Emerging Fungal Pathogen Causing a Persistent Rash

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Abstract

Candida haemulonii is a rare, fungal organism. This emerging, multidrug resistant pathogen can cause many different types of infections. We present a case of a previously healthy, 16-year-old girl with a lower extremity rash. The rash persisted despite treatment with a variety of oral and topical antifungal medications. It eventually resolved after treatment with intravenous echinocandins, a class of antifungal drugs that target the fungal cell wall. This case emphasizes the importance of forming a broad differential diagnosis. When a skin lesion does not respond to empiric treatment based on the presumptive diagnosis, one must consider atypical presentations and rare causes. *C haemulonii*, in particular, can be easily misidentified as other fungal pathogens. Therefore, genetic identification and antimicrobial susceptibility tests may be crucial in guiding diagnosis and treatment.

Key words: *Candida haemulonii*, multidrug resistant pathogens, antifungal

A 16-year-old girl with no significant medical history presented to her pediatrician's office with a 3-week history of an enlarging, pruritic patch on her left thigh that had not responded to topical lotion. The family history was noncontributory. The family owned a hamster, a cat, and dogs as pets.

Physical examination revealed a 1.2 cm slightly scaly, round, red lesion with central clearing **(Figure 1)**. The clinical appearance suggested a partial diagnosis of tinea corporis. The patient was advised to treat the rash with over-the-counter (OTC) clotrimazole or another topical antifungal cream 3 times per day for 2 weeks or until the skin was clear for 2 to 3 days.

Two and a half months later, the patient returned to her pediatrician's office with no improvement of the lesion after treating with either topical clotrimazole or butenafine 1%. Examination of the patient's left inner thigh showed a 3.5-cm circular area of red pinpoint papules with scaly

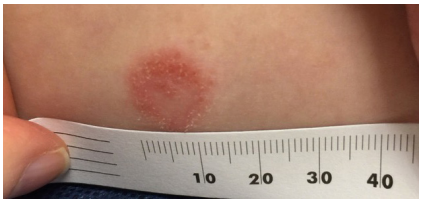

Figure 1. Photograph depicting the initial presentation of the patient's lesion, a round patch with central clearing.

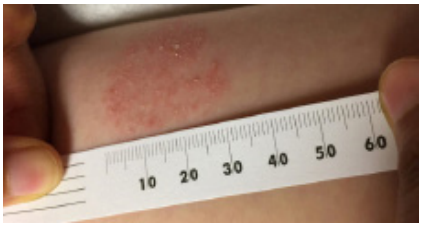

Figure 2. Enlarged area of red pinpoint papules with scaling on the patient's left inner thigh.

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CITATION:
von Zabern LB, Carter CG. Emerging fungal pathogen causing a persistent rash. *Consultant*. Published online July 14, 2022. doi:10.25270/con.2022.04.00005

Received December 29, 2021; accepted January 11, 2022.

DISCLOSURES:
The authors report no relevant financial relationships.

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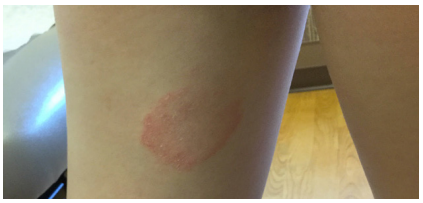

Figure 3. Pink, annular plaque with scale on the patient's left inner thigh.

skin and no central clearing **(Figure 2)**. The pediatrician referred the patient to a dermatologist. The patient was seen by the specialist one month later during which time the rash had continued to spread. Physical examination showed an 8-10 cm, annular, scaly, thin, pink plaque on the patient's left inner thigh **(Figure 3)** and a 2 cm, annular patch on her right inner thigh. A potassium hydroxide (KOH) preparation test and fungal culture were taken. Although the KOH prep test was negative, empiric treatment with daily oral terbinafine 250 mg for 30 days and twice-daily application of OTC terbinafine cream until the rash resolved was advised. The rash continued to worsen, becoming increasingly pruritic and beginning to weep.

Preliminary culture results showed *Candida haemulonii*, for which the dermatologist prescribed a 14-day course of once-daily oral fluconazole 100 mg and twice-daily topical ketoconazole; the previous terbinafine regimens were stopped. At a follow-up visit 2 weeks later, the patient's rash was less pruritic, but overall, the area was tender and unchanged in size. At this visit, an additional fungal culture was taken with orders for antifungal susceptibility testing, and the patient was switched to a 6-week course of daily oral itraconazole 200 mg. The patient was urgently referred to an infectious disease specialist.

At the specialist appointment 5 days later, the patient reported she was unable to obtain itraconazole due to insurance issues. The thigh lesions had continued to increase in size, and she had developed itching on the right-upper side of her abdomen. Examination showed a 4 × 3 cm lesion on her right thigh and a 9.5 × 3 cm lesion on her left thigh. Both were elevated,

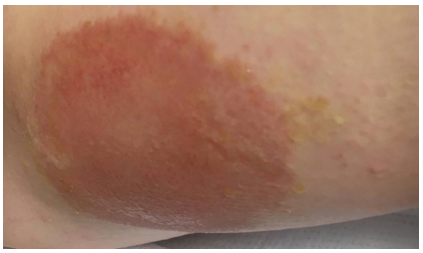

Figure 4. Erythematous lesion weeping brown exudate.

