PRIMARY CUTANEOUS TRICHOSPORONOSIS CAUSED BY TRICHOSPORON ASAHII IN A SEVERE IMMUNOSUPPRESSED WOMAN

TRICOSPORONOZĂ CUTANATĂ PRIMARĂ INDUSĂ DE TRICHOSPORON ASAHII LA O PACIENTĂ SEVER IMUNODEPRIMATĂ

Keywords:
Trichosporonosis, Trichosporon asahii, yeast, immunosuppression.

Abstract

Trichosporon species are non-encapsulated yeasts that commonly inhabit the soil and are part of normal flora of the gastrointestinal tract, upper respiratory tract, and human skin. Sixteen of the 51 species in the genus Trichosporon have been associated with human infection. The vast majority of human infections is caused by T. asahii, followed by T. dermatis. Trichosporon spp. has been increasingly recognized as an important pathogen for systemic infections, affecting mainly immunocompromised patients. Most commonly, the infection presents as fungaemia, and approximately half of the cases are associated with metastatic skin lesions. In immunocompromised patients, trichosporonosis has been increasingly associated with a high mortality rate of up to 55% - 80%. We present a case of primary cutaneous trichosporonosis without systemic involvement despite patient’s severe immunosuppression.
Introduction
Trichosporon species (Trichosporon spp.) are non-encapsulated basidiomycetous yeasts that are widely distributed in nature, and commonly inhabit the soil, but can also be isolated from water, decomposing matter, and bird and bat droppings (1). They are regularly found on normal skin, especially in the peri-genital areas, but also on nails and occasionally as part of the normal gastrointestinal tract or upper respiratory microflora (1,6).

At present, the genus contains 51 species, but only 16 species have been associated with human infection (1). Trichosporon spp. are considered to be the second most commonly isolated yeast species in clinical laboratories (7-9). The vast majority of human infections is caused by Trichosporon asahii (74%), followed by Trichosporon dermatis (12%) (6,10). Trichosporon spp. has been classically associated with white piedra, a distal infection of the hair shaft (11), and with hypersensitivity pneumonitis syndrome, particularly in hot and humid climates (1,12-15). However, in recent decades, Trichosporon spp. has been increasingly recognized as an important pathogen for systemic infections, i.e. fungaemia, endocarditis, peritonitis and meningitis, affecting mainly immunocompromised patients (10,16-18). Various immunosuppressive states are risk factors for invasive trichosporonosis (10,16,17,19-21).

Most commonly, the infection presents as fungaemia (75%), and approximately 50% of the cases are associated with metastatic skin lesions (10,19). In immunocompromised patients, trichosporonosis has been increasingly associated with a high mortality rate of up to 55% - 80% (10,14,22,23). We present a case of primary cutaneous trichosporonosis without systemic involvement despite patient’s severe immunosuppression.

Patient, Methods and Results
A 65-year-old woman presented with a 10-month history of numerous painful cutaneous erythematous papules and nodules on the lower legs, especially on the left calf. The lesions progressively enlarged, and became ulcerated and confluent.
The patient had been treated intermittently with various systemic antibiotics, including amoxicillin and clavulanic acid, along with various topical treatments such as sulfadiazine cream and clobetasol cream. A skin biopsy taken elsewhere raised the suspicion of deep fungal mycosis. Consequently, the patient underwent systemic antifungal treatment with itraconazole 100 mg twice daily for 10 days, but without clinical response. Importantly, the patient also had associated comorbidities. She had a long history of rheumatoid arthritis, systemic lupus erythematosus, autoimmune thrombocytopenia and autoimmune hepatitis. She received various antimetabolite and immunosuppressive regimens including methotrexate, sulfasalazine, nonsteroidal anti-inflammatory drugs, leflunomide, azathioprine, hydroxychloroquine, and methylprednisolone. She also developed insulin-necessant diabetes mellitus type 2, chronic peripheral arterial insufficiency, and glaucoma.

Cutaneous examination revealed numerous painful ulcers and lesions with a vasculitic appearance on the left calf (Fig 1, A). The ulcers measuring up to 15 cm in diameter had erythematous and slightly elevated borders and their surfaces were covered with seropurulent and necrotic debris (Fig 1, B). As various treatments did not improve her clinical status, the patient requested a new skin biopsy. Ten months after the onset of the cutaneous disease a new biopsy was performed from the periphery of an ulcerated lesion and sent for histological evaluation. The surgical specimen was routinely fixed and paraffin embedded. Four-μm-thick serial sections were stained with Hematoxylin–Eosin (HE) and Periodic acid-Schiff diastase (PAS-D). Examination of the biopsy showed a suppurative and granulomatous dermatitis and panniculitis, pseudoepitheliomatous hyperplasia and areas of hemorrhage in the reticular dermis (Fig 2, A). In the granulomatous and suppurative areas (Fig 2, B) many haloed yeast-like cells in a mucoid background (Fig 2, C), very reminiscent of cryptococcus yeasts, could be appreciated. However, the yeast-like structures were accompanied by numerous septate hyphae which were highlighted by a PAS-D stain (Fig 2, D). Tissue specimens were cultured at 27 °C on Sabouraud dextrose agar (SDA) and yielded numerous yellowish-white, finely wrinkled, and bu- tyrous colonies after one week (Fig 3, A). Slide culture microscopic examination revealed pseudohyphae,
branched septate hyphae, arthroconidia, and blastoconidia (Fig 3, B). The isolate was identified as T. asahii based on the phenotypic and genotypic features. An in vitro antifungal susceptibility test was performed and indicated that the strain was very sensitive to amphotericin B, moderately sensitive to fluconazole, and resistant to itraconazole and ketoconazole. Blood and imaging tests, including a chest radiography and an abdominal ultrasonography revealed an elevated ESR and fibrinogen, thrombocytopenia (81,000/mm3), and hypoproteinemia (5.6 g/dl). The biochemical parameters including serum glucose, and liver and renal function tests were within normal limits. Blood and urine cultures did not yield any fungal growth. Our final diagnosis was primary cutaneous trichosporonosis caused by Trichosporon asahii. The patient immediately started a regimen with fluconazole, 100 mg twice daily (200 mg/day) for 6 month, with a very good clinical response (Fig 4. A, B).

