A rare SARS-CoV-2 complication: *Candida* spondylodiscitis following SARS-CoV-2 infection—two case reports

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Background: In the context of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, opportunistic fungal co-/super-infections have surged globally. This report focuses on *Candida* spondylodiscitis (CS), an uncommon complication of severe SARS-CoV-2 infection without classical risk factors for invasive candidiasis.

Case Description: The first case involved a Hispanic 65-year-old man with severe SARS-CoV-2 infection, developing low-back pain. Magnetic resonance imaging (MRI) and biopsy revealed *Candida albicans* L4–L5 spondylodiscitis. Initial treatment with fluconazole showed limited improvement; subsequently, liposomal amphotericin and increased fluconazole were administered. Despite treatment adjustments, clinical response was delayed. After a switch to itraconazole, the patient experienced a 17-month antifungal regimen, leading to clinical and radiological improvement. The second case featured an 86-year-old Caucasian man with a history of chronic obstructive pulmonary disease, hypertension, chronic kidney disease, and a recent positive blood culture for *Candida tropicalis* during severe SARS-CoV-2 infection. An MRI confirmed spondylodiscitis at L3–L4 and L4–L5, and left psoas muscle involvement. Treatment included fluconazole, later interrupted due to worsened liver function tests. Following a regimen with liposomal amphotericin B and fluconazole, the patient exhibited clinical improvement, supported by a positron emission tomography-computed tomography (PET-CT) showing regression of spondylodiscitis.

Conclusions: These cases, unlike previous literature, involved intensive care unit-admitted SARS-CoV-2 patients, emphasizing the need for tailored coronavirus disease 2019 (COVID-19) management. Literature review indicated limited reports of CS in COVID-19 patients. In conclusion, severe SARS-CoV-2 infection creates a conducive environment for fungal proliferation, especially in critically ill patients subjected to various predisposing factors. Fungal aetiology should be considered in spondylodiscitis cases in this patient group.

Keywords: Coronavirus disease 2019 (COVID-19); candidiasis; spondylodiscitis; case report

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Introduction

Background

During the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, a surge in opportunistic fungal co-/super-infections worldwide has been observed. Invasive fungal infections (IFI) linked to viral respiratory diseases, including SARS-CoV-2, necessitate further investigation. SARS-CoV-2 sets the stage for fungal spore germination and proliferation, fueled by tissue hypoxia, epithelial damage, heightened ferritin, and dysregulated immune responses. The proinflammatory state in severe coronavirus disease 2019 (COVID-19), along with predisposing factors such as steroid use and prolonged hospitalization, enhances susceptibility to IFI, fostering yeast super-infections (1-3).

Rationale and knowledge gap

Patients with invasive Candida infections (ICI) in the context of COVID-19 have been extensively documented, indicating a 2- to 10-fold surge in candidiasis incidence compared to individuals hospitalized in intensive care unit (ICU) without SARS-CoV-2 infection (1,4). The reported ICI incidence ranges from 0.7% to 23.5%, with mortality rates varying between 46% and 92.5%, contingent on factors such as species, susceptibility, and antifungal therapy (1,4). While bloodstream infections are the predominant manifestation, secondary foci like endophthalmitis, retinitis, endocarditis, costochondritis, and spondylitis have also been reported (3). Fungal spinal infections, though rare, occur opportunistically, especially in immunocompromised hosts (5).

Objective

Given the novelty of *Candida* spondylodiscitis (CS) post severe SARS-CoV-2 infection, we highlight two case reports and conduct a literature review. Co-managing SARS-CoV-2 and CS poses a clinical dilemma, particularly with the rising use of steroids. Notably, treating CS demands an extended antifungal regimen, posing risks of adverse effects, potential loss to follow-up, and a heightened social and economic burden. We present both cases in accordance with the CARE reporting checklist (available at https://jphe.amegroups.com/article/view/10.21037/jphe-22-71/rc).

Highlight box

Key findings

- *Candida* spondylodiscitis (CS) is a rare medical condition, which occur predominantly in immunocompromised patients. Invasive candidiasis, and specifically CS, should be considered as a possible complication in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection that requires intensive care unit admission even in previously immunocompetent patients.

What is known and what is new?

