First Case of Trichoderma longibrachiatum Infection in a Renal Transplant Recipient in Tunisia and Review of the literature

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Premier cas d'infection à Trichoderma longibrachiatum chez un transplanté rénal en Tunisie et revue de littérature

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RÉSUMÉ

Prérequis : Trichoderma est un champignon filamenteux, longtemps considéré comme un contaminant des cultures. Récemment, avec l'augmentation du nombre de patients à risque, il est décrit comme un pathogène émergent chez les sujets immunodéprimés. Trichoderma longibrachiatum est l'espèce la plus fréquemment impliquée dans les infections à Trichoderma.

But : Nous rapportons le premier cas tunisien d'une infection cutanée à Trichoderma longibrachiatum

Observation : Il s'agit d'un homme, âgé de 46 ans, transplanté rénal. Le champignon a été isolé à partir d'un abcès inguinal et, également de la biopsie cutanée. L'identification de l'espèce a bénéficié d'une approche moléculaire. Les tests de sensibilité du champignon aux antifongiques réalisée selon la méthode standardiisée du Comité Européen a révélé que l'organisme était résistant à l'itraconazole, intermédiaire à l'amphotéricine B et sensible au voriconazole, au posaconazole et à la caspofungine. L'infection a bien évolué sous voriconazole.

MOTS-CLÉS

Trichoderma longibrachiatum; Transplantation rénale; Tunisie ; Infection de la peau

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SUMMARY

Background : Trichoderma species are filamentous fungi that were previously considered to be culture contaminants. Recently, with the increasing number of risk population, they are described as an emerging pathogen in immunocompromised patients. Trichoderma longibrachiatum is the most common species involved in Trichoderma infections.

Aim : Here, we report the first case in Tunisia of skin infection caused by Trichoderma longibrachiatum in a renal transplant recipient.

Case : The fungus was isolated from fluid puncture of an inguinal abscess and from skin biopsy from a 46-year-old male patient who had been receiving immunosuppressive therapy. Species identification benefited from a molecular approach. Susceptibility tests performed with the use of the European Committee on Antimicrobial Susceptibility Testing standardized methodology revealed that the organism is resistant to itraconazole, intermediate to amphotericin B and sensitive to voriconazole, posaconazole and caspofungin. The infection was successfully treated with voriconazole.

KEY-WORDS

Trichoderma longibrachiatum; kidney transplantation; Tunisia; Skin diseases, infectious

Trichoderma (T.) species are saprophytic filamentous fungi with worldwide distribution in the soil, plant material, decaying vegetation and wood. They are used in biotechnology as sources of enzymes [1] and antibiotics [2]. Moreover, they are applied to agricultural crops as plant growth promoters and biofungicides [3]. But actually, Trichoderma shows increasing medical importance as an opportunistic human pathogen particularly in immunocompromised patients. Trichoderma species can cause localized infections, such as pulmonary mycetoma, peritonitis, sinusitis, otitis, or brain abscess, and fatal disseminated disease. These infections are characterized by the presence of fine septate hyphae in tissue sections, entities called hyalohyphomycosis, for which differential diagnosis with invasive aspergillosis is difficult.

T. longibrachiatum had been identified as the causal agent in the majority of reported Trichoderma mycoses. We report the first case of Trichoderma longibrachiatum skin infection in Tunisia, in a renal transplant patient. This report is the fourth report documenting this species of Trichoderma as an etiologic agent of infection in an immunocompromised host after solid-organ transplant, and the second to suggest the skin lesion as a portal of entry.

CASE REPORT

A 46-year-old Tunisian male was diagnosed with chronic renal failure in 2002, the cause of the nephropathy was not identified. He started haemodialysis at the hospital between May 2005 and March 2007.Through the period of dialysis, he needed multiple periodic blood product transfusions because of severe anaemia. Then, he underwent a renal transplantation in March 2007. Immunosuppressive therapy included solumedrol, anti-thymocyte globulin (Thymoglobuline, Fresinius) and mycophénolate mofétil (MMF). Prograf was introduced at day 13 post transplantation. The patient's initial course post transplantation was complicated by insulin-dependant-diabetes, anaemia showing heterozygote sickle cell disease and cytolysis with cholestasis presumed to be secondary to medications. He was discharged from the hospital 63 days after transplantation; his medications were prograf and prednisone.

Ten months after transplantation, the patient was admitted for pneumonia of the right upper lobe and abscess in the right arm. Nocardia was isolated from the fluid puncture of the arm's abscess. He was successfully treated with imipenem and amikacyn.

During hospitalisation the patient showed an inguinal intertrigo; a local treatment (terbinafin) was administred, without any improvement.

