

Cutaneous Fusariosis by a Species of the *Fusarium Dimerum* in Acute Myeloblastic Leukemia Patient: A Case Report

Ikram Sebbane^{1, *}, Fatimaezzahra Lahlimi¹, Illias Tazi¹, Asmaa Lahrougui², Said Amal²

¹Department of Hematology and Bone Marrow Transplantation Mohammed VI University Hospital, Cadi Ayyad University, Marrakesh, Morocco

²Department of Dermatology Mohammed VI University Hospital, Cadi Ayyad University, Marrakesh, Morocco

Email address:

ikramsebbane24@gmail.com (I. Sebbane)

*Corresponding author

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Abstract: *Fusarium* is the second most common cause of fungi infections in the immunocompromised patients with the mortality rate over 80%. *The Fusarium Dimerum* is the less common species. In immunocompromised patients, spatially with prolonged neutropenia, the presenting features of *Fusarium* infections include persistent refractory fever, localised symptoms such as invasive infections, sinusitis, pneumonia, deep cutaneous infections, and disseminated infections. The dermatological manifestations include onychomycosis, a localised cellulitis at the site of injection, diffuse skin nodules or vesicles in disseminated disease. The diagnosis of skin fusariosis mainly based on cultures from the skin growing *Fusarium* species and skin biopsy. Amphotericin B represent the potential treatment for *Fusarium* infection, however, voriconazole is increasingly being used to treat infections unresponsive to the more conventional antifungals. Despite medical intervention, treatment of emerging fungal infections is a major challenge, with no standardized therapy and high mortality rates. We describe the case of Cutaneous fusariosis in a patient with acute myeloid leukemia (AML) undergoing induction chemotherapy. The patient had profound neutropenia and developed multiple ulcerous lesions. The diagnosis of cutaneous infection with *Fusarium Dimerum* was made on the basis of histopathological findings and skin biopsy culture. The patient was treated with liposomal amphotericin B but, neutropenia perduring, her clinical condition deteriorated with fatal outcome.

Keywords: Cutaneous Fusariosis, *Fusarium Dimerum*, Acute Myeloid Leukemia

1. Introduction

Fusarium Dimerum is a well known opportunistic mould capable of producing life-threatening diseases. It is an extremely prevalent cause of mycotic infections, particularly in immunocompromised patients. It is associated with poor outcome [1].

The most encountered *Fusarium* mold includes the *Fusarium solani* species complex whereas *Fusarium dimerum* is a rare plant pathogen [2].

Infections caused by *Fusarium* are often localized on the skin, presenting as purple nodules with central necrosis. A higher risk of dissemination is noted in patients with

hematologic malignancies, and those undergoing chemotherapy. Mortality from *Fusarium* infections in immunocompromised patients ranges from 50% to 80%. Optimal treatment has not been established [3].

Here, we describe the case of a patient with Acute Myeloblastic Leukemia (AML) who developed fusariosis by a species of the *Fusarium Dimerum* species complex.

2. Case Presentation

A 57-year-old women with medical history of thyroid Hodgkin's lymphoma treated in 2014, presented with secondary AML. She was hospitalized in the department of

Hematology for induction chemotherapy (daunorubicin, cytarabine) without antibiotic or antifungals prophylaxis.

While hospitalized for induction chemotherapy on October 2021, the patient had a prolonged neutropenia and at the 19th day of chemotherapy-induced neutropenia, the patient presented necrotizing fasciitis and she was immediately treated by cephalosporin, metronidazole and Vancomycin. Because of neutropenia and persistent fever, thoracic scanning was performed and demonstrated an invasive pulmonary aspergillosis. The patient was treated empirically with Voriconazole that was switched to amphotericin B because of neurologic toxicity. The patient's fever resolved two days later.

On the 26th day of chemotherapy-induced neutropenia, the patient presented the multiple skin lesions with different appearances: red and gray macules and papules with central necrosis, purpuric papules, pustules, and subcutaneous nodules and deterioration of clinical condition (figure 1).



Figure 1. Multiples pseudococcaroid nodular skin lesions poorly limited, non-fistulated with a necrotic centre and purpuric periphery of varying sizes ranging from 1cm to 2cm located on the face and knee.

On the 28th day and the 13th day of amphotericin B, Skin biopsy with mycologic examination confirmed the diagnosis of *fusarium Dimerum* (figure 2). The blood culture test was negative.