- CS in patients with SARS-CoV-2 has been observed to occur relatively soon after the critical phase of the viral infection or the discharge.
- The study emphasizes the importance of heightened vigilance for CS in post-coronavirus disease 2019 (COVID-19) patients with predisposing factor, highlighting the need for early recognition and treatment.

What is the implication, and what should change now?

- This study sheds light on the potential risk of CS in severe SARS-CoV-2 cases, urging a more focused approach to post-COVID-19 care and research to improve understanding and management of CS in this context.

Case presentation

We present two cases of CS following severe SARS-CoV-2 infection, occurring in patients without typical predisposing factors (*Table 1*), at Amedeo di Savoia Hospital, University of Turin, from 2020 to 2022.

Patient 1

A 65-year-old Hispanic man, with a history of B hepatitis, was discharged to our outpatient clinic after prolonged hospitalization for severe SARS-CoV-2 infection. He was diagnosed with *Candida albicans* (*C. albicans*) L4–L5 spondylodiscitis and bilateral myositis involving iliopsoas.

In the past 3 months, he endured ICU admission for severe SARS-CoV-2 pneumonia, requiring intubation and treatment with high-dose steroids, low molecular weight heparin, and tocilizumab. Complications ensued, including a spontaneous psoas hematoma, potentially linked to heparin, resulting in anemia. Additionally, catheter-related *C. albicans* candidemia was treated with caspofungin and step-down fluconazole, and *Enterobacter cloacae* bacteremia was managed with trimethoprim/sulfamethoxazole. While hospitalised, the patient had developed low-back pain [constant 7/10 on numeric rating scale (NRS) pain scale] and fatigue, difficulty bending over, without neurological symptoms, and a magnetic resonance imaging (MRI) scan and subsequent computed tomography (CT) guided biopsy

Table 1 Table summarizing highlight data from our cases (case 1 and case 2) and data from the two patients with Candida spondylodiscitis associated to COVID-19 described in literature

Patient	Case 1	Case 2	Moreno-Gòmez *et al.*	Gorospe-Sarasúa *et al.*
Age (years)	65	86	47	53
Sex	Male	Male	M	M
Ethnicity	Hispanic	Caucasian	Hispanic	Hispanic
Comorbidity	Previous B hepatitis	Chronic obstructive pulmonary disease, hypertension, heart attack, CKD	AI, obesity	None
Duration of the hospitalisation (days)	90	30	30	10
Mechanic ventilation	Yes	No	Yes	Yes
Antimicrobial therapy during hospitalisation	Trimethoprim/ sulfamethoxazole	NA	Azithromycin, meropenem, linezolid, daptomycin, fluconazole and anidulafungin	Azithromycin, ceftriaxone
Immunomodulatory therapy	Corticosteroids, tocilizumab	Corticosteroids	Hydroxychloroquine, interferon	Corticosteroid (80 mg/24 h) and tocilizumab (600 mg, two doses)
Candida blood stream infection during the hospitalisation	*C. albicans*	*C. tropicalis*	*C. albicans*, catheter-related	*C. albicans*, catheter-related
Localisation of the spondylodiscitis	L4–L5	L3–L4 and L5–S1	D8–D9	L3
Antifungal therapy of the spondylodiscitis	Fluconazole 400 mg QD > fluconazole 800 mg QD + L-AmB 300 mg QD > fluconazole 800 mg QD > itraconazole 100 mg q12h	Fluconazole 400 mg QD > caspofungin 35 mg QD > fluconazole 400 mg QD > fluconazole 200 mg L-AmB 300 mg QD > fluconazole 400 mg QD	Fluconazole (400 mg/24 h) + anidulafungin (100 mg/24 h) > fluconazole (600 mg/24 h) + liposomal amphotericin B (100 mg/24 h)	Fluconazole (800 mg/24 h)

COVID-19, coronavirus disease 2019; CKD, chronic kidney disease; AI, aortic insufficiency; NA, not available; QD, once a day; L-AmB, liposomal amphotericin B.

of the spine had been performed, confirming the diagnosis of L4–L5 *C. albicans* spondylodiscitis, without surgical indications.

Treatment with intravenous (IV) fluconazole was initiated (400 mg IV) at our infectious diseases ward. Due to ongoing symptoms, liposomal amphotericin B (L-AmB 300 mg IV) and increased fluconazole dosage were implemented (800 mg IV) daily.

