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CASE REPORT

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Disseminated sporotrichosis in a person with human immunodeficiency virus disease

Vhudzani Tshisevhe[1,2,*], Lebogang Skosana[2,3], Kagiso Motse[4,5], Tinashe Maphosa[6] and Barend Mitton[2,3]

Abstract

Introduction. Disseminated sporotrichosis is an incapacitating infection caused by the dimorphic fungus *Sporothrix schenckii*. Because this condition may mimic the presentation of tuberculosis, syphilis and other bacterial infections, the diagnosis may be missed or delayed.

Case Presentation. We describe a case of disseminated sporotrichosis in a patient with poorly controlled human immunodeficiency virus infection. The patient was initially treated for bacterial skin infections. The differential diagnosis also included tuberculosis and syphilis. Only after appropriate specimens had been sent for microbiological and histopathological investigations was the diagnosis of disseminated sporotrichosis made and appropriate treatment started. The patient showed a good clinical response to itraconazole.

Conclusion. This report highlights the importance of having a high index of suspicion of endemic mycoses when managing immunocompromised patients. The report also demonstrates that a delay in the diagnosis of sporotrichosis increases morbidity and results in unnecessary and inappropriate treatment with associated costs and adverse effects.

INTRODUCTION

Sporothrix schenckii is a dimorphic fungus that was first described by B.R. Schenck in 1898 as a fungus that caused 'abscesses' (cutaneous sporotrichosis) in humans [1]. Although the body of knowledge about human infections due to *S. schenckii* has grown, the clinical index of suspicion remains low in general practice [2]. Clinical features are known to vary geographically, although the majority of patients present with implantation mycoses [2]. Phylogenetic analysis and multidisciplinary consultation with members of The International Society for Human and Animal Mycology (ISHAM) identified heterogeneity within the *S. schenckii* genome and six species are now included within the *S. schenckii* complex [2]. Four of these species are clinically relevant in humans (*S. schenckii sensu stricto*, *S. brasiliensis*, *S. globosa* and *S. luriei*) and two are environmental fungi (*S. albicans*, *S. mexicana*) [2]. Most of the species are distributed widely around the globe (South America, the USA, Europe, Japan, South Africa) [2]. The ecological niche for *S. schenckii* is decomposing vegetation and soil, where it grows as a filamentous fungus (mould), mostly in tropical to sub-tropical regions [2, 3]. *S. schenckii sensu stricto* is the predominant aetiological agent in human sporotrichosis cases in South Africa (94%), Australia (94%) and the Americas (89%), while *S. brasiliensis* causes 88% of sporotrichosis in Brazil and *S. globosa* causes 99.3% of human cases in Asia [3]. *S. schenckii sensu stricto* has been associated with outbreaks in mine workers in South Africa and will be the focus of this report as it is endemic in this setting [4].

CASE REPORT

A male in his 40s, who had been diagnosed with HIV 6 years previously, presented with a 7-month history of disseminated nodular and ulcerating lesions (Figs 1 and 2). Verbal informed

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Author affiliations: [1]Lancet Laboratories, Rustenburg, South Africa; [2]Faculty of Health Sciences, Department of Medical Microbiology, University of Pretoria, Pretoria, South Africa; [3]Tshwane Academic Division, National Health Laboratory Service, Pretoria, South Africa; [4]Department Internal Medicine, Job Shimankana Tabane Hospital, Rustenburg, South Africa; [5]Faculty of Health Sciences, Department Internal Medicine, University of the Witwatersrand, Johannesburg, South Africa; [6]Faculty of Health Sciences, Department Dermatology, University of Pretoria, Pretoria, South Africa.
***Correspondence:** Vhudzani Tshisevhe, vhudzani@gmail.com

Keywords: disseminated sporotrichosis; human immunodeficiency virus; sporotrichosis; *Sporothrix schenkii*.

Abbreviations: AB, alcian blue; AFB, acid-fast bacilli; ART, antiretroviral therapy; CD4, cluster of differentiation 4; HIV, human immunodeficiency virus; IDSA, Infectious Diseases Society of America; ISHAM, International Society for Human and Animal Mycology; MALDI-TOF, matrix-assisted laser desorption/ionization-time of flight; MS, mass spectrometry; PAS, periodic acid-Schiff; PAS-D, periodic acid-Schiff-diastase; PCR, polymerase chain reaction; RPR, rapid plasma reagin; TB, tuberculosis; TPHA, *Treponema pallidum* haemagglutination.

