Medical Mycology Case Reports 15 (2017) 21–24

Contents lists available at ScienceDirect

Medical Mycology Case Reports

journal homepage: www.elsevier.com/locate/mmcr

A rare fungal infection: Phaehyphomycosis due to *Veronaea botryosa* and review of literature

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ARTICLE INFO

Keywords:
Phaeohyphomycosis
Immunosuppression
Heart transplant recipient
V. botryosa

ABSTRACT

We report a rare case of phaehyphomycosis in a 71-year-old heart transplant recipient Togo native patient. Four months after the transplant, he presented painless nodules on the right heel with superficial ulceration. The polyphasic identification uncovered a rare cause of phaehyphomycose: V. botryosa. The treatment combined surgical excision of the lesions and anti-fungal therapy with posaconazole. We discussed eleven reported cases in literature since 1990.

1. Introduction

Infectious complications, especially fungal, are common in transplant recipients due to the underlying immunosuppression. We report a rare case of phaehyphomycosis Veronaea (V.) *botryosa* in a heart transplant recipient. The originality of this phaehyphomycosis is the rarity of the species identified. In the literature, 11 other cases of *V. botryosa*-induced cutaneous phaeohyphomycosis have been reported since 1990 including 3 cases in transplant recipients. This case highlighted the importance of careful research of fungal infection in immunocompromised transplant recipients and monitoring of the immunosuppressive regimen.

2. Case

A 71 year old native Togo patient, who has been living in France since 1970 and has not been back to Africa for 20 years, also a heart transplant recipient, was hospitalized for nodules on his right heel. The nodules were painless and slowly progressive with superficial ulceration (1A and 1B). His significant medical history included hypertension, insulin-dependent diabetes mellitus, and ventricular tachycardia with implantable defibrillator. He had a history of hypertrophic cardiomyopathy that required a heart transplantation on May 2014 (day 1), and was complicated by several bacterial infections (Enterobacter cloacae, *Enterococcus faecalis, Pseudomonas aeruginosa*), fungal infections (*Fusarium* sp. ascites), and a postoperative CMV reactivation. His immunosuppressive treatment included mycophenolate mofetil 500 mg×2/d, corticosteroids 10 mg/d, and cyclosporine 125 mg×2/d, (concentration of 197 ng/ml target 200–250). The skin nodules developed a few months after transplantation, on August 2014. In December 2014 (day 210), histological analysis of skin biopsy demonstrated multinucleated giant cells, epidermal hyperplasia, abscesses with neutrophil infiltrates (1C) and pigmented conidia with positive Grocott staining (1D).

The isolate was sent to the National Reference Center for Invasive Mycoses and Antifungals (NRCMA), Institut Pasteur, Paris, for speciation. The microscopic examination of a velvety blackish-brown colony on 2% malt agar (MEA), revealed straight to flexuous, smooth-walled melanized conidiophores (2A and 2B). Conidiogenous cells were mostly terminal, bearing 1-septate smooth-walled cylindrical conidia truncated at the base. On the basis of its morphological features, the filamentous fungus was identified as *Veronaea botryosa*. Molecular confirmation was ascertained by the amplification and sequencing of the ITS1-5.8S-ITS2 region of the ribosomal DNA [1]. Comparison of the nucleotide sequence of the isolate (623 bp) with GenBank database showed a 99.8% identity (623/622) with *V. botryosa* type strain CBS 254.57 (GenBank NR_103593.1).

Due to the immunodeficiency of the patient, a staging was performed (PET scan and brain imaging) which returned normal. Lymphopenia (210/mm3) was noted in the blood test. The treatment included surgical excision of the lesions and anti-fungal therapy with posaconazole 400 mg twice a day for 3 months. The evolution of the lesions was favorable, but a few months later (day 330), the patient died from septic shock (*Klebsiella pneumonia* and *Escherichia coli septicemia*) (Figs. 1 and 2).

