Disseminated sporotrichosis following iatrogenic immunosuppression for suspected pyoderma gangrenosum

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Sporotrichosis is an infection caused by the dimorphic fungus *Sporothrix schenckii* and related species that often arises from traumatic inoculation of inhabited soil and organic debris into skin. The infection is usually limited to the skin in immunocompetent patients, usually as lymphocutaneous sporotrichosis. Accurate diagnosis rests on clinical data and culture, and might be facilitated by biopsy identification of suppurative and granulomatous inflammation with fungal elements. In this Grand Round, we present a dramatic case of cutaneous sporotrichosis initially presented with an atypical large ulcer without associated lymphocutaneous spread, clinically mimicking pyoderma gangrenosum, and subsequently progressed to disseminated sporotrichosis in the setting of iatrogenic immunosuppression. We further review the clinical features, risk factors, and treatment of these disseminated sporotrichosis cases, and discuss the need for improved awareness of this fungus' potential link to cause disseminated and invasive fungal infections.

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Introduction

Sporothrix schenkii is a common saprophytic fungus found in soil, tree bark, hay, rose shrubs, and decaying wood. This dimorphic fungus is usually present in warm, tropical regions, but is seen worldwide.[1,2] Clinically, the fungus causes deep cutaneous mycoses, which usually involves a traumatic disruption of the skin or subcutaneous tissues, or both, of immunocompetent hosts by plant materials.[3,4] In the USA, on average 200–250 cases of sporotrichosis occur annually, and usually in rural areas where individuals are handling plants or they are farmers.[3] Clinical presentation is seen approximately 3 weeks after exposure. Individuals develop multiple skin papulo-nodules near the site of inoculation. These nodules progressively enlarge and might become ulcerated causing a so-called sporotrichotic chancre without the presence of systemic symptoms. Further clinical progression might present as lymphocutaneous sporotrichosis, occasionally fixed cutaneous, and rarely disseminated sporotrichosis. These manifestations tend to worsen in immunocompromised patients. Here we present a case of disseminated sporotrichosis in a man after immunosuppressive treat-ment for a lesion on his left leg that was initially suspected of pyoderma gangrenosum.

Case presentation

A 62-year-old man with a past medical history of coronary artery disease status after stenting and atrial fibrillation presented with an enlarging left lateral thigh ulcer that was clinically suspicious for pyoderma gangrenosum. The patient first noticed an approximately 2 cm lesion on his left lateral thigh approximately 1 month after playing golf in Nebraska, USA, in an area with abundant vegetation. He did not recall any trauma to his leg at that time but was wearing shorts. Of note, his golfing partner on that trip developed an ankle ulceration with swelling and was subsequently diagnosed with sporotrichosis, which resolved after prompt diagnosis and treatment.

The patient subsequently sought care in an outpatient setting. Two biopsies showed a non-specific ulcer with acute and chronic inflammation, consistent with cellulitis. Fungal stains, at this point, were negative. The initial wound culture grew group B streptococcus. The ulcer continued to progress despite 2 weeks of treatment with cephalexin. At 4 months after his initial presentation, the patient's ulcer was approximately 5×5 cm with undermined and erythematous borders and was surrounded by small satellite ulcerations (figure 1A), and on the basis of this clinical appearance he was given the presumptive diagnosis of pyoderma gangrenosum. He was treated with prednisone (60 mg daily) and ciclosporin (200 mg twice daily) for 3 months and ustekinumab for 2 months. He also received one dose of intravenous immunoglobulin (200 mg/kg).

However, his ulcer continued to progress despite immunosuppressive therapy and he presented to Johns Hopkins Dermatology Clinic, Baltimore, MD, USA, with a large 9×9·5 cm ulcer with a depth of 1 cm on his left upper thigh with black necrotic debris in the centre with yellowish and greenish exudate and surrounding marked erythematous borders with oedema (figure 1B). In addition, on his left posterior thigh he had an additional 2×1·8 cm ulcer with a similar appearance to the larger ulcer. At that time, two additional skin punch biopsies were done for pathology and microbiology analysis. On histology, a mixed dermal inflammatory infiltrate was present with associated histiocytes and numerous oval-cigar shaped elements on haematoxylin and eosin stain (figure 2A, B) that were highlighted by Periodic acid-Schiff (figure 2C) and Grocott's methenamine silver (figure 2D) stains.

