell transplantation. Notwithstanding, in developing countries it occurs in diabetic patients or after major trauma. The global rate is increasing, and it is the third most common cause of invasive mycosis, following candidiasis and aspergillosis \(^3\). Mortality rate is quite important, ranging from 25 to 85% \(^4\).

Mucormycosis is a rare life-threatening infection caused by fungi of the order Mucorales, previously referred as Zygomycetes. It is an angioinvasive disease provoked by filamentous fungi normally found in decaying organic matter. Inhalation of fungal spores or direct inoculation into disrupted skin or mucosa induce most infections. Nevertheless, immunocompromised people are mostly affected by this disorder \(^5\). Invasive mucormicosis is classified as rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated and other rare forms. The most widespread reported sites are the sinuses (39%), lungs (24%), and skin (19%) \(^6\). Rhinocerebral presentation is the most common form, normally associated to diabetes mellitus. Necrotizing fasciitis is characterized by necrosis of skin, subcutaneous tissue and fascia, and is normally caused by a polymicrobial infection \(^7\).

The definitive diagnosis is histologic, and lipid-based amphotericin B is considered the primary medical therapy. This formulation enables better solubility into the central nervous system, what makes it suitable for rhinocerebral forms. Moreover, the lethal dose is much higher than that of conventional amphotericin B, with less renal toxicity. In consequence, when large doses for long periods of time are required, lipid-base formulation is the drug of choice. Liposomal amphotericin B together with surgical debridement and caspofungin seems the best therapeutic choice in order to improve survival \(^7\). Several studies found that the combination of medical and surgical treatment decreases the mortality rate under 20%, in contrast with only medical treatment, whose survival is 57.2% \(^5-9\). Recently, new therapies are emerging, as posaconazole, but concluding studies are required \(^10\).

As conclusion, mucormycosis is a rare but life-threatening disease. Mortality rate is quite important, ranging from 25 to 85%. Necrotizing fasciitis due to zygomicosis is an uncommon and often fatal complication, with scarce reports in the literature, mostly in patients with underlying immunosuppressive conditions such as diabetes, immunosuppressants or corticosteroids. The definitive diagnosis for invasive mucormycosis is histologic, and lipid-based amphotericin B is considered the primary medical therapy. Recently, new treatments have been proposed, although research must continue to find antifungal alternatives and new combinations of existing drugs. We must emphasize the impact of an early diagnosis and treatment in morbimortality rate. To our knowledge, this is the first report of a perineal necrotizing fasciitis due to *Mucor*.

**CONFLICT OF INTEREST STATEMENT**

No conflicting financial interests exist.

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