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Cutaneous mucormycosis by *Rhizopus arrhizus* treated with isavuconazole as first line therapy: A case report

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ABSTRACT

Mucormycosis are a group of infections that affect principally immunocompromised host and have a high mortality. Liposomal amphotericin B is the first-line treatment with combined surgical removal of the infectious focus. We report the case of 67-year-old man with idiopathic granulocytic aplasia and a cutaneous lesion caused by *Rhizopus arrhizus* treated with isavuconazole. Its safety profile and spectrum of activity make it an important therapeutic option.

1. Introduction

Cutaneous mucormycosis include a group of infections caused by environmental fungi. They affect principally the immunocompromised host and have a high mortality. The ECIL guidelines recommend liposomal amphotericin B as first line treatment and, whenever possible, the surgical toilette [1]. The azoles are used as possible oral therapy and for patients intolerant to liposomal amphotericin B [1]. In 2015, isavuconazole, a new azole, has been approved for invasive aspergillosis and invasive mucormycosis [2]. Its safety profile, wide spectrum of activity and no need for therapeutic drug monitoring make it an attractive alternative to the older drugs. Its efficacy for mucormycosis is based on VITAL trial where no difference in mortality was found between patients treated with Amphotericin B or isavuconazole [3]. We here report the case of a patient with a skin lesion caused by *Rhizopus arrhizus* and successfully treated with oral isavuconazole.

2. Case

In July 2016, a 67-year-old man, without relevant medical history, was diagnosed with idiopathic granulocytic aplasia and started on antithymocyte globulin, cyclosporine and steroids. In August 2018 (−100 days), he was on cyclosporine (130 mg twice daily) and prednisone (25 mg daily). During homework, he got injured by a dirty penetrative trauma on his left harm, resulting in a necrotic wound. He started empirical treatment with amoxicillin/clavulanic acid for 12 days (from day −100 to −88 day) and an escharotomy was successfully performed by the plastic surgeon with complete healing. In November 2018 (−21 days), a new and similar lesion occurred close to the site of the previous one. He was prescribed levofloxacin for 7 days (from day −21 to −14) and then amoxicillin/clavulanic acid per *os* for 14 days (from day −14 to −1) with no substantial benefit. He presented to the ER department with fever (38,1 °C) and persistence of the skin lesion (Fig. 1) on 30th November 2018 (day 0). He was admitted to hospital and started endovenous amoxicillin/clavulanic acid (2.2 gr) and clindamycin (600 mg) three daily. As no benefit occurred, a skin biopsy was performed on day +4, showing the presence of degenerate hyphae, while the culture of biopsy yielded *Rhizopus arrhizus*. The patient was started on isavuconazole 200 mg daily (after a loading dose) for a total of 3 months (from day +4 to +94) day and weekly medications at plastic surgery ambulatory with exposition of the wound, disinfection, position of non-adherent surgical dressing containing a disinfectant and gauzes for bandage. The evolution of the skin lesion is shown in the Fig. 2 after 98 days. The drug was well tolerated, with no toxicity. No recurrence occurred at 6-month follow up (day +274).

3. Discussion

Mucormycosis are uncommon, frequently fatal diseases caused by fungi of the order Mucorales. The *Mucorales* species most often recovered from clinical specimens are those of the genera *Rhizopus* (the most common genus associated with mucormycosis), *Lichtheimia* and *Mucor* [4]. In a study conducted from 1992 to 1993 in San Francisco population the annual incidence was 1.7/1,000,000 individuals. Roden et al. reported 929 cases of mucormycosis from 1885 to 2004 [5]. The major risk factors for the development mucormycosis are malignant

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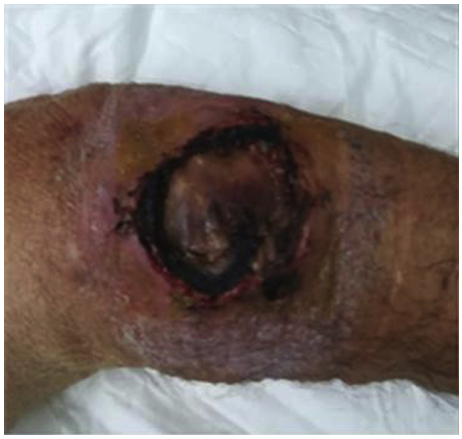

Fig. 1. Day 0.

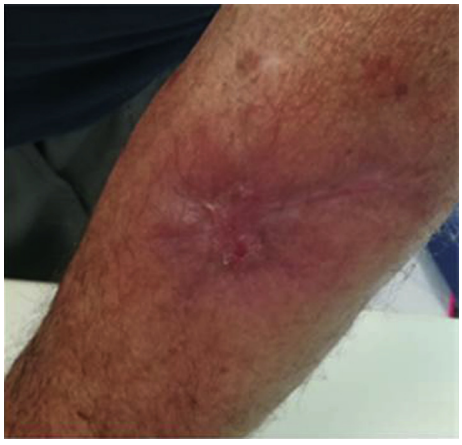

Fig. 2. Day + 94.

haematological disease with or without stem cell transplantation, prolonged and severe neutropenia, poorly controlled diabetes mellitus with or without diabetic ketoacidosis, iron overload, major trauma, prolonged use of corticosteroids, illicit intravenous drug use, neonatal prematurity and malnourishment [4]. In the Buchanan et al. review, the most common reported sites of invasive mucormycosis have been the sinuses (39%), lungs (24%), and skin (19%) [5]. Disseminated infection developed in 23% of these cases. Cutaneous mucormycosis results principally from direct inoculation of fungal spores in the skin, which may lead to disseminated disease. Skiada et al., in a review published in 2009 found 78 cutaneous cases reported in literature from 2004 to 2008 [6]. The principal risk factors are the same of invasive forms although the cutaneous form also occurs in immunocompetent or individual with no underlying conditions in a relevant percentage of cases [5–7]. Zahoor et al. in a review reported 99 cases secondary to a penetrative trauma [8]. It was found that the recurring episodes of sepsis, shock, multiple blood transfusions, which occur in many trauma patients, reduced an immune-deficient state predisposing the development of mucormycosis [8]. The mortality and morbidity of mucormycosis remains very high, also for cutaneous forms. In an old study conducted in 1994, the mortality was estimated at 35% [9]. In a review that has compared mucormycosis following traumatic injury in civilians and soldiers, the surgical amputation rate was 12–83% in civilians and 19–77% in military, with an overall mortality rate of 7.8% and 25–41% respectively [10]. According to ECIL guidelines the surgical management is the first therapeutic option [1]. In a retrospective study conducted in French of posttraumatic mucormycosis, 80% of the patient received combination of surgical and medical management, with multiple debridement in 6 patients and amputation in 2 cases [11]. The mortality in the entire cohort was 12.5%. Some authors even suggest that If the disease is locally advanced in extremities, a limb amputation may be considered [12]. The antifungal drug recommended by guidelines is Amphotericin B [1]. The dosage recommendation is up to 10 mg/kg of Liposomal Amphotericin B but a significant nephrotoxicity can develops if administered for more than a few days. In 2015, FDA approved isavuconazole for treatment of invasive mucormycosis [2]. There is no clinical data about the usage of isavuconazole for cutaneous mucormycosis except a case report where it is used in disseminated form with skin involvement with complete healing [13]. In recent review isavuconazole showed an excellent *in vitro* activity against *Rhizopus arrhizus* and it has an optimal safety profile [14]. In conclusion, our case suggests that isavuconazole may be an option in cutaneous mucormycosis as an oral and well tolerated drug.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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