S schenkii was subsequently recovered from the patient's wound culture and in blood cultures with MycoF Lytic blood culture bottles (BD Biosciences, Sparks, MD, USA). The blood culture turned positive on day 7, and Gram stain showed budding yeast cells (figure 3A) that subsequently grew on a colistin naladixic acid plate incubated at 37°C, representing the yeast phase of the organism (figure 3B). The subculture of the organism on the potato flake agar plate incubated at 25–30°C showed fluffy and dark brown pigmented colonies, representing the filamentous or mould phase of the organism (figure 3C). A direct

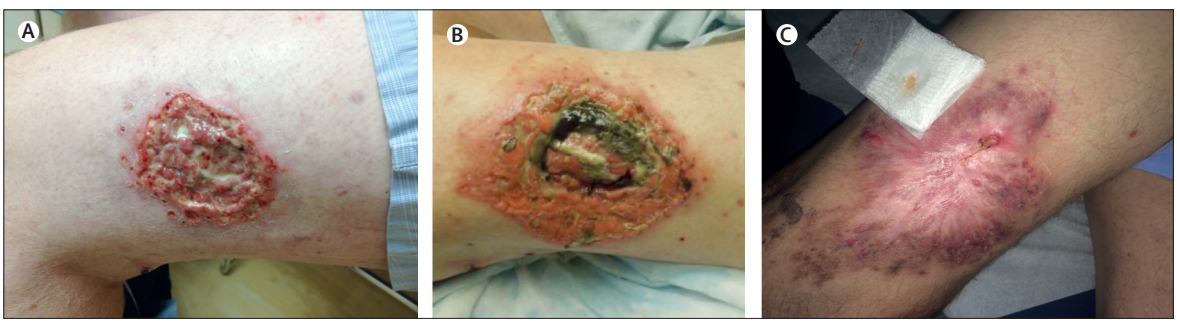

Figure 1: **Expanding left lateral thigh ulcer**
(A) A 5×5 cm ulcer with undermined and erythematous borders with surrounding small satellite ulcerations. Photograph taken at the time of the presumptive diagnosis of pyoderma gangrenosum and start of immunosuppressant therapy. (B) A 9×9·5 cm ulcer with a depth of 1 cm with black necrotic debris in the centre with yellowish and greenish exudate and surrounding marked erythematous borders with oedema. Photograph taken after approximately 5 months of immunosuppressant therapy at which time skin biopsies and cultures showed sporotrichosis. (C) Healing lesion approximately 6 months from the start of antifungal therapy.