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http://dx.doi.org/10.1016/j.mmcr.2017.02.001
Received 23 October 2016; Received in revised form 25 January 2017; Accepted 3 February 2017
Available online 05 February 2017

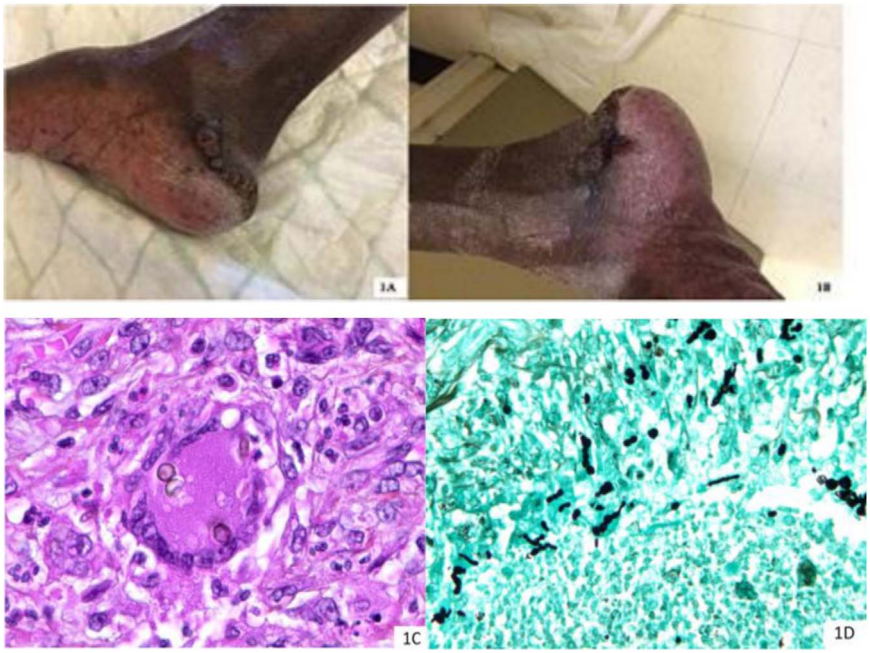

Fig. 1. painless nodules, with superficial ulceration (1A and 1B). (1C and 1D) original magnification ×400 Histological analysis of skin biopsy demonstrated multinucleated giant cells containing pigmented spores, (hematoxylin eosin stain) (1C) Grocott staining showed numerous spores (1D).

3. Discussion

Phaehyphomycosis is defined by the presence of melanized yeast-like cells or hyphae in tissues. Patients diagnosed with phaeohyphomycosis are often immunocompromised (diabetics, transplant recipients, patients on immunosuppressive drugs or steroids). These fungi induce subcutaneous and systemic opportunistic and cosmopolitan infections [2]. They are saprophyte of plants, water, and earth. Their transmission mode is land-based, through contaminated water or vegetable items. The melanin present in the cell wall is a known virulence factor. The physiopathology of the infection remains unclear, but some authors speculate that the organism is acquired previously, remained quiescent, and is reactivated due to immunosuppression [3]. [4], The uniqueness of this phaehyphomycosis case is that the species found is extremely rare. To date, only 11 cases of *V. botryosa*-induced cutaneous phaeohyphomycosis have been reported since 1990. We report here the main characteristics of these patients (Table 1): most patients were native**s** from Asia, the mean (age: 51,7 years old, and most of them were males (8 men/12 cases with our case). This is the third reported case of *V. botryosa* infection in a transplant-recipient. The clinical presentation was papulo-nodules or ulcerations, mainly on the lower limbs. All patients were treated by anti-fungals and four with surgery leading to a favorable outcome with resolution of the lesions for 7 patients.

V. botryosa can induce both chromoblastomycosis (chronic disease of the skin and subcutaneous tissues in tropical regions characterized by the presence of fumagoid cells and phaeohyphomycosis). The clinical presentation of phaehyphomycosis is polymorphic (only skin involvement, systemic, superficial, or deep infection). It requires both histopathological and mycological analysis. Histological diagnostic criteria include the presence of brown hyphae, septate vesicular thickened wall to dark brown accompanied by yeast-like elements poorly systematized in an inflammatory granuloma. The cell wall is pigmented and stained by Gomori Grocott. Histology displays a cystic abscess with granulomatous reaction. Identification of the species involved is essential since many different species can be responsible for phaeohyphomycosis. Lack of sporulation for the isolate prevented antifungal susceptibility testing. However, previous studies have shown that the species usually exhibits high minimal inhibitory concentrations (MIC) of amphotericin B, terbinafine, voriconazole and echinocandins with lower MICs of itraconazole and posaconazole [5]. The patient was thus prescribed posaconazole together with surgical resection of the lesion. Most of the cases reported were only prescribed antifungal drugs. Phaeohyphomycosis should be kept in mind in transplant recipients.

