BRIEF REPORT

COVID-19 associated with disseminated histoplasmosis in a kidney transplant patient

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Abstract We report a case of disseminated histoplasmosis and COVID-19 infection in a renal transplant recipient in Argentina. The patient exhibited respiratory symptoms, and a chest computed tomography scan (CT) showed multiple bilateral centrilobular opacities with a tree-in-bud pattern in both lobes. The patient was initially treated as having bacterial community-acquired pneumonia, and then tuberculosis. A month later, histoplasmosis was diagnosed, and Histoplasma capsulatum LAmB clade was isolated from sputum, skin and oral lesions. The patient was hospitalized and treatment was started with intravenous liposomal amphotericin B. During the course of the antifungal therapy the respiratory symptoms worsened, a new chest CT showed a unilateral lesion with a ground glass appearance and SARS-CoV-2 was detected in a new nasopharyngeal sample. In addition, plasma therapy was administered, and the immunosuppressive regimen was adjusted (everolimus was interrupted, mycophenolate mofetil reduced, and meprednisode increased). Finally, the patient’s progress was favorable and was discharged after five days on oral itraconazole treatment for histoplasmosis.

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COVID-19 asociado a histoplasmosis diseminada en un paciente trasplantado renal

Resumen Se presenta un caso de histoplasmosis diseminada e infección por COVID-19 en un paciente trasplantado renal en Argentina. El paciente presentó un cuadro clínico respiratorio, y la tomografía computarizada (TC) de tórax mostró múltiples opacidades centrilobulillares bilaterales con patrón de árbol en brote. El paciente fue tratado inicialmente con antibióticos para agentes causantes de neumonia bacteriana adquirida en la comunidad y luego como tuberculosis. Un mes después se le diagnosticó una histoplasmosis diseminada y el hongo fue aislado del esputo, la piel y la mucosa oral. El hongo fue tipificado molecularmente como *Histoplasma capsulatum* clado LamB. El paciente fue hospitalizado y se inició tratamiento con anfotericina B liposomal vía intravenous. Durante el transcurso de la terapia antifúngica los síntomas respiratorios del paciente empeoraron, una nueva TC de tórax mostró una lesión unilaterial con apariencia de vidrio esmerilado y se detectó SARS-CoV-2 en el hispasa nasofaringeo. El paciente fue tratado con plasmoterapia y se modificó el régimen de inmunosupresión (se interrumpió everolimus, se redujo micofenolato de mofetilo y se incrementó la mepredisona). La evolución del paciente fue favorable y fue dado de alta con tratamiento oral con itraconazol.

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the results showed low albumin (2.50 g/dl), elevated lactate dehydrogenase (266 UI/l), as well as C-reactive protein (66.8 mg/l), and ferritin (1728 ng/ml).

Considering the pandemic situation, new samples of nasopharyngeal swab were collected for the SARS-CoV-2 test and the results of the RT-PCR test were negative for the virus. Biopsies of both lesions were performed for histological and microbiological studies and a new sputum sample was processed for fungus and mycobacterial culture.

The microbiological direct microscopic examination of the oral mucosa smear showed intracellular yeasts measuring 2–5 μm in diameter compatible with *H. capsulatum* on the Giemsa stain. Under direct microscopic examination the skin and sputum samples were negative for fungi and acid-fast bacilli. Coinciding with the previous findings, histopathology showed yeasts compatible with *H. capsulatum* in the oral mucosa. Urinary antigen detection was positive with a value of 2.1 ng/ml using the Histoplasma GM enzyme immunoassay kit (IMMY, Norman, Oklahoma).

The cultures for fungi on SDA at 28°C showed mold in both oral, skin and sputum samples, after 10 and 18 days, respectively. All isolates were identified by their microscopic characteristics and MALDI-TOF MS (matrix-assisted laser
desorption/ionization time-of-flight mass spectrometry) as *H. capsulatum*.

The serum sample, isolates, and Formalin-Fixed Paraffin-Embedded (FFPE) tissue slices of the oral mucosa and skin samples were sent to the National Reference Laboratory for Mycology of Argentina-INEI ‘Carlos G. Malbrán’ – ANLIS for additional tests. Anti-*H. capsulatum* antibodies were not detected in the serum sample using counterimmunoelectrophoresis and immunodiffusion methods.

In addition, FFPE tissue specimens were analyzed using both PCRs, a nested conventional PCR that amplified a fragment of the HP100 gene and a real-time quantitative PCR that amplified the ITS1 fragment\(^1\). The nested PCR amplified a 220 bp fragment specific for *H. capsulatum* while the quantitative PCR detected 2.2 \(\times 10^2\) fg DNA/\(\mu\)L in the oral mucosa sample. Neither of the two PCRs detected *Histoplasma* DNA in the skin samples.

The isolate was analyzed using phylogenetic multilocus sequence analysis according to Kasuga et al.\(^2\), and the fungus was identified as *H. capsulatum* clade LamB. Gene sequences of *H. capsulatum* strain (Culture collection DMic206235) were deposited in GenBank under accession numbers MW027017 (arf), MW027018 (ole), MW027019 (tub1) and MW002769 (H-anti).