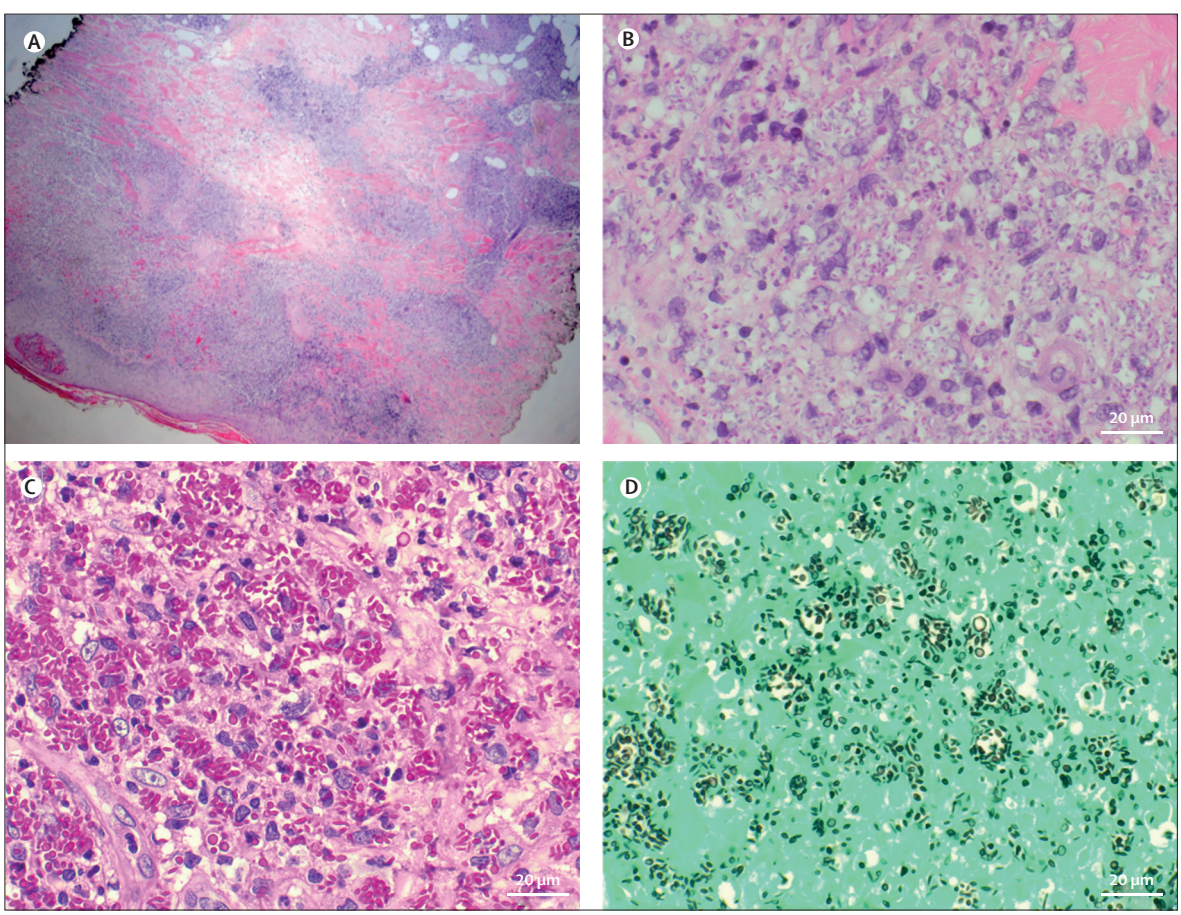

Figure 2: **Histology of the biopsy tissue of the ulcer**
(A) Superficial and deep mixed inflammatory infiltrate (2× magnification). (B) Mixed dermal inflammatory infiltrate with numerous histiocytes and yeast forms identified on haematoxylin and eosin stain (60× magnification). (C) Oval cigar-shaped yeast forms with single or multiple budding highlighted by Periodic acid-Schiff stain (60× magnification). (D) Oval cigar-shaped yeast forms with single or multiple budding highlighted by Grocott's methanamine silver stain (60× magnification).

lactophenol cotton blue preparation from the mould phase culture showed branching septate hyphae with slender short conidiophores with tapering tips and surrounding pyriform conidia in a flower-like arrangement (figure 3D), consistent with the microscopic features of *S schenkii* that was further confirmed by molecular identification. Antifungal susceptibility testing showed the minimal inhibitory concentration (MIC) for the