Upon achieving clinical stability, the patient transitioned to our outpatient clinic for continued IV fluconazole at 800 mg/day. A subsequent MRI, conducted 2 months post-discharge, revealed persistent inflammation and erosion in multiple areas. Consequently, therapy persisted with a switch to oral administration. In response to inadequate clinical improvement, oral fluconazole was halted, and L-AmB initiated but discontinued due to adverse effects. After a 20-day treatment hiatus, itraconazole was introduced without issues. Antifungal treatment spanned 17 months post-discharge, culminating in noticeable clinical and radiological enhancements, as evidenced by the final MRI (*Figure 1*).

Patient 2

An 86-year-old man with a history of chronic obstructive pulmonary disease, hypertension, chronic kidney disease,

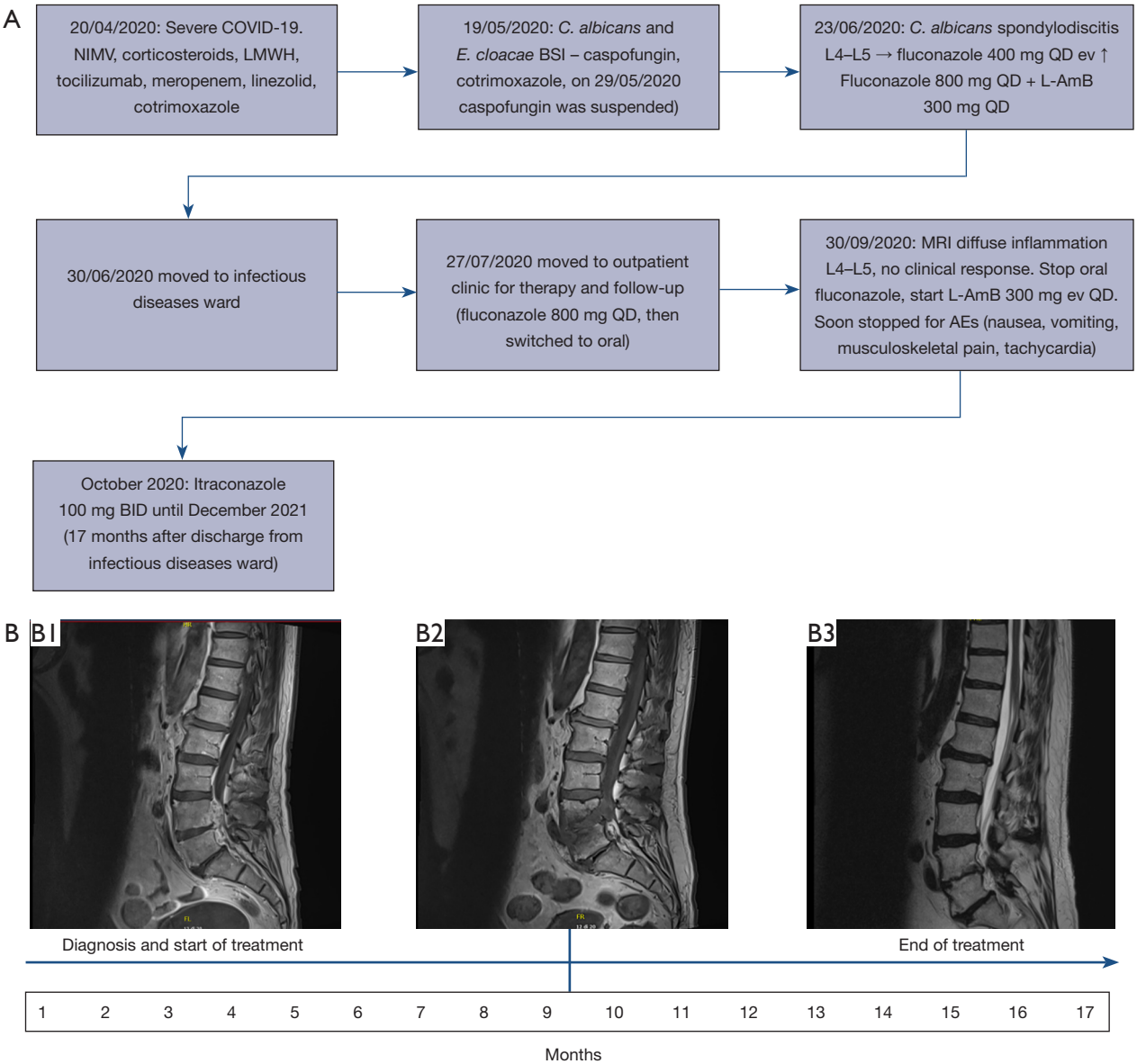

Figure 1 Timeline of the clinical, therapeutic and radiological progression of the CS in patient 1. (A) Timeline for patient 1. (B) Radiological evolution with RM of patient 1 at the start of the diagnosis (B1), after 8 months of therapy (B2) and at the end of treatment (B3) (left to right: 06/2020, 02/2021, 12/2021). This image is published with the patient/participant's