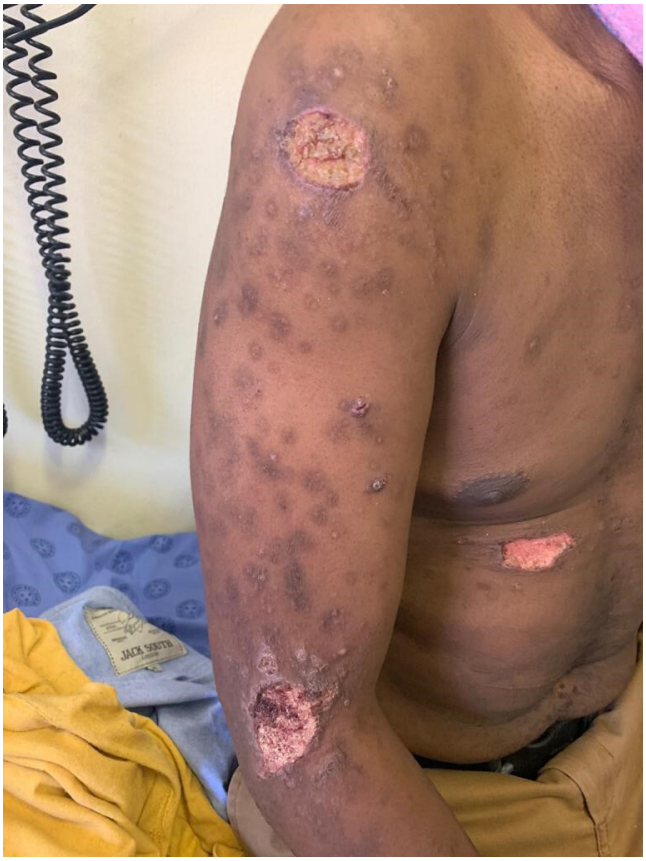

Fig. 1. Disseminated ulcerative lesions.

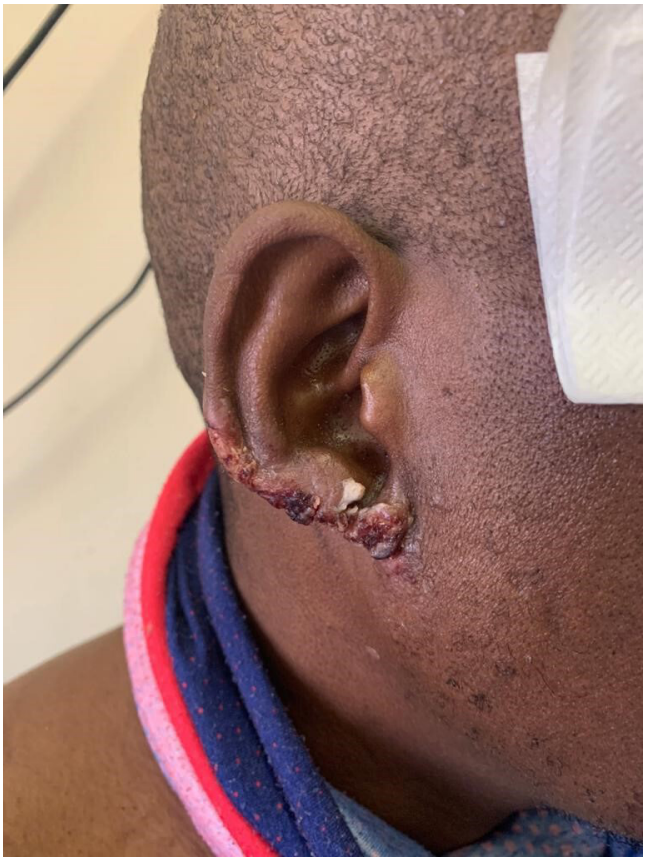

Fig. 2. Right ear ulcerating lesions.