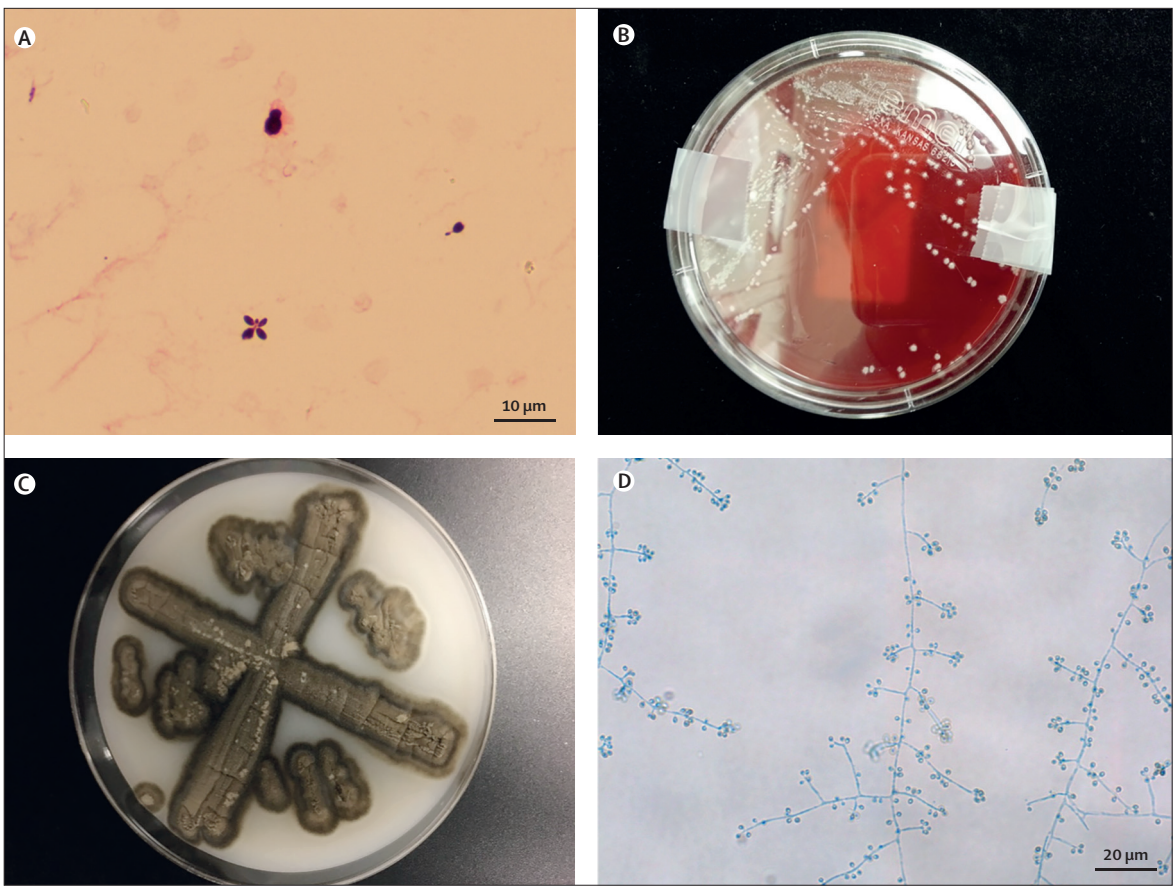

Figure 3: **Mycology culture and identification**
(A) Gram staining of the positive blood culture showed yeast forms with single and multiple budding. (B) Yeast form of the organism grown on a colistin naladixic acid plate at 37°C. (C) Filamentous mould form of the organism grown on a potato flake agar plate at 25–30°C. (D) Lactophenol cotton blue preparation of the mould form cells showed delicate branching septate hyphae with slender conidiophores with tapering tips surrounding pyriform conidia in flower-like arrangements.

antifungal drugs tested for: amphotericin B (MIC 2·0 µg/mL), itraconazole (MIC 1·0 µg/mL), posaconazole (MIC 1·0 µg/mL), and terbinafine (MIC 0·06 µg/mL).

On the basis of the cultures and histological findings immunosuppression was stopped and the patient was admitted and treated for disseminated sporotrichosis with AmBisome (5 mg/kg intravenous daily) and posaconazole (300 mg orally twice daily followed by 300 mg orally daily thereafter). Posaconazole was chosen over itraconazole at that point because of a concern of interference of itraconzaole with his antiarrhythmic treatment. The initial concern for fungal endocarditis was because of possible aortic valve vegetations seen on transoesophageal echocardiogram. However, subsequent echocardiogram studies suggested that these vegetations were likely to be an anatomic variant of the aortic valve.

In addition to widely disseminated systemic sporotrichosis, he also developed *Pneumocystis jirovecii* pneumonia with superimposed hospital-acquired pneumonia, acute lower extremity deep venous thrombosis, *Clostridioides difficile* colitis, thrombocytopenia, and acute kidney injury. The acute kidney injury was thought to be multifactorial, but was partly attributed to treatment with AmBisome. His posaconazole was changed to itraconazole (200 mg orally every 8 h for the first nine doses, followed by 200 mg orally every 12 h thereafter) because of concern regarding progression of his ulcerations despite posaconazole and AmBisome treatment. He was ultimately discharged from the hospital to his home after a 69-day admission. He completed 8 weeks of treatment with AmBisome, and stayed on itraconazole treatment 10 months after discharge. Terbinafine (250 mg daily) was added as an adjunctive therapy because of the wound progression. The cutaneous wounds on his left thigh took approximately 6 months to heal from the start of antifungal therapy (figure 1C).