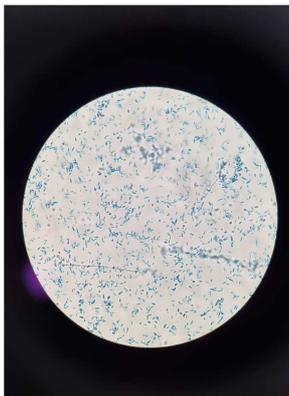


Figure 2. Microscopic view of *fusarium dimerum* isolated in this observation.

Bone marrow aspiration at 29 days of chemotherapy confirmed the failure of induction by medullary infiltration of 58% blasts.

After 3 weeks of amphotericin B treatment, no improvement of skin lesions was observed and the patient died of septic shock.

3. Discussion

The *fusarium dimerum* is rare emergent opportunistic mould infection, disease caused by filamentous, hyaline fungi of the *Fusarium* genus. It was described at first by Johann Heinrich Friedrich Link in 1809 and includes over 100 species. it represents the second major cause of fungal infection after Aspergillosis in immunocompromised patients. It is ubiquitous and distributed in soil, plants and air. They are common in tropical and temperate regions but are also found in desert, alpine and arctic areas [3].

The most commonly involved in human disease are *Fusarium solani*, *Fusarium oxysporum*, and *Fusarium moniliforme*, and the less is *fusarium dimerum*.

The *fusarium* may affect the human and cause a superficial, locally invasive or disseminated infection. Its depend of the mode of contamination and the host's immune status [4].

Patients with hematologic malignancies often have a decreased integrity of host defense mechanisms, remain at particularly risk of infections, including invasive fungal infections.

Fusarium Dimerum is a very rare opportunistic fungus, and considering patients with hematological malignancy, recent real-world data showed the incidence of proven or probable invasive fungal infections was 11% in patients with acute myeloid leukemia (AML) [5].

The first induction therapy is associated with the highest risk of fungal infections in patients treated for AML affecting 61% of cases as in the case of our patient, and much higher in patients with severe neutropenia (95%) compared with those with moderate neutropenia (5%).

Much like other *Fusarium* species, it causes infections in immunocompromised patients especially burn victims, patients with hematologic malignancies, and those undergoing chemotherapeutic treatments with high risk of dissemination [6]. The incidence of lethal fungal infections has risen dramatically in patients with prolonged neutropenia due to leukemia therapy [7].

Although primary antifungal prophylaxis is routinely administrated in patients with acute myeloid leukemia during induction chemotherapy, the incidence of rare mold infections is still described and is associated with treatment failure and high mortality rate. Its remains a challenge for both clinicians and microbiologists [7].

Despite marked advances in antifungal therapy, fusariosis in immunocompromised individuals infections continue to be associated with high morbidity, mortality, and poor prognostic, mainly because of the low sensitivity of these fungi to the antifungal drugs available [8].

The patients acquire infection occurs through inhalation of airborne conidia or through skin lesion [9].

Fusarium clinical manifestations include refractory fever (> 90%) unresponsive to broad-spectrum antibiotic therapy in a neutropenic patient, such as the patient studied, invasive sinus infection, cutaneous and soft tissue infection, fungemia, pulmonary infection and dissemination to multiple organs with arthritis and osteomyelitis. Ocular infections such as keratitis, endophthalmitis both in immunocompetent and in immunosuppressed patients are also reported [7].

In disseminated fusariosis, the skin is affected in more than 70 percent of cases [4].

Skin lesions typically appear as red or grey macules, which may develop central ulceration and black eschar. Secondary dissemination to extracutaneous organs may occur in immunocompromised hosts, especially those with prolonged and severe neutropenia [10].

Fusarium species possess several virulence factors including the ability to produce mycotoxins such as trichothecenes, which suppress humoral and cellular immunity, infect and damage various plants and also to produce proteases and collagenases [1].

An extensive evaluation including computed tomography scan, echocardiogram and blood cultures should be performed to look for possible occult seeding [11].

Identification at species level is important and recommended for an epidemiological statistic but also for the choice of appropriate antifungal treatment because of the variable antifungal susceptibility between the different *Fusarium* species [12, 13].

Three levels of probability of fusariosis are proposed: “proven,” “probable,” and “possible.” The definitions are intended for use in the context of clinical and/or epidemiological research, not for clinical decision making.

The diagnosis is confirmed by positive fungal cultures and histopathological examination.

Confirmatory diagnosis of fusariosis by histopathology is strongly recommended by the European Confederation of Medical Mycology and European Society of Clinical Microbiology and Infectious Diseases (ECMM/ESCMID) guidelines [14].