consent was obtained from the patient. However, because the patient was lost to follow-up and attempts to contact him or his family has been unsuccessful, written consent could not be obtained. No patient-identifying details are included in this paper. The lesions worsened in the month prior to presentation and became predominantly ulcerative, with partial loss of the nose. The lesions were multiple, well-circumscribed, round to oval, hyper-pigmented ulcers with elevated borders ranging in size from 2–6 mm. The lesions were located on the face, scalp, chest, back, and upper and lower limbs. The patient reported associated generalized body pains, fatigue, night sweats, loss of appetite, loss of weight and a productive cough. Various antibiotics alone or in combinations were used without success. The patient also confessed to poor adherence to his antiretroviral therapy (ART), which consisted of abacavir, lamivudine and lopinavir/ritonavir. His HIV viral load was 149, 455 copies ml^{-1}, and his CD4 count was 34 cells mm^{-3} at the time of presentation. He previously had pulmonary tuberculosis in 2009 and in 2017, which was treated successfully.

Investigations

Chest X-ray showed bilateral reticulonodular infiltrates. Investigations for syphilis showed a positive *Treponema pallidum* haemagglutination (TPHA) test result and a non-reactive rapid plasma reagin (RPR) test. Other investigations included a serum cryptococcal antigen test, which was negative, a blood culture, which showed growth of *Staphylococcus hominis*, and a tuberculosis (TB) polymerase chain reaction (PCR) (Xpert MTB/Rif Ultra; Cepheid, Sunnyvale, CA, USA) test performed on sputum, which did not detect *Mycobacterium tuberculosis* complex. Multiple skin punch biopsies from the left and right cheeks, right elbow, right chest and back were taken and submitted for mycological culture and histological examination. Sputum samples were also collected and submitted for mycological, mycobacterial and general bacterial cultures. Sputum and tissue microscopy revealed no acid-fast bacilli (AFB). Mycological culture of tissues and sputum revealed colonies at 25 °C that were slow growing, moist and glabrous, with a wrinkled and folded surface. Colonies were white with an orange–brown reverse (Figs 3 and 4). The lactophenol cotton blue stain showed solitary and erect conidiophores arising at right angles from thin septate hyphae that tapered toward the apex. Conidia were formed in clusters on tiny denticles at the apex of the conidiophore, with their arrangement being suggestive of a flower (Fig. 5). Conidia were ovoid, hyaline, one-celled and smooth-walled. On blood agar, incubated at 37 °C, colonies were tiny, glabrous, white to greyish and yeast-like, and consisted of spherical or oval budding yeast cells on Gram stain microscopy.

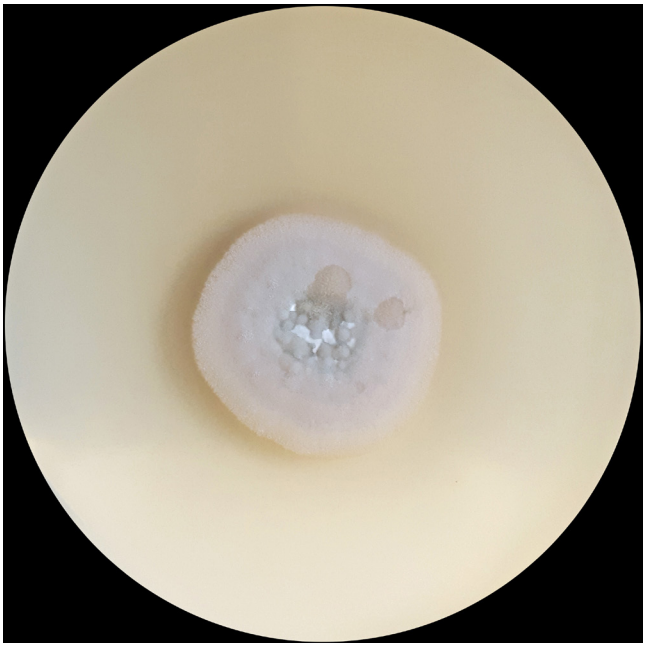

Fig. 3. *S. schenckii* colonies on Sabouraud's dextrose agar at 25 °C (front).