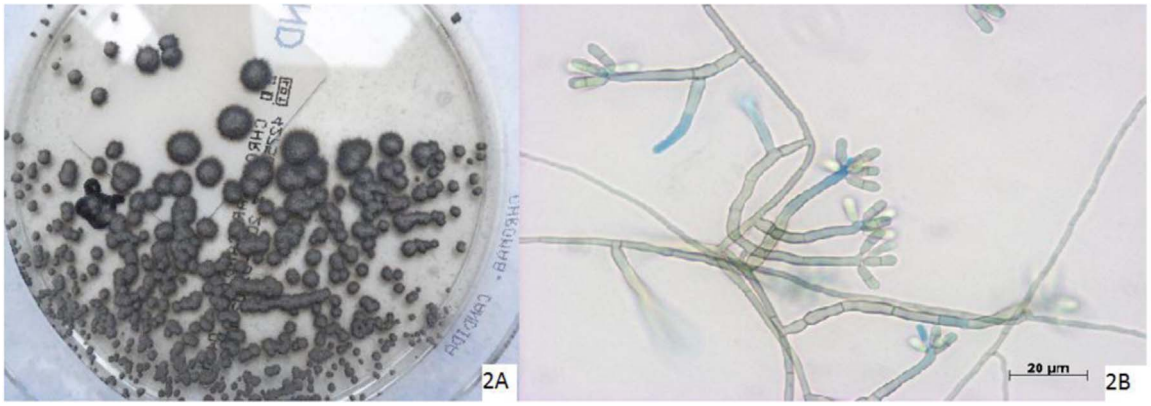

Fig. 2. Culture on Sabouraud chloramphenicol at 27 °C (2A). Micromorphology of conidiophores, conidiogenous cells and conidia of *V. botryose* (2B).

Table 1
Reported cases of *V. botryosa* induced cutaneous phaeohyphomycosis.

Case (ref.)	Years	age/Sex	Country origin	Immunosuppression/comorbidities	Soil or plant exposure	Clinical presentation	Treatment	Follow-up
1/[6]	1990	24M	China	NA	Farmer	Black, verrucous nodules and cysts on back of hands, cheeks, and forearm	AmB and lesional excision without efficacy;	NA
2/[7]	1995	28F	Libya	NA	NA	Nodular-ulceronodular lesions on thumb and fifth finger, upper limb, nasal mucosa, and palate	NA	NA
3/[8]	1998	37M	Philippines	NA	No	erythematous, pruritic papules on the right deltoid and left shin	Itracozazole	Healing
4/[3]	1999	57M	France	Liver transplant: appearance of lesions 11 weeks after transplantation	No	Multiple painless dermal nodules that coalesced and spontaneously yielded pus	Itraconazole	Healing
5/[9]	2003	81M	Taiwan	No/Chronic renale failure	Farmer	Swelling plaque, papulonodules on Left leg and dorsal foot	Debridement and Itraconazole	Healing
6/[10]	2003	12M	China	Unknown	No	Disseminated nodular lesions on face, upper limbs, legs, scrotum, and buttocks	Herbal medication thermotherapy, local AmB injection; Terbinafine, itraconazole	No effect
7/[4]	2004	62M	USA	Heart transplant	No	Area of chronic induration and tenderness over the dorsum of the right hand	Itraconazole and Vorinonazole (gastrointestinal complaints) and incision	Healing
8/[11]	2006	76M	Taiwan	No	Farmer	Crusted nodules and plaques. Right forearm and knee, left upper limb	Itraconazole/amB	No effect
9/[12]	2007	65F	Japan	VHC	Farmer	A erythematous, slightly scaly, indurated plaque on the dorsum of the left wrist of more than 3 years' duration	Surgical excision	Healing
10/[13]	2010	16F	China	No within 2–5 months of receiving an ear piercing	No	crusted, verrucous lesions, initially on the left ear and later on the left buttock	Itraconazole	Healing
11/[14]	2012	32F	Mexico	aggravated by pregnancy	No	Chronic dermatosis which started 10 years earlier with multiple Exophytic, multilobulated, soft, and penduculated or sessile neoformations of diverse sizes from 2 to 10 cm in diameter, which became verrucose and increased in size.	Posaconazole	Improvement of the lesions
12/[15]: Case reported in this article	2015	71M	France	Heart Transplant, four months after the transplant	NO	Painless, slowly progressive on the leg with superficial ulceration	Excision and Posaconazole	Death

Conflict of Interest

There are none.

Acknowledgements

We thank Dea Garcia-Hermoso (National Reference Center for Invasive Mycoses & Antifungals, Molecular Mycology unit, Institut Pasteur, Paris, France) for identification of the isolate and for the picture.

We thank Virginia Nguyen (Department of cardiology, Hospital Bichat, University Paris Diderot, Paris).

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