consent. (B1) Extended alteration of signal involving L4–L5 vertebral bodies, partly involving the interposed disc, with contrast enhancement suggesting spondylodiscitis; (B2) compared to the former image, there is persistent L4–L5 alteration, with reduced contrast enhancement, which persists in the posterior part of L4–L5 bodies; (B3) persistence of known lesion, but without contrast enhancement, showing fibrotic and scar tissue. COVID-19, coronavirus disease 2019; NIMV, non-invasive mechanical ventilation; LMWH, low molecular weight heparin; *C. albicans*, *Candida albicans*; BSI, bloodstream infection; QD, once a day; ev, endovenous; L-AmB, liposomal amphotericin B; MRI, magnetic resonance imaging; AEs, adverse effects; BID, two times a day; ID, infectious diseases.

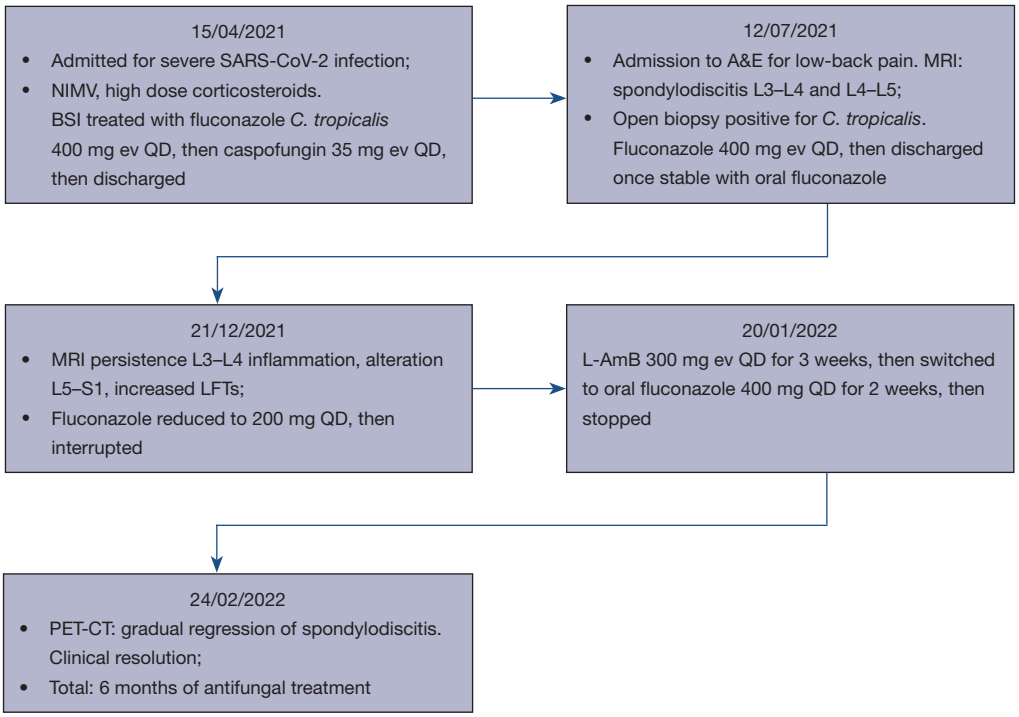

Figure 2 Timeline for patient 2. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; NIMV, non-invasive mechanical ventilation; BSI, bloodstream infection; C. tropicalis, Candida tropicalis; ev, endovenous; QD, once a day; A&E, Accident and Emergency; MRI, magnetic resonance imaging; LFTs, liver function tests; L-AmB, liposomal amphotericin B; PET-CT, positron emission tomography-computed tomography.