Discussion

Trichosporon species are urease-positive, non-encapsulated basidiomycetous yeasts that commonly inhabit the soil [1], and are part of normal flora of the gastrointestinal tract, upper respiratory tract, and human skin [1-6]. Sixteen of the 51 species in the genus Trichosporon have been associated with human infection [1]. Occasionally, particularly in circumstances of high humidity, the fungus can proliferate, causing an unpleasant hair condition known as white piedra. The species responsible for this condition include T. ovoides, T. inkin, T. asahii, T. mucoides, T. asteroids, and T. cutaneum. Multiple Trichosporon species, including T. asahii and T. mucoides, are associated with summer-type hypersensitivity pneumonitis in Japan [13]. Trichosporon spp. have increasingly become important opportunistic pathogens and cause of systemic illness in immunocompromised patients [24]. The vast majority of human infections is caused by T. asahii (74%), followed by T. dermatis (12%) [6,10]. The risk factors for invasive infections are underlying malignant hematological diseases with long-term neutropenia [10,17,19], diseases with neutrophil dysfunction such as chronic granulomatous disease [20], cystic fibrosis [21], hemochromatosis, end-stage renal disease, HIV/AIDS [1,23], diabetes mellitus [25], presence of a central venous catheter, Intensive Care Unit stay, peritoneal dialysis, steroid use and cytotoxic chemotherapy [10,16,17]. Even though these
infections frequently present as fungaemia and the skin is secondarily involved in approximately 50% of the cases [14,16]. There are rare reported cases of primary cutaneous trichosporonosis, as was the case with our patient. Indeed, extensive workup did not reveal spread of the infection beyond skin, in spite of the patient's many immunosuppressive conditions. It is known that trichosporonosis is associated with a high mortality rate of up to 55% - 80% [10,16,22,23]. Various virulence factors of Trichosporon species include enzyme products of Trichosporon such as proteases, lipases, and phospholipases. Also, Trichosporon cell wall contains a component similar to that of Cryptococcus neoformans (C. neoformans) which inhibits phagocytosis by macrophages [24]. Interestingly, in our case the histopathological aspect of trichosporonosis on H&E stain was very reminiscent of a cryptococcal infection that typically presents with halosed yeast-like cells in a mucoid background. However, the concomitant presence of septate hyphae made a cryptococcal infection very unlikely (cryptococcus presents in biopsy specimens only as yeast-like cells) and pointed toward another closely related yeast infection. In tissue sections, the Trichosporon spp. can be recognized as pleomorphic blastoconidia, 3 to 8 micrometer in diameter, along with septate hyphae and arthroconidia that are produced by fragmentation of hyphal segments. Trichosporon spp. and C. neoformans are closely related organisms and share a number of surface antigens. As such, the latex agglutination test results for serum cryptococcal antigen are often positive in the setting of disseminated trichosporonosis [24]. This widely used, rapid, and inexpensive test may provide an early clue to a Trichosporon infection. However, the precise identification of the fungus is possible only after the evaluation of phenotypic and genotypic culture characteristics. Similar to our case, purpuric cutaneous lesions are a frequent clinical manifestation. The clinical aspect corresponds histologically to dermal hemorrhage and vasculitic changes due to direct invasion of blood vessels by the fungi. Trichosporon has the capacity to produce a biofilm that facilitates colonization of indwelling devices and permits both adherence to prosthetic material and reduction of the fungus's exposure and susceptibility to antifungal drugs [24]. Hence, trichosporonosis requires a long term treatment regimen with an association of systemic antifungals.

Conclusions
Trichosporon spp. have increasingly become important opportunistic pathogens and cause of systemic illness in immunocompromised patients and are associated with a high mortality rate of up to 55% - 80%. Even though these infections frequently present as fungaemia and the skin is secondarily involved in approximately 50% of the cases, there are rare reported cases of primary cutaneous trichosporonosis, as was the case with our patient. Trichosporon spp. and C. neoformans are closely related organisms and share a number of surface antigens. The histopathological aspect of trichosporonosis on H&E stain may be very reminiscent of a cryptococcal infection that typically presents with halosed yeast-like cells in a mucoid background. Thus, the precise identification of the fungus is possible only after the evaluation of phenotypic and genotypic culture characteristics. Trichosporonosis requires a long term treatment regimen with an association of systemic antifungals due to fungus capacity to produce a biofilm that permits reduction of the fungus's exposure and susceptibility to antifungal drugs.