The patient was admitted a second time, 13 months post transplantation for a suprapubic abscess next to the old intertrigo lesion. A direct microscopic examination of fluid puncture, revealed the presence of fungal septate hyphae. The culture of all samples with use of Sabouraud dextrose agar at 35°C yielded a fungus identified as a Trichoderma species on the basis of microscopic examination. A skin biopsy performed further showed the same fungal septate hyphae. No bacterial organisms were isolated from the culture of the specimens.

Fluconazole was administered at a dosage of 100 mg daily for 24 days. Following the antifungal susceptibility testing, fluconazole was replaced by voriconazole at a dosage of 400mg per day and the patient received this treatment over a 52-day period.

The patient tolerated the treatment, and he completely recovered.

Mycology study

The fungal isolates were cultured on Sabouraud chloramphenicol and Sabouraud cycloheximide. A rapidly growing fungal organism was observed at 48 and 72h of incubation at 35 and 27°C.

The colonies were floccose with concentric white and pale green to green rings. The colony reverse was colourless. The appearance was initially suggestive, although not characteristic, of Aspergillus sp.

Microscopically, the hyphae were smooth, septate and ramified with long conidiophores branched at wide angles and flask-shaped phialides (Figures 1 and 2).

Figure 1: Microscopic examination showing conidiophores long branched whorl (a)

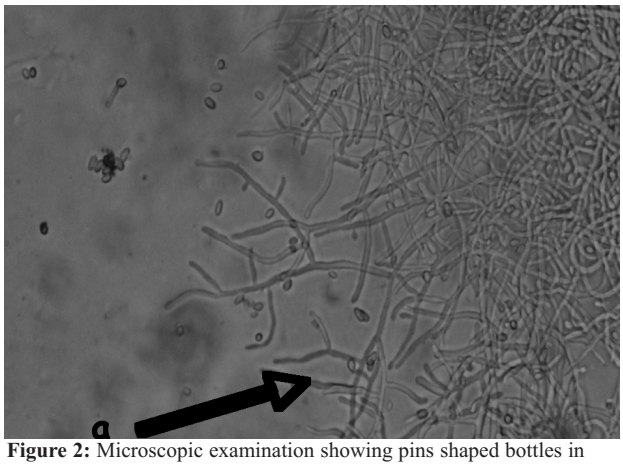

Figure 2: Microscopic examination showing pins shaped bottles in groups of 3 (b) and conidia grouped into "false head" (c).

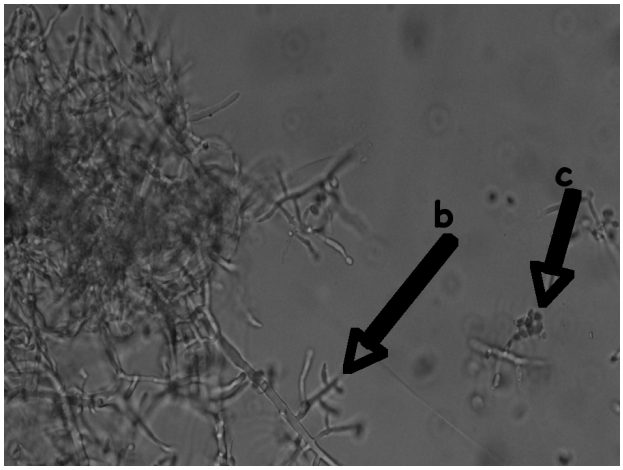

Table1: Clinical characteristics of systemic and disseminated infections due to Trichoderma species