and cardiac ischemia presented with low-back pain (NRS 6/10) and malaise at our outpatient clinic. Previously hospitalized for severe SARS-CoV-2 infection, he had bilateral interstitial pneumonia, requiring non-invasive ventilation and high-dose steroids. During hospitalization, blood cultures confirmed *Candida tropicalis* (*C. tropicalis*). Initial fluconazole treatment was stopped due to elevated transaminases, followed by IV caspofungin. An MRI revealed abscessed spondylodiscitis (L3–L4, L4–L5) and left psoas muscle involvement. A percutaneous needle biopsy showed no microorganisms. An open biopsy cultured *C. tropicalis* sensitive to fluconazole. Initial treatment included vancomycin, piperacillin/tazobactam, later switched to fluconazole. Heart ultrasound ruled out dissemination. Upon stability, the patient was discharged with oral fluconazole (400 mg daily). Five months later, a contrast MRI revealed persistent inflammation (L3–L4) with involvement of the intervertebral space; altered signal in L5–S1 vertebral bones. Initial regression of the vertebral infection was noted. Clinically improving, the patient experienced reduced lumbar pain. Due to elevated cholestasis enzymes, fluconazole was initially reduced to 200 mg daily and later discontinued with rising gamma-glutamyl transferase (GGT) levels.

After nearly a month without antifungal treatment, persistent high GGT levels (651 IU) were observed, with no hepatic lesions on abdominal ultrasound. Subsequently, L-AmB treatment was initiated, well-tolerated without adverse effects. Following 3 weeks of IV L-AmB, oral fluconazole 400 mg was reintroduced for another 2 weeks, completing 6 months of effective antifungal therapy. Seven weeks post-treatment, a positron emission tomography (PET)-CT displayed residual spots near L3–L4 and L5–S1, indicating gradual spondylodiscitis regression with low standardized uptake values (2.17 and 2.04, respectively). Due to clinical improvement and low inflammation levels, no additional antifungal treatments were initiated, and the patient continues follow-up (*Figure 2*).

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committees and with the Helsinki Declaration (as revised in 2013). Written informed consent

was obtained from the patients for publication of this case report and accompanying images. A copy of the written consents is available for review by the editorial office of this journal.

Discussion

Comparison with similar research

We conducted a comprehensive literature search using PubMed and Google Scholar databases, employing the terms "Candida spondylodiscitis" and "COVID-19" or "SARS-CoV-2" for cases associated with severe SARS-CoV-2 infection. Additionally, we extended our search to cover other severe pulmonary viral infections, such as influenza, respiratory syncytial virus, SARS-CoV-1, and Middle East Respiratory Syndrome coronavirus. The review considered case reports and case series published from January 2020 to May 2022.

Our literature search identified only two relevant case reports by Moreno-Gòmez *et al.* and Gorospe-Sarasúa *et al.* (6,7). These cases involve relatively young men with previous severe SARS-CoV-2 infection and no classical predisposing factors for IFI. Both reports highlight similarities in patients' baseline conditions and disease clinical presentations, as summarized in *Table 1*.

Both patients, requiring ICU admission and mechanical ventilation, received antimicrobial and immunomodulatory treatments for severe SARS-CoV-2 infection. Moreno-Gòmez's patient was treated with hydroxychloroquine and interferon (6), while the other received high-dose corticosteroids and tocilizumab (7), reflecting the evolving COVID-19 treatment guidelines. Both developed catheter-related candidiasis with *C. albicans* during their ICU stay, promptly managed with device removal and antifungal therapy. No secondary localizations were reported.

Spondylodiscitis symptoms surfaced approximately 4 months post-ICU discharge, featuring intense back pain without fever. Gorospe-Sarasúa's patient successfully recovered with medical treatment, including high-dose fluconazole (800 mg/24 h). In contrast, Moreno-Gòmez's patient necessitated intensified antifungal therapy (fluconazole 600 mg/24 h and L-AmB 100 mg/24 h) along with surgical vertebral hardware placement.

