

## Deep cutaneous *Trichosporon asahii* infection in a patient recovering from toxic epidermal necrolysis

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### ABSTRACT

Patients with toxic epidermal necrolysis, a condition that causes full thickness epidermal necrosis that affects over 30% of the skin surface and mucosal membranes, often develop comorbid infections throughout the recovery of the disease [1]. While most commonly these are related to a bacterial source, infections due to viral, mycobacterial, and rarely fungal organisms occur. We present a case of a patient who developed a deep cutaneous fungal infection caused by *Trichosporon asahii* and discuss the management.

### 1. Introduction

*Trichosporon asahii* is a dermatophyte that when provided the opportunity can cause invasive infection. Invasive Trichosporonosis is rare but has typically been described in patients who have hematologic malignancies with profound neutropenia and other risk factors for invasive fungal disease [2]. In this report we present a case of a young lady with migraine headaches who presented with toxic epidermal necrolysis (TEN) after taking an over the counter combination medication for migraine (acetaminophen/butalbital/caffeine) and subsequently developed a deep cutaneous Trichosporonosis. *Trichosporon* species are yeast-like organisms that are found in the soil, air, woods, and droppings of several animals throughout the tropical and temperate climates [2]. They can be found as normal biota in the oral and GI tract in humans and transiently colonize the respiratory tract and skin [3]. As a pathogen, they can cause superficial or deep infections. Invasive Trichosporonosis has been documented predominantly in patients with hematologic malignancy or other relative immunosuppression such as critical illness, degenerative disease with organ failure or multiple invasive procedures, whereas superficial infections are usually in immunocompetent hosts. There is an allergic pneumonia related to *T. cutaneum* which is most often associated with hot and humid weather combined with environmental contamination [2]. The most common of the superficial infections from *Trichosporon* is white piedra, which is characterized by white to light brown nodules that are loosely attached to hair shaft. It can disseminate in those who are neutropenic or those with HIV and presents as widespread papules or purpuric nodules. Because of the novelty of her presentation management of her case was challenging. In general the azoles are recommended as first line therapy

for invasive Trichosporonosis. To our knowledge this is the first case of invasive cutaneous *Trichosporon asahii* secondary to TEN.

### 2. Case

A 24 year old African American female was transferred to our Burn Intensive Care Unit from an outside hospital with concern for toxic epidermal necrolysis (TEN). Upon presentation (Day 0), in addition to sloughing of the oral mucosa, the patient had erosions involving her ocular mucosa and vaginal mucosa. Over 50% of her skin was denuded or had a dusky-red hue that was Nikolsky sign positive. A biopsy was obtained for frozen section, which confirmed the diagnosis of TEN by demonstrating full thickness epidermal necrosis.

The patient was started on cyclosporine at a dose of 1.5 mg/kg IV divided into two daily doses. This was discontinued after one dose due to an increase in creatinine that progressed to renal failure requiring continuous renal replacement therapy (CRRT) for 2 weeks. The patient was then started on IVIg, which she was maintained on for 5 days at a dose of 1 g/kg/day. Supportive wound care was initiated upon admission and continued throughout her stay. Her initial cutaneous and mucosal injury improved with these interventions over the course of her hospitalization.

Two weeks into the patient's hospital stay (Day +14), she started to develop a collection of 3–5 mm, indurated, crusted, grouped papules on the forehead that began to spread down the temples to the cheeks (Figs. 1–3). A Tzanck smear performed on one of the papules was inconclusive, but a PCR from affected skin was positive for HSV-1. The patient was started on IV acyclovir for suspected herpetic infection. After two days of being on IV acyclovir (Day +16), the number and size

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Fig. 1. Day +14 of hospital stay the patient developed papules shown above.

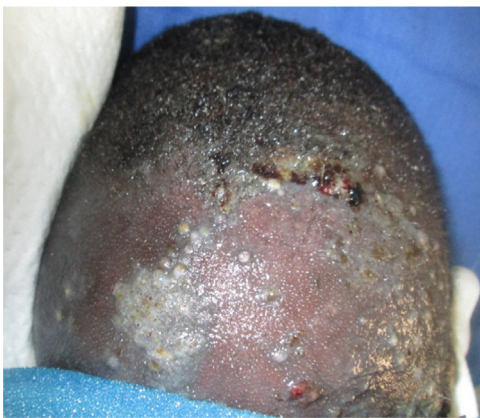


Fig. 2. There was some coalescence of the papules.

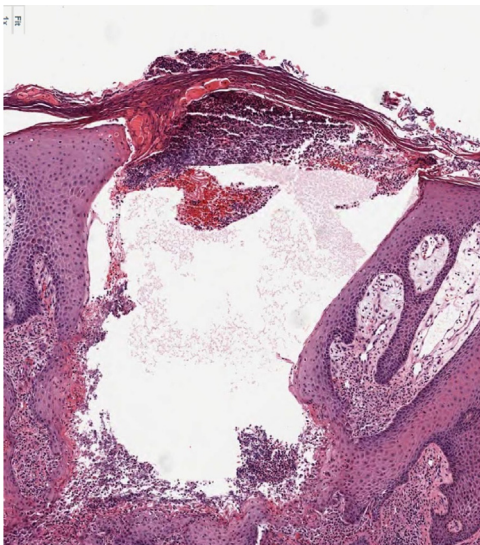


Fig. 3. H&E stain of the papule biopsy demonstrating pseudoepitheliomatous hyperplasia with mixed inflammation and fibrosis in a follicular pustule.