Mycology

S schenckii is a dimorphic fungus found in soil and decaying plant material.[2,5] Molecular studies[5–7] show that *S schenckii* is a species complex of six distinct species, rather than one. The species in the complex that are most

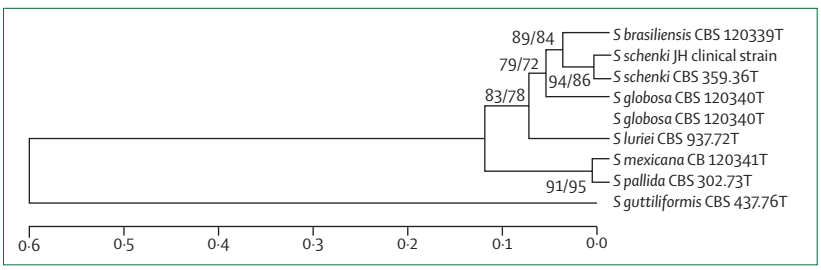

Figure 4: **Phylogenetic tree generated by maximum likelihood and neighbour-joining with partial nucleotide sequences of the calmodulin-encoding gene**
Bootstraps were added both branches.

frequently associated with human infection are *Sporothrix brasiliensis, Sporothrix globosa, Sporothrix luriei,* and *S schenckii*.[5,7,8] Geographical distribution of each species varies. In Asia, particularly in China, *S globosa* is the causing agent accounting for 99% of the human cases of sporotrichosis.[6,7] In the south and southeast of Brazil, *S brasiliensis* is responsible for most human and animal sporotrichosis cases.[9–11] *S schenckii* is widely distributed geographically, including Australia, South Africa, parts of South America, and North America.[5,12]

Our clinical strain (*S schenckii* Johns Hopkins clinical strain) was sequenced targeting the internal transcribed spacer region and was identified as *S schenckii*. To further confirm the identity of our strain within the *S schenckii* species complex, we amplified and sequenced the calmodulin gene and aligned the nucleotide sequences of the calmodulin gene with the ones from type strains of the six members within the *S schenckii* species complex.[6] This phylogenetic analysis indicated that our clinical strain was in line with the *S schenckii* type strain but distinct from the others, confirming that our strain was indeed *S schenckii* within the species complex (figure 4).

Clinical presentation and disseminated sporotrichosis

Most cases of sporotrichosis occurring in immunocompetent patients are seen between the ages of 40 years and 70 years, with no observed differences in gender. These infections are common in tropical or subtropical climates in which sporotrichosis is endemic, including South American countries, China, and South Africa.[7] Most patients have a history of agricultural work or hobbies, or exposure to infected animals such as cats.

Sporotrichosis is a cutaneous fungal infection classically characterised by ascending lymphocutaneous spread or sometimes presents with fixed cutaneous, extracutaneous, or disseminated infection. Sporotrichosis is transmitted by traumatic inoculation with soil, decaying plant material, bites or scratches from infected animals such as cats in endemic regions, or rarely by inhalation of fungal conidia.[4,13] The lymphocutaneous infection is the classic presentation characterised by multiple nodular ulcerative lesions showing secondary ascending linear lympho-cutaneous spread. The lympho-cutaneous or fixed cutaneous nodules are most encountered on the hands, arms, legs, and face, frequently associated with a site or history of traumatic inoculation.[14] Atypical presentations of sporotrichosis include multiple cutaneous lesions with a non-linear or non-lymphatic distribution.[15] Other atypical presentations include osteoarticular, pulmonary, sinonasal, or, less frequently, disseminated infections.[16,17]

Disseminated infections are more frequently seen in immunocompromised patients than in immunocompetent hosts, with most occurring in patients with a history of HIV or iatrogenic immunosuppression. A systematic review[2] reported that patients with HIV with sporotrichosis infections were more likely to present with disseminated infection than patients without HIV, with a median CD4 T-cell count of 97 cells per µL. However, another study[18] did not show an association between the CD4 T-cell count at clinical presentation and survival outcome. Disseminated infections in profoundly immunocompromised patients might result in severe disease with systemic dissemination, including cardiac, ocular, or CNS involvement.[1,19,20]