We identified one more case of delayed CS linked to H7N9 virus in a non-immunocompromised 73-year-old without typical IFI risk factors (8). Steroids and antivirals successfully treated viral pneumonia during hospitalization. Three months post-discharge, fever and back pain led to a diagnosis of *C. albicans* spinal infection. L5/S1 interbody fixation, auto-bone graft, and fluconazole resolved symptoms a year post-surgery

Key findings

We described two cases of CS in patients admitted to our outpatient clinic because of recent severe COVID-19 requiring hospitalisation and long management.

Yeast species belonging to the *Candida* genus are the most prevalent commensal fungal species in the human host (4,9,10). Any variable that alters the commensal relationship between *Candida* species and the host could be considered as a predisposing factor for IFI (11). Therefore, colonisation is regarded as a prerequisite for subsequent infection (12).

Classically, numerous host risk factors have been associated with candidemia and ICI, including neutropenia, bone marrow transplantation, solid organ transplantation, parenteral nutrition, solid neoplasm, liver cirrhosis, diabetes mellitus, corticosteroids, broad-spectrum antibiotics, burns, recent surgery or severe trauma, haemodialysis and prolonged ICU stay, especially requiring mechanical ventilation (13). ICI is a major cause of morbidity and mortality in the health-care setting (12).

Patients admitted to ICU are 10 to 20 times at higher risk for invasive candidiasis than patients in non-ICU setting (14). Eighty percent of the colonisation occurs in the ICU patients during the first week from the hospitalisation (11,15). "Candida Score" allows differentiating between *Candida* colonisation and infection in non-neutropenic ICU patients (16).

Candida is among the most frequently identified pathogens in ICU, affecting between 6–10% of patients (4). The estimated mortality attributed to invasive candidiasis is 19–40% in the general population and climbs up to 70% patients hospitalised in ICU (4,17).

Moreover, ICI is 2- to 10-fold more frequent in patients with COVID-19 than in patients without COVID-19, independently to others risk factors for IFI. *C. albicans* represents the most frequent isolated among yeast in COVID-19 patients (44,1%) followed by *C. auris* (23,2%), *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis* and *Saccharomyces cervisiae* (4.6% each) (4).

Primary co-infections are rare among COVID-19 patients (18,19). However, critically ill patients, which represent one fifth of the hospitalised patients, and especially those admitted to the ICU (approximately 5%)

have higher risks of developing secondary infections, due to multiple factors (20).

Immune system dysregulation in critically ill COVID-19 patients plays a major role in the evolution of this viral disease and in predisposing to fungal co-infection but this pathway is yet to be clearly understood (1). In fact, SARS-CoV-2 elicits an immune response that triggers an inflammatory cascade as the result of the activity of innate immune cells which is at the base of the physiopathology of the lung damage in the SARS-CoV-2 infection (4). However, other immune mechanisms remain unclear.

Explanation of findings

The ICU is a critical setting for developing IFI in COVID-19 patients, underscoring the importance of early recognition and treatment. The Candida Score may help in screening. *Candida* infections present diverse clinical syndromes, from local to invasive manifestations. Invasive candidiasis involves bloodstream infection and deep-seated infections like intra-abdominal abscesses, peritonitis, or osteomyelitis, with or without candidemia, often part of disseminated candidiasis (11-13). Common causes of candidemia, with or without evidence of invasive fungal disease, include catheter-related candidiasis, suppurative thrombo-phlebitis, and *Candida* endocarditis (12,13). In patients with intravascular catheters, candidemia from the gut or skin forms biofilm, causing persistent and possibly disseminating candidemia (17). Diagnosis is challenging, often based on clinical suspicion, as blood cultures are negative in 40% to 60% of patients with disseminated candidiasis. Physical examination is typically unhelpful, with fever being the primary sign, though macronodular skin lesions and endophthalmitis may occur in up to 10% of documented candidemia cases (13).