Case	Ref	Yr	Age (yr)	Sex	Underlying condition(s)	Fungal infection	Fungal species	Treatment	utcome
Peritonitis									
1	7	2006	67	M	End-stage renal disease due to diabete, CAPD	Peritonitis and inta-abdominal abscess	*T. longibrachiatum*	Anti-fungal	Survived
2	8	2004	13	F	Glomerulosclerosis, peritoneal dialysis	Peritonitis	*T.longibrachiatum*	AmB	Died unrelated to fungal disease
3	9	1995	48	M	Systemic vascularitis, renal transplant, CAPD	Peritonitis	*T. longibrachiatum*	AmB	Died (day 28)
4	10	1983	47	F	Amyloidosis, Renal failure, CAPD	Peritonitis	*T. viride*	AmB	Died (day 11)
5	11	1996	40	M	Diabetic nephropathy, CAPD	Peritonitis	*T. koningii*	Catheter removal, Fluconazole, flucytosine, and amphotericin B	Death
6	12	1984	63	F	Chronic renal failure, CAPD	Peritonitis	*T. koningii*	Miconazole; catheter removal	Survived
7	13	2000	33	M	IgA nephropathy, CAPD	Peritonitis	*T.pseudokoningii*	Removal of catheter	Cure
8	14	1996	82	M	Non-insulin-dependant diabetes	Peritonitis	*T. harzianum*	Ketoconazole, ip flucytosine	Death
9	15	2003	NK	NK	CAPD	Peritonitis	*Trichoderma spp.*	Catheter removal and ampho B	Death
10	16	1998	NK	NK	CAPD	Peritonitis	*Trichoderma spp.*	Catheter removal	Cure
Opportunistic infection in immunocompromised patients After solid-organ transplantation									
11	This study	2009	46	M	Renal transplant, insulin-dependant diabetes	Skin infection	*T. longibrachiatum*	Triflucan, voriconazole	healed
12	17	1998	63	F	Liver transplant because of hepatitis C virus-induced cirrhosis	Sub capsular hepatic collection	*T.longibrachiatum*	Surgical debridement, povidone iodine	Cure
13	17	1998	11	M	Lung transplantation	Bronchi-alveolar lavage, pleural drains	*T. longibrachiatum*	Lipid-associated amphotericin B	Death
14	18	1998	29	F	Small bowel and liver transplant	Acute invasive sinusitis	*T. longibrachiatum*	AmB followed by itraconazole, surgical debridements	Healed
15	19	1992	44	F	Alcoholic cirrhosis, liver transplant	Perihepatic hematoma infection	*T. viride*	AmB; fluconazole	Died (day 91; unrelated to fungal disease)
16	20	1999	68	M	Chronic renal failure, renal transplant, moderate systemic hypertension	Disseminated	*T. harzianum*	None (fungal infection discovered in post-mortem)	Died
17	21	2008	49	M	Alcoholic cirrhosis, hepatocellular carcinoma, liver transplant	Infection of liver transplant	*T. atroviride*	Fluconazole, then replaced by voriconazole	Death
Opportunistic infection in immunocompromised patients With hematologic/ other malignancies									
18	22	2007	16	M	B cell acute lymphoblastic leukaemia	Invasive Pulmonary Infection	*T. longibrachiatum*	Voriconazole Combined with Caspofungin	Survived
19	23	2002	66	F	Malignant lymphoma	stomatitis	*T. longibrachiatum*	AmB, itraconazole	Death
20	24	1999	29	M	ALL, bone marrow transplant	Disseminated	*T. longibrachiatum*	AmB, itraconazole	Died(day 58)
21	25	1997	11	M	Severe aplastic anaemia	Skin infection	*T. longibrachiatum*	AmB, then ABLC	Survived
22	26	1995	17	F	ALL, prolonged neutropenia	Brain abscess	*T. longibrachiatum*	Surgical resection; AmB and 5FC or ketoconazole; itraconazole	Survived
23	27	2005	54	F	LAM, chemotherapy	Pulmonary infection	*T. viride*	Liposomal AmB, then voriconazole and capsofungin added later	Survived
24	28	1995	45	F	Erythroleukaemia, BMT	Disseminated	*T. pseudokoningii*	Fluconazole; AmB; ABLC and 5FC	Died (day 43)
25	29	2008	NK	NK	LAM	Pneumonia	*T. atrinoviride*	NK	Survived
26	30	1976	46	M	Chronic lung disease	Pulmonary mycetoma	*T. viride*	Surgical resection	Cure
Miscellaneous infection									
27	31	1969	26	F	IV infusion contaminated with Trichoderma species	Blood	*Trichoderma* species	Amphotericin B	Cure
28	32	2000	66	M	Aorta replacement	Endocarditis	*Trichoderma* species	Graft replaced; antifungal NS	Cure
29	31	1989	NS	NS	NS	Keratitis	*Trichoderma* species	NS	NS
30	PC	1992	NS	M	None	Keratitis	T. viride	No antifungal	NK
Others									
31	32	2003	52	F	Chronic sinusitis, atopy and asthma	Sinusitis	*T. longibrachiatum*	Itroconazole	Healed
32	33	2000	NK	NK	NK	Otitis	*T. longibrachiatum*	NK	NK

LAM, acute myeloid leukemia; ALL, acute lymphatic leukemia; BMT, bone marrow transplant; CAPD, chronic ambulatory peritoneal dialysis; M, male; F, female. NK, not known; NS, not specified; PC, personnal communication; AmB, amphotericin B.

The organism was tentatively identified as a species of Trichoderma based on its growth characteristics and the appearance of the conidia [4].
The fungal culture obtained from the fluid puncture specimen was sent to the National Centre of Reference of the Mycology and the Antifungals "Pasteur's Institute of Paris", for species' identification and sensibility study.
The molecular analysis of ribosomal DNA internal transcribed spacer (ITS-1 and ITS-2) sequences revealed that the isolate was T. longibrachiatum [5].
Antifungal susceptibility was determined with European Committee on Antimicrobial Susceptibility Testing (EUCAST) standardized methodology [6]. It revealed that the organism was resistant to itroconazole (minimum inhibitory concentration (MIC), ≥8 µg/ml), intermediate to amphotericin B (MIC, 1 µg/ml) and sensitive to voriconazole, posaconazole and caspofungin.