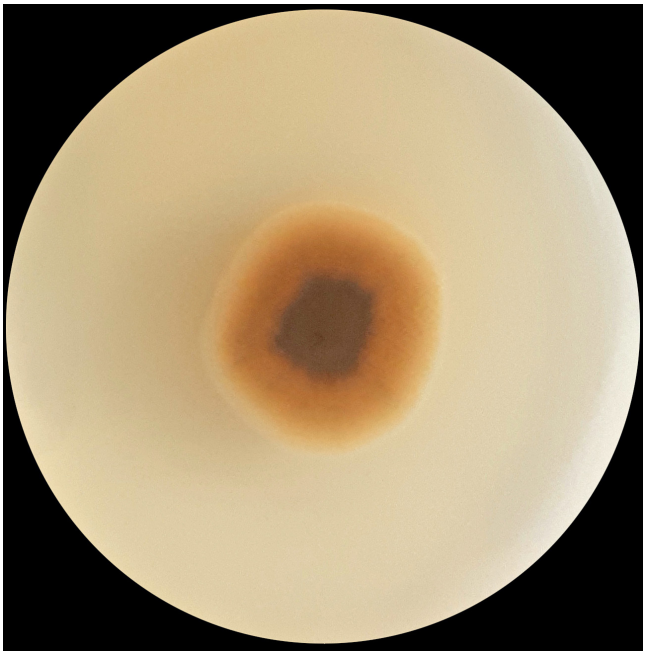

Fig. 4. *S. schenckii* colonies on Sabouraud's dextrose agar at 25 °C (reverse).

Diagnosis

The organism was identified as *S. schenckii* based on macroscopic and microscopic characteristics. The identification was confirmed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (VITEK mass spectrometer, bioMérieux, Marcy I'Etoile, France). Histological examination showed variable epidermal ulceration, which was undermined by acute inflammation admixed with fibrin and granulation tissue. The dermis contained a dense chronic inflammatory infiltrate composed of lymphocytes, plasma cells, histiocytes and numerous giant cells. In addition, numerous small, round to oval, cigar-shaped fungal elements and asteroid bodies were observed. The subcutis was unremarkable. The periodic acid–Schiff–diastase (PAS-D), Alcian blue (AB), PAS and Grocott stains highlighted the fungal organisms. The Warthin–Starry stain showed no micro-organisms. *T. pallidum* immunostaining showed negative immunoreactivity.

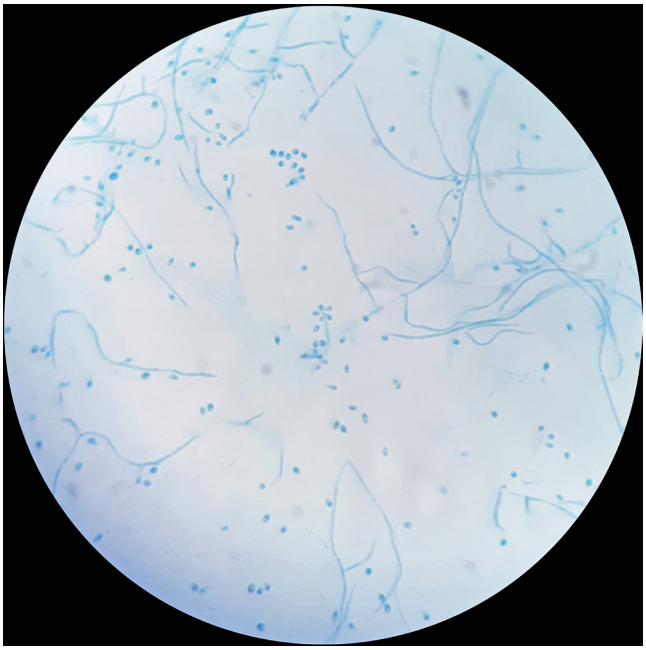

Fig. 5. *S. schenckii* lactophenol cotton blue stain microscopy at 1000× magnification showing thin, 1–2 µm in diameter, septate, branching hyphae that give rise to delicate conidiophores and pyriform conidia that are arranged in a daisy flower like pattern on tiny denticles at the apex of the conidiophore.

Treatment

Oral fluconazole, dosed at 400 mg per day, was initiated empirically 2 days after hospital admission. No itraconazole was available at the treating facility at that time. The patient showed minimal improvement on fluconazole. Itraconazole 200 mg 12 hourly was initiated after confirmation of sporotrichosis.