of the lesions increased. Two punch biopsies were performed (Day 16). One biopsy was sent for Hematoxylin and Eosin (H&E) (Figs. 3 and 4a.) stain and showed pseudoepitheliomatous hyperplasia with mixed inflammation and fibrosis and a follicular pustule with true hyphae (Fig. 4b). Gomori-Grocott methenamine silver stain highlighted additional fungal forms consistent with true hyphae throughout the epidermis and dermis not seen on H&E (Fig. 4b). Staining for HSV-1/-2 was negative and no viral cytopathic changes were seen. Subsequent sputum culture and blood cultures with fungal isolator tubes were

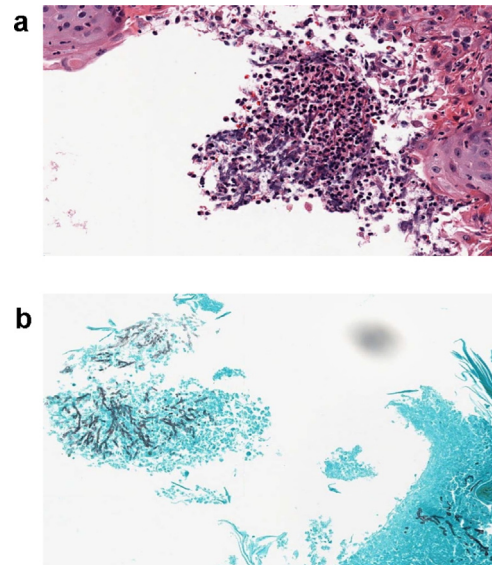


Fig. 4. a. Mixed inflammation with hyphal elements on H&E. b. GMS stain with the darker elements demonstrating true hyphae.



Fig. 5. At follow up two months after hospital discharge with notable resolution of previous skin findings.

negative. The infectious disease service was consulted, and the patient was placed on intravenous (IV) isavuconazole (372 mg daily) after being loaded (372 mg IV every 8 h for six doses) while awaiting growth and speciation of the biopsy culture. Over the next week, the patient's cutaneous lesions began to resolve. Further workup of her tissue culture with lactophenol cotton blue staining revealed fungal elements with true septate hyphae, blastoconidia, and rectangular arthroconidia which grew at 37 °C and were urease positive. These morphologic characteristics along with Matrix Associated Laser Desorption Ionization Time-of-Flight Mass Spectrometry analysis (Vytek MS Biomerieux 2016) identified the organism as *Trichosporon asahii*. At that time (Day +23), the patient was transitioned to oral posaconazole (300 mg daily) which led to continued improvement and ultimately complete resolution of the cutaneous lesions at follow up two months (day +90) after hospital discharge (Fig. 5).

### 3. Discussion

Diagnosing invasive Trichosporonosis can result in two categories of probability: proven or probable [2]. Proven requires demonstrating at least one of the following: *Trichosporon* organism growth in blood cultures with temporally associated symptoms, CSF cultures or biopsy specimens that are culture positive and histopathologically consistent. Probable disease requires the patient to have a predisposing host factor, culture or presence of fungal elements and clinical evidence of invasive fungal disease. With her biopsy and culture demonstrating *Trichosporon asahii*, our patient met criteria for proven invasive disease.

Management of invasive trichosporonosis is anchored by the azoles. As is often the case with severe invasive fungal infections, Amphotericin B is commonly thought of as initial management, however there is some evidence that this does not have clinically efficacious activity against the *Trichosporon* species. In a 1986 review of 25 neutropenic patients from MD Anderson Cancer Center who were diagnosed with invasive Trichosporonosis and treated with Amphotericin B, only four patients survived [4]. Other small case series, usually with patients that had active hematologic malignancies demonstrated that only 23% of patients treated with Amphotericin B survived and that the addition of flucytosine did not offer additional benefit [5,6]. The echinocandins have little to no activity against *Trichosporon* species and are not recommended for managing these infections [7].

This leaves the azoles as first line therapy for this type of infection. A review of 33 cases of *Trichosporon* fungemia in patients with hematologic malignancies was able to demonstrate a significant cumulative survival benefit in those treated with azoles compared with those that were not [8]. Practice pattern data for management of this type of clinical scenario have also supported the gradual shift from Amphotericin to the azoles [9]. This raises the question though of which azole and how a clinician can be reasonably certain of clinical efficacy. There are no breakpoints for the azoles in the Clinical Laboratory Standards Institute guidelines for these organisms in large part because they are rare and not well described. The new azoles have excellent *in vitro* activity but this still leaves questions about their efficacy *in vivo* and the duration of therapy [10]. In our case we elected to use an azole that is known to have excellent mould and yeast coverage, given the patient's critical illness, and adjust her therapy based off her clinical response. As she continued to improve and was able to be switched to orals we elected oral posaconazole as this ultimately had the least amount of drug-drug interactions with her planned discharge medication list. She was treated for three months and had resolution of her lesions at follow up.

To our knowledge, this is the first reported case of a deep cutaneous infection of *Trichosporon* species in a patient recovering from SJS/TEN. This raises interesting questions about the nature of colonizers and their ability to invade once a host becomes immunosuppressed as well as the pathophysiology of that invasion in the case of *Trichosporon* – as burn unit temperatures are kept higher due to the defect in the patients integumentary system and patient's skin moist this potentially provides an environment for invasion of dermatophytes. Management of *Trichosporonosis* infections are challenging but should include an azole

as first line therapy for extended durations on the order of weeks to months.

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## Conflict of interest

The authors have no conflicts of interest to declare. The view(s) expressed herein are those of the author(s) and do not reflect the official policy or position of Brooke Army Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Air Force, the Department of the Army or the Department of Defense, or the U.S. Government.

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