Less frequently, disseminated infections occur in immunocompetent patients, with most involving cutaneous dissemination rather than systemic fungal dissemination. A large series[21] from China reported eight cases of cutaneous dissemination without clinical evidence of immunosuppression out of a total of 457 cases of sporotrichosis. However, in these cases, the authors suggested that the cutaneous dissemination was potentially the result of multisite inoculation rather than true dissemination. A smaller series[4] from Malaysia reported two cases of cutaneous dissemination out of a total of 19 cases of sporotrichosis, from which one patient was a 61-year-old man with a history of lepromatous leprosy treated in the 1960s who owned a plant nursery, whereas the other was a 71-year-old woman with a history of hypertension and ischemic heart disease. The clinical history of lepromatous leprosy was suggested to predispose the patient to developing a disseminated infection, whereas the female patient might have been predisposed to disseminated infection because of age. In all cases, only cutaneous dissemination was found, without organ involvement. Disseminated cutaneous sporotrichosis is frequently observed during endemic zoonotic sporotrichosis in non-immunosuppressed patients infected by cat zoonotic transmission of the fungus, which is attributed to several inoculations in different locations either during treatment or playing with animals.[9,22,23] Extensive ulcerative cutaneous sporotrichosis has also been documented in patients with diabetes and chronic alcoholism.[22,24]

Our case initially showed an atypical presentation due to the presence of a cutaneous ulcer without lympho-cutaneous spread. However, the clinical history of a 2-cm-sized cutaneous lesion suggests that the patient initially had a fixed nodular infection, which subsequently became

superinfected with group B streptococcus, possibly accounting for the atypical clinical appearance of extensive ulceration at the time of presentation. Although the patient had an additional ulcer on the posterior thigh, this ulcer was not consistent with typical lymphocutaneous spread, which would have occurred proximally, approaching the draining inguinal lymph nodes. This non-lymphocutaneous large ulcerative lesion is notable despite haematogenous dissemination of the *S schenckii* infection in the setting of immunosuppressive therapy. Our patient received ustekinumab, a very specific immunosuppressant that blocks the function of cytokine interleukins 12 and 23. To our knowledge, the use of ustekinumab has not been reported to cause disseminated sporotrichosis. The case we present was an initially localised cutaneous sporotrichosis infection that subsequently became widely disseminated after treatment for pyoderma gangrenosum.

Clinical mimics of sporotrichosis

That sporotrichosis might mimic other infectious and non-infectious dermatological conditions is well documented.[25,26] A small case series[25] reported that seven of 19 cases of sporotrichosis were initially misdiagnosed as mycobacterial or other fungal infections or non-infectious dermatological condition. Four of those misdiagnosed patients ultimately received immunosuppressive agents after being diagnosed with either polyarteritis nodosa, sarcoidosis, vasculitis, or pyoderma gangrenosum. Sporotrichosis might also mimic malignant dermatological processes. In 2016, a case of disseminated cutaneous sporotrichosis in an patient with HIV was initially diagnosed as Kaposi's sarcoma.[27]

In our case, the patient was initially given a diagnosis of pyoderma gangrenosum. This diagnosis was partly given because of the atypical clinical presentation of a large ulcer, without associated lymphocutaneous spread. This presentation was quite similar to the lesions seen in classic pyoderma gangrenosum, which are typically ulcerative lesions with raised edges with rolled-borders, necrotic base, purulent discharge, and surrounding erythema.[28] The ulcers might either be solitary, or multiple in cases with rapid progression. Although pyoderma gangrenosum can result in multiple ulcerations, classic pyoderma gangrenosum is not associated with lymphocutaneous spread, which is an important clinical distinction. The absence of lymphocutaneous spread in this case made rendering an accurate diagnosis very challenging.

As this case shows, the clinical distinction between these entities is crucial given the substantially different treatment and the severe clinical implications of a misdiagnosis. Not only did our patient develop sporothrix fungaemia, but he also developed other opportunistic and hospital-acquired infections that were probably secondary to the immunosuppressive treatment for pyoderma gangrenosum.