Outcome and follow-up

The patient made significant improvement and was discharged from the hospital after 5 weeks of itraconazole treatment. Unfortunately, he was lost to follow-up, as he did not return for scheduled appointments and attempts to reach him after discharge were unsuccessful.

DISCUSSION

We describe a case of a male patient with advanced HIV infection who presented with disseminated sporotrichosis. The patient presented with generalized ulcerated nodular cutaneous lesions and pneumonia. Similar to observations from other reports of disseminated sporotrichosis associated with HIV, the patient in our case had a low CD4 count (34 cells mm^{-3}) due to years of failure to adhere to ART [5–9]. Lymphocutaneous sporotrichosis is the most frequent clinical presentation (60–80% of cases) of *S. schenckii* infection and begins with a nodule at the site of inoculation, followed by ulceration and regional lymphangitis [3, 6, 7]. Typical clinical features may include single or multiple ulcers or granulomatous nodules with lymphangitis [8, 10]. The linear arrangement of multiple skin lesions along the lymphatic drainage is a strong clue to sporotrichosis [8, 10]. *S. schenckii* infection may also manifest as extra-cutaneous sporotrichosis [6, 7, 11]. The following clinical manifestations have been described: meningitis; endophthalmitis; osteoarticular, pulmonary and conjunctival sporotrichosis [6, 7]. Pulmonary sporotrichosis is the most common extra-cutaneous presentation and this was seen in the described case [5–7]. Disseminated sporotrichosis typically presents as diffuse, cutaneous, crusty, ulcerated nodular lesions with extra-cutaneous manifestations [6, 7, 12, 13]. Patients infected with HIV with CD4 counts below 200 cells mm^{-3} are at high risk of developing disseminated sporotrichosis, as seen in this patient, whose CD4 count was 34 cells/mm^{-3} [8, 10]. *S. schenckii* is an important opportunistic pathogen in this patient group and the diagnosis may be missed if the clinician's index of suspicion is low [14]. In the case described, the condition was initially misdiagnosed as a bacterial infection and treatment with antibiotics was unsuccessful. Syphilis and tuberculosis were also considered in the differential diagnosis.

Transmission of *S. schenckii* infection is usually by traumatic inoculation of fungal elements into the human host through cutaneous trauma with contaminated plant material or bites from infected animals [3, 4]. Transmission by inhalation is rare [15]. Occupational infection is common with gardeners, hence the term 'rose gardener's disease' [5]. The route of transmission in the case described is unclear. Unfortunately, the occupational history of the patient is unknown. The yeast form is disseminated haematogenously by adhering to host endothelial cells and by transendothelial migration [5].

The classic lymphocutaneous form of sporotrichosis is easily recognized by the typical satellite lesions that track along the lymphatics [16]. Uncommon manifestations of sporotrichosis, which may pose a diagnostic challenge, are more frequently encountered in immunocompromised persons [17]. The diagnosis of sporotrichosis relies on the correlation of clinical, epidemiological and laboratory data [5]. Laboratory diagnosis of sporotrichosis traditionally includes microscopy and culture of tissue biopsy specimens or pus from lesions [5, 5]. Direct microscopic examination of specimens treated with 10% potassium hydroxide may reveal budding yeast cells [5]. The yeast cells are characteristically described as cigar-shaped and measure 2–3×3–10 µm in size [5]. Other staining methods, including the Gram stain, fluorescent antibody stains and the PAS stain, may also be used to visualize the yeast cells [18]. Histopathological examination should include the use of the PAS and Grocott–Gomori silver stains [18]. Yeast cells surrounded by host immunoglobulins referred to as asteroid bodies or Splendore–Hoeppli phenomenon are characteristic of sporotrichosis [18]. The histopathological features of granulomatous inflammation with cigar-shaped organisms and asteroid bodies are supportive of the diagnosis of sporotrichosis, but have low sensitivity [18]. The definitive method to confirm the diagnosis of sporotrichosis is the culture identification of *S. schenckii* from an invasive specimen [19]. *S. schenckii* is a thermally dimorphic fungus that grows as a white to cream-coloured yeast on sheep blood agar or brain heart infusion agar at 35–37°C and as a cream-coloured mould that later turns black on Sabouraud's dextrose agar at 25 °C (Figs 3 and 4) [16]. The yeast phase typically shows growth in 24–48 h of incubation, whereas the filamentous growth may only be visible after 5–7 days [16, 18]. Microscopy of the filamentous form is typically performed using the lactophenol cotton blue stain (Fig. 5) [19]. Recently, molecular techniques typically based on the polymerase chain reaction (PCR), targeting beta tubulin, calmodulin, chitin and translation elongation factor genes, have been employed in the diagnosis of sporotrichosis [16]. MALDI-TOF MS may also be used in the identification of this *Sporothrix* species, as was done in the case described [16]. Other rarely used diagnostic methods include serology and the sporotrichin skin test [18]. Antifungal susceptibility testing is rarely performed, due to lack of standardization in methods and the absence of clinical breakpoints [16].

