Peer Review File
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Review Comments

First, in the title please consider to use the term co-infection of SARS-CoV-2 and Candida spondylodiscitis. I do not think "case series" is suitable for this study, since there must be at least 5 cases for a case series. The current study is a case report only.

Reply: Dear reviewers, thank you for this point. The title has been changed using the term "following" as the infections did not happen at the same time. This study involves two cases . The exact number of cases required to define one study a case series is debatable, although we agree that two cases may not be adequate. We have now updated the subheading.

Changes in the text: A pain in the back: Candida spondylodiscitis following SARS-CoV-2 infection - Two cases and narrative literature review.

Second, in the abstract, please indicate the potential unique clinical contributions of the two cases and explain why they are deserved to be reported. The authors need to provide information on the clinical characteristics, laboratory findings, COVID-19 symptoms, diagnoses, treatment, progression, and prognosis of the two cases. It is also necessary to summarize similar cases in the literature. In the conclusion, please have comments on the clinical management of similar cases and clinical lessons from this case report.

Reply: dear reviewer, thank for your comment. We provided changes to the abstract, even though abstract size limits the details that can be summarized in a limited space. Further clinical cases reported in literature are discussed in the paper. No other clinical reports apart from those cited in our paper are available to the best of our knowledge.

Changes in the text: The first patient was a man with no serious past medical history (PMH) who developed severe SARS-CoV-2 infection, and developed loe-back pain. An MRI and CT-guided biopsy showed with Candida albicans L4-L5 spondylodiscitis, initially treated with during the hospitalisation with fluconazole. Due to lack of clinical improvement, liposomal amphotericin was added and fluconazole dose was doubled. Once clinically stable, the patient was discharged and admitted to our outpatient clinic to follow-up and continue intravenous fluconazole, then switched to oral. A follow-up MRI scan showed persistence of CS. In the absence of response, oral fluconazole was interrupted and administration of L-AmB was started, but soon abandoned for the onset of adverse effects (AEs). An MRI of the spine was repeated, showing no radiological improvement. Hence, after 20 days of washout from therapy, oral solution of itraconazole was started, without AEs. The patient underwent a total of 17 months of antifungal treatment after discharge from the Infectious Diseases ward, with progressive clinical and radiological improvement. An MRI was performed at the end of treatment, showing reduction in contrast enhancement of L4-L5 and the iliopsoas muscles.

The second patient was a man with a history of COPD, hypertension, CKD and heart attack admitted to our outpatient clinic after accessing the Emergency Room (ER) with a 1-month history of low-back pain and severe SARS-CoV-2 infection requiring hospital admission less than 3 months before, during which he developed positive blood culture for C. tropicalis. When admitted to our clinic an MRI assessed the presence of abscessed spondylodiscitis at L3-L4 and L4-L5 level and involvement

of left psoas muscle with an open biopsy of the spine confirming positive cultures for C. tropicalis, initially treated with iv fluconazole, then to oral fluconazole when the patient was clinically stable. Follow-up MRI showed initial regression of the vertebral infection. The patient was clinically improving, with progressive reduction of the lumbar pain. Due to worsened liver function tests (LFTs), we decided to interrupt antifungal treatment, later restarted with L-Amb and gradually reintroducing fluconazole to complete treatment. A follow-up PET-CT was performed, still showing two spots of radioactive tracer uptake referable to gradual regression of spondylodiscitis. Considering the patient's clinical and improvement, blood tests showing low inflammation levels and the low values of SUV uptake in the PET-CT exam, no further antifungal treatments were started. At the moment, the patient is still on bimestrial follow-up.
To the best of our knowledge, only 3 similar cases have been described in previous literature so far, involving patients who did not have a history of common risk factors for candidemia and CS. Instead, all the cases we describe involve patients who had been admitted to ICU with severe SARS-CoV-2 requiring immunosuppressant agents and life-supporting devices. In addition, time latency between SARS-CoV-2 infection and the onset of back pain reported in literature is variable, with a shorter interval in our 2 cases. This could prompt clinicians in tailoring COVID-19 management and CS disease suspicion.

Third, in the introduction, comments on the potential clinical contributions and the clinical significance of this case report are needed. Please also have comments on the challenges in managing the co-infection of SARS-CoV-2 and Candida spondylodiscitis.
Reply: dear reviewer, thank you for this comment. We provided changes as follows in the text (LL 94-99)
Changes in the text: Since Candida Spondylodiscitis (CS) following severe SARS-CoV-2 infection is a relatively recent and exceptional clinical item, it is appropriate to report these two cases and review literature on this topic. As data on this subject matter are limited in literature, depicting such clinical cases could improve scientific knowledge in diagnosis and management of this condition. In addition, managing coinfection by SARS-CoV-2 and CS represents a clinical challenge, as the number of patients receiving steroids increased during the pandemic, resulting in a higher risk of CS cases. Importantly, CS requires a prolonged course of antifungal agent, with subsequent risk of adverse effects and loss to follow-up, together with a higher social and economic burden.

Fourth, in the case report, a timeline figure is needed to briefly summarize the clinical symptoms, diagnosis, progression, treatment, follow up, and prognosis of the two cases.
Reply: dear reviewer, a brief summary of the patients' timeline has been added athe end fo the paper.
Changes in the text: please, see the end of the paper for the brief timelines.

Finally, in the discussion, please have comments on the diagnosis and treatment strategies of similar cases, and have more detailed comments for the unaddressed clinical questions of this report.
Reply: dear reviewer, thanks for your comment. As required, we added comments on this topic (LL 337-344).
Changes in the text: 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, namely fluconazole lasting 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 liposomal amphotericin B, 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, in particular to what pertains to surgical procedures and optimal antifungal strategies considering dosing and penetration of the molecules based on PK/PD principles.

Further Comments

1. In Figure 3, Please label the three MR images from left to right as A, B, and C, and provide descriptions for each. Additionally, to illustrate more clearly, it is preferable to use arrows or other symbols to indicate key locations in the images.
Answer: dear reviewer, the images were labeled

2. We found table 3 was from reference 17 (may require permission to use), so please consider deleting it.
Answer: dear reviewer, we removed table 3 from our manuscript, as requested.

3. Introduction, para 1: “Invasive fungal infections (IFI) in the setting of other viral respiratory diseases have been previously well characterised, especially in influenza and RSV”, the corresponding references should be cited.
Answer: dear reviewer, we edited the expression, since further literature is needed.

4. Please note that ALL abbreviations should be defined upon their first use in both the abstract and main text, such as “SARS-CoV-2”, “RSV”, “CS”, “CKD”, “L-AmB” in the abstract, and “SARS-CoV-2”, “COVID-19”, “COPD”, “CKD” in the main body.
Answer: dear reviewer, we defined all the abbreviations as requested.

5. The full form of any abbreviation in the figures and tables need to be explained in the legends and notes, such as “ev”, “QD”, “ID”.
Answer: dear reviewer, we added these details.

6. Introduction, para 1: “Invasive fungal infections (IFI) in the setting of other viral respiratory diseases have been previously need further characterisation.” There seems to be a part of the sentence missing. It appears you’re trying to say something along the lines of, “Invasive fungal infections (IFI) in the setting of other viral respiratory diseases have been previously observed/documented/reported and need further characterization”.
Response: Introduction, Paragraph 1: The missing part of the sentence has been addressed