CS is an exceptionally rare condition, occurring in 0.3–2.0% of reported spine infection cases (21,22), typically seen as an opportunistic infection in immunocompromised hosts. *C. albicans*, responsible for 62% of CS cases (22,23), is the most prevalent species in osteoarticular infections. CS is increasingly observed in severely ill patients with candidemia and prior azole exposure (24,25). *Candida* species spondylodiscitis is typically linked to candidemia in IV catheter holders and drug users, especially with biofilm-forming species like *C. tropicalis* (23). CS may be deemed a late complication of candidemia (26). Early CS symptoms can be nonspecific, warranting suspicion in patients with risk factors or prior *Candida* spp. bloodstream infection (23,26). Fever occurs in 32% of patients, often linked with non-infectious back pain and later-stage radicular neurological symptoms (23). The utility of serum biomarkers like 1-3-beta-d-glucan is not widely recognized in this late-onset complication. No treatment guidelines exist for patients with less common manifestations of deep-seated invasive candidiasis, including those with osteoarticular involvement. Treatments typically rely on expert opinion rather than prospective data (12,23), particularly in immunocompetent patients.

Implications and actions needed

Candida spp. bone involvement benefits from surgical debridement combined with antifungal therapy (27). Recommendations for surgical treatment vary (23); conservative approaches suit overall critically ill or symptomatically improving patients (28). Yet, 33% required surgical revision after conservative treatment in a small CS patient group (29). Surgical debridement is advised for persistent candidemia and progressing pain; stabilization is necessary for spinal instability, deformity, large abscesses, and neurological deficits (30).

The ideal duration and medication for CS treatment lack clear establishment (23,24). Antifungal therapy must align with species identification and resistance testing. Acquired resistance against azole and echinocandins in *Candida* spp. is rising; consideration of virulent or biofilm-forming subspecies is vital. Current Infectious Diseases Society of America (IDSA) guidelines recommend fluconazole at 400 mg (6 mg/kg) for 6–12 months or L-AmB induction at 3–5 mg/kg for 2 weeks, followed by fluconazole for 6–12 months (27). Successful alternatives include L-AmB at 0.5–1 mg/kg, echinocandins, posaconazole, and voriconazole (27,31). European guidelines align with these recommendations (31). Evaluating antifungal bone penetration when selecting regimens remains crucial. We described two cases, in which CS was treated with triazoles as first choice drug. Fluconazole indeed is an acceptable therapy in patients who are not critically ill and have negative repeat blood cultures following initiation of antifungal therapy, according to IDSA guidelines. Patient 1, although being initially treated with fluconazole and then L-AmB for a short period of time, was switched to oral itraconazole, which is not a suggested treatment, according to guidelines. This choice was based on higher clinical tolerance to the drug and good tissue penetration (32). To the best of our knowledge, no cases of CS successfully treated with itraconazole have been described in literature.

The three cases described in literature and the clinical cases described in this paper involved patients who did not have classical risk factors for candidemia or CS. Instead, all the cases described involved patients who had been admitted to ICU with severe SARS-CoV-2 requiring immunosuppressant agents and life-supporting devices. In addition, all patients showed variable time latency between SARS-CoV-2 infection and the onset of back pain. In our two cases this interval was relatively shorter than described in literature (1 *vs.* 3–4 months).

As for diagnosis and treatment, former cases reported in literature showed different approaches and evolutions. The patient described by Gorospe-Sarasúa *et al.* was diagnosed based on clinical symptoms and serial MRI, with positive cultures for *C. albicans*. Patient improved and recovered with medical treatment alone, (fluconazole for over 12 months). The patient of Moreno-Gòmez *et al.* had positive culture for *C. albicans* and required an escalation in the antifungal therapy with the association of fluconazole and L-AmB and the surgical positioning of vertebral hardware.

Both our patients had positive cultures and underwent medical treatment alone, without surgical treatment. These different approaches underline the uncertainty in diagnosis and medical and non-medical treatment.

Strengths and limitations

Our study has several limitations, as it was conducted retrospectively, the number of cases is confined and the cohort was monocentric.

Conclusions

CS, usually found in immunocompromised individuals, is increasingly observed in ICU patients with severe SARS-CoV-2 infection due to their critical condition and predisposing factors. Our report underscores the importance of recognizing this rare, delayed complication in SARS-CoV-2 patients without classical risk factors for invasive candidiasis. Fungal etiology should be considered for spondylodiscitis in this group. Given study limitations, further research is crucial to investigate the approach and management of post-COVID-19 CS.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committees and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for publication of this case report and accompanying images. A copy of the written consents is available for review by the editorial office of this journal.

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