Our cultures grew slowly and it took more than 10 days for mould conversion to take place. This and the fact that sporotrichosis may mimic other dimorphic fungi, such as *Blastomyces* spp. and *Histoplasma* spp., as well as tuberculosis, cryptococcosis and syphilis, make diagnosing sporotrichosis challenging [5, 18]. The diagnosis may also be delayed while the above conditions are being pursued, underscoring the importance of having a high index of suspicion in those with outdoor exposure. In the case described the patient was also given several treatments for bacterial skin infection for months, which also delayed the diagnosis.

The Infectious Diseases Society of America (IDSA) has published guidelines for the management of sporotrchosis [20]. The guidelines are based on open-label clinical trials as well as anecdotal experience, and provide guidance on the treatment of lymphocutaneous and cutaneous sporotrichosis, invasive forms of sporotrichosis and disseminated sporotrichosis [20]. Treatment of lymphocutaneous sporotrichosis entails the use of itraconazole 100–200 mg daily for 3–6 months [20]. The dose can, however, be increased to twice daily if no response is noted [20]. Furthermore, terbinafine, fluconazole and potassium iodide are acceptable treatment alternatives [20]. A lipid formulation of amphotericin B, or alternatively amphotericin B deoxycholate, is recommended for the initial treatment of disseminated sporotrichosis [20–22]. Oral itraconazole (200 mg

twice daily) is recommended as step-down therapy to be given for at least a 12-month duration [20]. Because of the complex pharmacokinetics and potential drug interactions associated with itraconazole, therapeutic drug monitoring of itraconazole is recommended [20, 23]. Lifelong oral itraconazole suppressive therapy is recommended for immunocompromised patients if the immunosuppression cannot be reversed [20]. A saturated solution of potassium iodide may be considered as an alternative to itraconazole if the latter is unavailable, but is associated with many adverse effects [19]. In this case, the patient initially had lymphocutaneous sporotrichosis, which subsequently disseminated to involve the lungs. The patient was commenced on fluconazole (due to lack of itraconazole at the time) with minor improvement and subsequently switched to itraconazole 400 mg daily divided into two doses with improvement after 5 weeks of treatment. The poor response to fluconazole in this case is consistent with recent *in vitro* susceptibility study findings in which fluconazole was ineffective against the *Sporothrix schenckii* complex [24]. Unfortunately, therapeutic drug monitoring of itraconazole was not available in our treatment setting. Although the patient was lost to follow-up, clinical improvement was noted on itraconazole alone before the patient was discharged from hospital.

CONCLUSION

Disseminated sporotrichosis is an important diagnostic consideration in immunocompromised patients presenting with skin lesions associated with systemic symptoms. This condition may easily be misdiagnosed unless appropriate diagnostic tests are performed and a high index of suspicion of endemic mycoses is developed. A delay in diagnosis may lead to increased morbidity, inappropriate treatment and increased costs. The report described a case of disseminated sporotrichosis in a patient with poorly controlled HIV infection, which was initially misdiagnosed. The patient showed a good clinical response to treatment with itraconazole.

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Author contributions
All authors contributed equally.

Conflicts of interest
The authors declare that there are no conflicts of interest.

Ethical statement
Ethical approval was obtained from the Research Ethics Committee, University of Pretoria, Faculty of Health Sciences, ethics reference number 867/2020. Verbal informed consent was obtained from the patient. However, because the patient was lost to follow-up and attempts to contact him or his family have been unsuccessful, written consent could not be obtained. No patient identifying details are included in this paper.

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