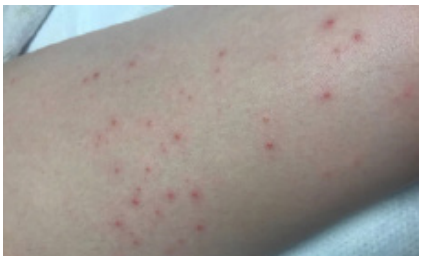

Figure 5. Scattered pink papules on thigh.

erythematous, and scaly with well-demarcated, irregular borders and no central clearing. There was an additional satellite lesion on her distal right, anterior leg, and excoriations on her right-upper abdomen overlying a few small pink papules.

Based on the appearance of new lesions, the patient was admitted to the hospital the following day for treatment with intravenous (IV) micafungin, an echinocandin. On the morning of her admission, the patient woke up with a new rash, consisting of scattered, pruritic, pink papules that began on her legs and ascended to her trunk. The lesions on her thighs were weeping brown exudate.

The following day, after receiving her first dose of micafungin, the weeping erythematous rashes **(Figure 4)** with satellite lesions on both of her legs had not increased in size. A maculopapular rash **(Figure 5)** that developed the day of her admission continued to spread. Biopsies of the left thigh lesion and the papular rash on her back showed spongiosis and lymphohistiocytic infiltrate with eosinophils, indicating a possible id reaction, or autoeczematization, overlying the initial fungal rash. Repeat fungal cultures were negative, so antifungal susceptibility testing was not completed. Immunodeficiency workup, including T- and B-cell subsets, immunoglobulin levels, and HIV serology, was negative.

The patient was discharged with a peripherally inserted central catheter and completed a 4-week course of IV micafungin, after which her thigh lesions resolved. The papular rash, which biopsy showed was likely an id reaction associated with Candida fungal infection, resolved with as-needed topical steroids.

Discussion

The *C haemulonii* complex is an emerging species of opportunistic yeast pathogens.[1] It includes *Candida haemulonii sensu stricto*, *Candida haemulonii var. vulnera*, and *Candida duobushaemulonii*.[1] It is considered closely related to other nonalbicans *Candida* species, such as *Candida auris*.[1] Given the rarity of this organism, detailed data of worldwide infection rates are not currently available. One study found that organisms from the *C haemulonii* comprised 1.7% of yeasts isolated from 2014 to 2019.[1] Available data show this species typically causes sporadic infections.[2] However, the prevalence may be underestimated since classical phenotypic identification methods cannot accurately ascertain these species.[1] Additionally, these species may be misidentified as *C auris* in laboratories that do not have access to DNA sequencing or other advanced mass spectrometry.[3] Therefore, in cases where a fungal infection is not responding to typical treatments, it is important to collect samples for specific genetic testing, as was done with our patient, to allow for pathogen identification and analysis.

C haemulonii can cause wound and other superficial infections, such as onychomycosis, vaginal candidiasis, and chronic otitis media.[2,3] More invasive infections associated with candidemia have also been reported, although these are typically seen in neonates, critically ill patients, and patients with comorbidities, such as cancer or diabetes mellitus.[1]

C haemulonii has a wide but variable resistance pattern, making it difficult to treat.[4] Many studies report high minimum

inhibitory concentrations (MIC) for amphotericin B,[1-3] which may indicate intrinsic resistance to this drug.[2] However, one case report describes a deep cutaneous infection successfully treated with a combination of amphotericin B, fluconazole, and surgical debridement,[5] showing this pattern is not universal. High MICs for fluconazole are also common, but this trait is not extremely widespread.[3] In one study, most azole-resistant isolates were from Latin America, with this trait being associated with an *ERG11* mutation.[3]

It is suggested that *C haemulonii* infections be treated with echinocandins.[1] This is a class of drugs that inhibit b-(1,3)-D-glucan synthase, limiting fungal cell wall synthesis.[6] However, isolated cases of echinocandin-resistant organisms have been reported.[7] The *C haemulonii* complex has wide genetic diversity, which is consistent with recent population expansion.[3] The emergence of this organism in different parts of the world, where certain antifungals may be used with different frequencies, could explain the varying resistance patterns as well as their association with certain geographical areas. Therefore, when treating unusual fungal infections, such as *C haemulonii*, detailed susceptibility testing of an isolate from the infection in question should be done to determine which treatment will be most effective. However, before these results are available, echinocandins can be used for empiric treatment.

Conclusion

The *C haemulonii* complex is an emerging, multidrug resistant fungal pathogen capable of causing a variety of superficial and invasive infections. *C haemulonii* can be misidentified as other fungal infections, so specific genetic testing is useful when an infection does not respond to typical treatment regimens. *C haemulonii* has a highly variable resistance pattern. Thus, detailed susceptibility should be performed to allow for focused and effective treatment. Until results are available, echinocandins can be used for empiric treatment.

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