Diagnosis

Prompt and accurate diagnosis of sporotrichosis is paramount to prevent improper treatment and dissemination, as highlighted by this case. Most frequently, definitive diagnosis relies on the use of either culture or histological examination of involved tissues; however, other laboratory testing methods might be used.

Standard cultivation should include culturing involved tissues on mycological media and incubating at 25–30°C. Filamentous growth should be visible after 5–7 days of incubation.[1] Initially, colonies will show a smooth, cream-coloured macroscopic appearance, but will subsequently turn black because of the presence of melanin (figure 3C). Microscopically, on a lactophenol cotton blue preparation the cells show delicate branching septate hyphae with slender conidiophores with tapering tips surrounding pyriform conidia in flower-like arrangements (figure 3D).

Biopsy of involved tissue might provide a rapid diagnosis in severe cases in which a high burden of fungal elements exists that increase the likelihood of visualising them on fungal stains. In our case, the long-term immunosuppression probably accounts for why fungal elements were readily seen on the histological examination, because to find yeasts in lymphangitic-cutaneous and fixed-cutaneous cases is usually rare. The high number of yeasts seen in the tissue biopsy in our case might be proportional to the degree of immunosuppression. If present, the fungal elements seen on special stains will be narrow-based budding or cigar-shaped yeast cells. However, the yeast cells are not always present in histology samples, limiting the utility of biopsy. In one case series,[29] the yeast cells were seen in only two of 60 cases. A larger case series[21] from an endemic region in China reported the presence of yeast cells visible on Periodic acid-Schiff staining in 20% of cases. Biopsies from tissues infected with sporotrichosis might show varying histological findings including non-specific acute and chronic inflammatory infiltrate, abscess formation, histiocytes, epitheliomatous hyperplasia, fibrosis, or vascular thrombosis, with or without an associated granulomatous component.[30]

Although fungal elements might not be readily seen on routine haematoxylin and eosin staining, the clinical history of a cutaneous lesion and the presence of abundant acute and chronic inflammation with a granulomatous component should prompt additional tests with stains for fungal organisms, specifically Grocott's methenamine silver and Periodic acid-Schiff staining. Additionally, staining for acid-fast bacteria should also be done to exclude a mycobacterial infection mimicking sporotrichosis. If observed, the presence of classic morphology of sporothrix should be directly communicated with the treating physicians and prompt a discussion regarding sporothrix as the potential organism. In such cases, cultivations should be done to confirm the diagnosis.

Similar to the overlap between the clinical presentation of sporotrichosis and pyoderma gangrenosum, the histological findings might also be similar, making an accurate diagnosis very challenging to establish. Biopsies done early on in pyoderma gangrenosum from the advancing erythematous border are typically characterised with a dense neutrophilic infiltrate in the dermis.[28] At the edge of the ulcer, similar findings sometimes exists that are seen in leukocytoclastic vasculitis such as perivascular immune infiltrate, thrombosis, extravasation of erythrocytes, and fibrinoid necrosis of the vessel walls. Additional chronic lesions might show varying focal neutrophilic abscesses surrounded by granulomatous inflammation with bordered lymphocytes and plasma cells. All these features might be observed in tissue biopsies from patients with an active sporotrichosis infection. The histological overlap with sporotrichosis emphasises the crucial role of communication across different specialties including pathology, infectious diseases, and dermatology. The communication of the clinical history of the patient and the clinical impression of the dermatologist and infectious disease physician are equally as important as the pathologists either doing or recommending ancillary studies. Despite effective communication across specialties, accurate diagnosis might still be challenging as this case shows. In this case, the initial negative fungal stains and cultures combined with the clinical history and presentation were more supportive of the diagnosis of pyoderma gangrenosum than sporotrichosis.