In contrast with aspergillosis, where blood cultures are nearly always negative, fusariosis is accompanied by positive blood cultures in 40–50% of the patients [15].

If the culture of *Fusarium* is positive, multi-locus sequence typing (MLST) identification is the best option for species-level identification. However, if these specific tools are not available in the laboratory, the use of another molecular and/or peptide-based tool is recommended. Techniques like microsphere/liquid phase arrays and MALDI-TOF may be faster in making a species-level diagnosis. Combining different tools will improve the specificity of identification [13].

Rapid identification of fungal isolates based on morphological characteristics of cultures, and, this is still the standard for identification for many laboratories allows rapid prescription of antifungals. However, it is not enough for a correct management of the infection. The diversity of species involved in fusariosis is underestimated because of the frequent lack of identification at a species level. The species distribution varies per geographic region and different species have different drug susceptibility patterns.

The most important antifungal agents (antimycotics) clinically used for treating fusariosis demonstrate poor efficiency in vitro and in vivo. Of the antifungal treatments available:

Several studies have shown the *Fusarium* to be a very resistant pathogen except amphotericin B which showed the best activity in vitro against most of the species responsible

for fusariosis. with about 50% of isolates being susceptible to this drug. Unfortunately the correlation between in vitro values and clinical efficacy is low and a few patients remain unresponsive to treatment despite in vitro susceptibility.

In vitro studies are encouraging, but the clinical data are insufficient to allow firm conclusions to be drawn [16].

In this case, our patient was already treated amphotericin B for her invasive pulmonary aspergillus when she developed the skin lesions and *F. Dimerum* was rapidly detected in her skin biopsy. we continued the amphotericin B because it is considered the mainstay of treatment for fusariosis [6]. In patients known to be intolerant or have conditions that contraindicate the use of amphotericin B, voriconazole is active against *Fusarium* species both in vitro and in vivo [17]. Posaconazole can be also suggested as a therapy for fusariosis.

The United States Food and Drug Administration (USFDA) has approved voriconazole and posaconazole as standard therapy for fusariosis in immunocompromised patients [18].

Although amphotericin B is the gold standard in the treatment of infections caused by *Fusarium Dimerum*, it wasn't enough to save our patient. One explanation might be related to the low sensitivity of these fungi to amphotericin B [15]. Another explanation might be that despite multiple negative blood cultures, the presence of a concomitant bacterial infection was the main cause of the septic shock causing the death for our patient.

Combination therapy with amphotericin B, voriconazole, itraconazole, and echinocandins have been previously reported, but more studies are required to explore the real benefit of this approach. Granulocyte transfusion is often considered as a supporting care for patients with prolonged and severe neutropenia or abnormal leukocyte function and severe infection. Although the efficacy is not well established, some authors suggest a beneficial effect, based on uncontrolled case reports and case series [19].

Evolution and treatment of mycotic infections are difficult to monitor because of multiples factors: direct microscopy and successive cultures are not always performed; antifungal susceptibility testing is not done; the limited prospective trials treated those particular species of fungus; Delayed treatment initiation of fusarium increases disease progression and development of complications which may lead to a higher level of infectiousness, clinical severity and increased mortality; the patient may have a critical immune status; poor compliance and follow-up because of lower socio-economic sector of population [20].

Fusarium Dimerum species is highly unusual contributing to less than 2% of cases with only few cases reported in the literature. Therefore, complete identification of the fungi and its antifungal susceptibility pattern is of high interest to improve our knowledge about the epidemiology of the disease. This case demonstrates the complexity of management of infections caused by *Fusarium Dimerum* species especially in neutropenic patients.

The high risk of mortality necessitates prompt screening using histologic and mycologic diagnostics.

Fusariosis is a rare fungal infection and thus does not have

substantial clinical evidence regarding its infectivity, management, and treatment options, especially in vulnerable population with others concomitant bacterial infections and comorbidities [15].

4. Conclusion

Fusariosis is a rare fungal infection but a more common fungal infectious agent in immunocompromised patients, especially in patients with hematologic malignancy or those undergoing chemotherapy. It should be considered in patients with signs of a systemic infection and not responding to conventional antimicrobial agents. The outcome in patients with of persistent and severe neutropenia has been almost universally fatal[6].

The case we report of a remarkable and unusual species involved on fungal infection and its poor outcome. The high-dose intravenous amphotericin B is considered the mainstay for the treatment of fusariosis but the mortality among neutropenic patients is high regardless of whether the lesions were localized or metastatic [3].

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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