DISCUSSION

Fungal infections by Trichoderma continue causing morbidity and mortality in immunocompromised patients. Trichoderma spp. had been reported as causes of opportunist infection in humans in 33 cases. Most reported cases are included in risk population: continuous ambulatory peritoneal dialysis (CAPD) patients (10 cases [7-16]), immunosuppressed patients after solid-organ transplantation (6cases [17-21]) and with hematologic or others malignancy (9cases [22-30]). Beside Trichoderma species disseminated infections, many localized infections had been described in the literature, such as, peritoneal, pulmonary, hepatic, brain, etc… In our case, the patient presented a skin infection, the old intertrigo lesion was probably the portal of entry. A similar superficial infection was described previously in paediatric patient with severe aplastic anaemia [25].
Overall cases, survival were 47 %. Regardless of the disease type and the therapy used the prognosis for Trichoderma infection is usually poor. While Trichoderma species have been recognized to be pathogenic in profoundly immunosuppressed hosts, the case number 19 was the first report of the primary oral focus causing a fatal infection in immunosuppressed host [23].
Regarding the species' identification, the definitive diagnosis is difficult to achieve because of the lack of specific diagnosis tools. Actually, species identification can benefit from a molecular approach. For our patient, such methods provided the definitive identification of this saprophytic fungal organism isolated from a human host.
Six species of the genus Trichoderma (T. longibrachiatum, T.harzianum, T. koningii, T. pseudokoningii, T. viride and T. citrinoviride) have been identified as etiologic agents of infections in immunocompromised hosts. More recently, a seventh species was implicated for the first time; T. atroviride was isolated from a liver transplant [21].
T. longibrachiatum is the main human pathogen species within the genus and had been isolated with increasing frequency in recent years. Table 1 summarizes 14 cases of T. longibrachiatum infections in human reported to date.
Potential virulence factors of T. longibrachiatum as an opportunistic pathogen include the ability of mycelia growth at 37º C and physiological pH, haemolytic ability, toxicity to mammalian cells [36] , the production of extracellular proteases [37] as well as the generally high levels of resistance to antifungal compounds including fluconazole, itraconazole and in some cases also amphotericin B [38].
We found only 3 other published cases of T. longibrachiatum infection among solid-organ transplanted patients. Invasive pulmonary T. longibrachiatum infection was fatal in one patient, he had undergone lung transplantation because terminal respiratory failure due to cystic fibrosis [17]. In the 2 other cases, the patients survived; the first had undergone liver transplant because of hepatitis C virus-induced cirrhosis, he developed subcapsular hepatic collection to T. longibrachiatum successfully treated by surgical debridement and povidone iodine, the second developed an acute invasive sinusitis due to T. longibrachiatum after undergoing small bowel and liver transplant and had successful treatment with surgical debridment and long-term antifungal therapy [17, 18]. Our patient's features were different: the invasive fungal infection was confined to the skin, and only fluid puncture and skin biopsy samples were found to contain filamentous fungal elements. Our patient had a favourable clinical outcome, with only antifungal therapy.
For our patient, susceptibility tests of T. longibrachiatum isolates were performed with use of the EUCAST standardized methodology. The MICs for the patient's isolates were as follows:
amphotericin B, 1 µg/ml; flucytosine,≥64 µg/ml; itraconazole, ≥8 µg/ml; voriconazole, 0,5 µg/ml; posaconazole, 0,5 µg/ml and caspofungin, 0.5 µg/ml. Fluconazole was not tested. These results are in keeping with the reported cases [17, 39].
Usually, patients were initially treated with amphotericin B (14 cases). Actually, other therapeutic options are available, such as voriconazole and capsofungin. Our patient is the fourth reported case treated with non amphotericin antifungal drug. Voriconazole and caspofungin have been shown to be effective in vitro against filamentous fungi, including a strain of Trichoderma with a MIC of 0.25 and b2 mg/L, respectively [39]. A more recent study demonstrated reduced activity of fluconazole and amphotericin B and higher in vitro activity of voriconazole against clinical and environmental Trichoderma isolates [40]. Our antifungal susceptibility testing showed in vitro sensitivity to voriconazole and caspofungin and the patient was successfully treated with voriconazole. In some cases given the lack of information about the efficacy of caspofungin or voriconazole monotherapy for Trichoderma infection in immunocompromised patients, they administered both drugs during the patient's acute phase. This combination proved very effective and was probably enhanced by leukocyte recovery [22, 27].
In conclusion, Trichoderma infection could be misdiagnosed as other types of hyalohyphomycosis. The risk factors of the host

could affect the success of therapy. The correlation between in vitro test results of antifungal susceptibility testing and clinical response remains difficult to interpret.

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