Other diagnostic approaches, besides culture and histological examination of tissue biopsies, include serological methods such as ELISA[31] and rapid species identification with rolling circle amplification method.[32] The use of PCR testing might be helpful in cases with high clinical suspicion of infection, despite negative cultures and biopsies.[1,7]

Treatment and prognosis

Standard treatment of sporotrichosis consists of itraconozole for cutaneous, lymphocutaneous, or osteoarticular infections, although AmBisome might be used in cases of disseminated or pulmonary infections.[33] Second-line treatment includes fluconazole, but this drug requires high doses to be effective. Alternative therapies include local hyperthermia, or saturated solution of potassium iodide. Local hyperthermia treatment is reserved for patients with fixed cutaneous sporotrichosis who cannot tolerate or receive recommended treatment.[33] Cryosurgery is another treatment option for sporotrichosis cases like incomplete response or failure to oral antifungals or inability to tolerate antifungals because of adverse reactions, and for pregnant women, chronic verrucous, or extensive ulcerated and vegetative lesions.[34–36]

Although cases of cutaneous sporotrichosis respond excellently to 3–6 months of itraconazole with a 90–100% response rate,[33] treatment of disseminated infections might be challenging to treat with some requiring long-term or lifetime antifungals, particularly in patients with a history of HIV. Treatment of the underlying immunocompromising condition is necessary for improvement of the disseminated fungal infection.[20,37]

In the presented case, the patient was initially treated with posaconazole out of concern for drug–drug interactions between itraconazole and his antiarrhythmic regimen. Posaconazole has known in-vitro activity against *S schenckii* and rare case reports exist documenting its success at treatment of sporotrichosis.[20,37,38] Despite data supporting its use, our patient had progression of his lesions on posaconazole. Therefore, his antiarrhythmic regimen was adjusted, and he was then started on itraconazole. His improvement, albeit gradual, did occur on itraconazole. In an attempt to improve his response to antifungal therapy, terbinafine was added because in-vitro data to support its use and previous reports confirming successful treatment of sporotrichosis in human patients with terbinafine exist.[37–40] Although he only received terbinafine for a short period of time, he did tolerate the drug well and had ongoing improvement in his wounds.

In this case, all immunosuppressive therapies were discontinued once an appropriate diagnosis was made, allowing for improvement in his overall condition. However, given the half-life of some of the agents he received (namely the ustekinumab), the duration of which he was effectively immunosuppressed probably contributed to the slow and gradual improvement seen, despite first-line and aggressive therapies.

Conclusion

That sporotrichosis mimics not only other cutaneous or subcutaneous fungal infections, but also neoplastic and non-neoplastic dermatological processes, is well documented. In our case, sporotrichosis was initially misdiagnosed as pyoderma gangrenosum, a dermatological condition with an uncertain pathogenesis and histological changes similar to those seen in sporotrichosis infections.

As our case clearly shows, rapid and accurate diagnosis of sporotrichosis is imperative to prevent improper treatment and possible dissemination. The features in this case were atypical, which made diagnosis quite challenging. The presence of a solitary large ulcer on the thigh was an atypical clinical presentation for fixed sporotrichosis. A superinfection of a primary fixed nodular sporothrix lesion with group B streptococcus accounting for the ulcerative appearance of the lesion is possible. In this setting, to diagnose sporotrichosis in the absence of positive fungal cultures or histology would be incredibly challenging. In these challenging cases, the clinical history and absence of response to antibiotic therapy and immunosuppressants should raise suspicion for atypical infections and prompt repeated biopsies and culture.

Contributors

MW and LA searched the scientific literature, collected and analysed data, prepared figures, and co-wrote and edited the manuscript. CP and GE

collected data, prepared figures, and edited the manuscript. MT, RL, and XL contributed to the collection and analysis of data, generation of figures, and editing of the manuscript. SM and LSM summarised the patient history, interpreted clinical findings, generated images, and co-wrote and edited the manuscript. SXZ designed the study, collected and interpreted data, developed figures, and co-wrote and edited the manuscript.

Declaration of interests

SXZ reports grants from T2 Biosystems and GenMark Dx, outside the submitted work. LSM reports grants and personal fees from AstraZeneca, MedImmune, Pfizer, Regeneron Pharmaceuticals, Boehringer Ingelheim, and Moderna Therapeutics, and personal fees from Integrated Biotherapeutics, Janssen Research and Development, Armirall, and Noveome Biotherapeutics, outside the submitted work. All other authors declare no competing interests.

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