After ten days in the hospital, the patient developed fever (38°C), night sweats, malaise and asthenia. Based on the recent diagnosis of disseminated histoplasmosis, treatment with intravenous liposomal amphotericin B (3 mg/kg/day) was initiated with daily renal function measurements, while maintaining the TB treatment. A new nasopharyngeal swab was collected for SARS-CoV-2 detection, which was not detectable by RT-PCR.

During his hospital stay, on June 16, due to a worsening of the symptoms, and chest CT findings (Fig. 2c), a new nasopharyngeal swab sample for SARS-CoV-2 detection was performed in the context of the COVID-19 pandemic, and viral RNA was detected. The patient’s immunosuppressive regimen was changed, everolimus was discontinued, mycophenolate mofetil was reduced and meprednisone was increased. The patient received convalescent plasma therapy (one unit, title 1:800 IgG), with good clinical evolution, afebrile, hemodynamically stable, eupneic, and without supplemental oxygen requirements.

Two weeks later, liposomal amphotericin B therapy was switched to oral therapy with itraconazole 200 mg t.i.d. for three days, and 200 mg b.i.d. for one year\(^4\).

On July 4, the patient was discharged with favorable evolution, and SARS-CoV-2 RNA was detected in a nasopharyngeal swab sample until July 24.

Figure 1 summarizes the timeline of symptom onset, chest CT, laboratory data, and treatment.

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**Figure 2** Evolution of chest computed tomography images. Multiple bilateral centrilobular opacities, with tree-in-bud pattern during first hospitalization. Slight increase of multiple bilateral centrilobular opacities during second hospitalization. Follow-up CT image obtained 10 days later of the third hospitalization shows multifocal peripheral abnormalities (circle) with ground glass pattern involve right lung.

**Figure 3** Mucocutaneous lesions. a. Right peri-tonsillar pillar injury (circle). b. Erythematous, indurated plaques on the left forearm.
Cases of COVID-19-associated histoplasmosis have already been reported in a patient living with HIV and advanced immunosuppression\(^5\). Here, we are describing a new case of disseminated histoplasmosis with mucocutaneous and lung involvement in a renal transplant patient who acquired SARS-CoV-2 infection probably during hospitalization for his treatment with amphotericin B.

Histoplasmosis is often mistaken for tuberculosis because this condition often shows similar chest CT images in patients with clinical epidemiological criteria. Furthermore, kidney transplant recipients seem to have greater predisposition to acquire tuberculosis\(^6\). In this case, the patient showed mucocutaneous lesions that led to the diagnosis of histoplasmosis. This mycosis has a low incidence rate in transplant recipients, and respiratory manifestations and cutaneous lesions are the most common\(^7\).

Finally, COVID-19 was suspected because, when the patient had already been diagnosed with histoplasmosis, on day 10 of the antifungal therapy, his respiratory symptoms had worsened. A new CT showed progression of abnormalities with unilateral and peripheral lesions in the right lung with a characteristic ground glass pattern compatible with coronavirus disease\(^8\).

Histoplasmosis has often resulted in allograft loss and overall mortality\(^9\). Moreover, COVID-19 co-infection may be severe, requiring intensive care admission of kidney transplant recipients due to long-term immunosuppression\(^10\). In the case reported here, the patient had a favorable outcome probably because histoplasmosis was rapidly diagnosed and treated. In addition, he was treated early, after the diagnosis of SARS-CoV-2, with convalescent plasma therapy in line with the management of COVID-19 in kidney transplant recipients published by some authors\(^11\).

The molecular analysis of four genes using MLST identified the isolate as belonging to the LamB clade, which did not surprise us since this clade is the predominant one in South America and the major clade circulating in Argentina\(^12\).

Twenty days after the last discharge, SARS-CoV-2 RNA was detected in a nasopharyngeal swab sample. This coincides with some authors who noted that in immunosuppressed renal transplant recipients SARS-CoV-2 viral shedding could be prolonged\(^13\).

The Centers for Disease Control and Prevention (CDC) listed patients requiring immunosuppressive therapy following organ transplantation, as being at high risk for severe SARS-CoV-disease. However, it is known that a low proportion of COVID-19 patients have post fungal co-infections\(^14\); in this case, histoplasmosis was prior to the viral infection, and subsequent hospitalizations and discharges could have been the factors influencing the acquisition of COVID-19 infection, in addition to the immunosuppressive status.

In the context of the COVID-19 pandemic it is important to pay attention to endemic mycoses such as histoplasmosis, since they exhibit respiratory symptoms that can be mistaken with viral or bacterial community-acquired pneumonia, and in pulmonary and disseminated histoplasmosis they can resemble other infections such as tuberculosis. To the best of our knowledge, this is the first report in the medical literature of COVID-19 associated with disseminated histoplasmosis in a renal transplant recipient. COVID-19 disease should be considered in patients with histoplasmosis, as well as other endemic mycoses and prolonged immunosuppression, particularly during the pandemic.

Conflict of interest

The authors declare that they have no conflicts of interest.

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