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LETTER TO THE EDITOR

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Insights in the approach of long-term liver transplant recipients with COVID-19

To the Editor,

Despite the great number of cases of COVID-19 around the world, data in liver transplant (LT) recipients are still settling down. We share our experience after the first four cases of long-term LT recipients admitted for hospitalization and the measures for suspicion and diagnostic investigation adopted after these cases. The mean time of initial symptoms at hospitalization was 8 days; only one case had the classical respiratory symptoms (Table 1). The most reported symptoms were diarrhea, fever, headache, and asthenia. This finding is in line with a series of 18 transplant recipients,[1] as well as a series[2] with kidney transplant recipients in which 22% of them referred diarrhea as a prominent symptom, compared to less than 10% in general population.[3] A recent series only with LT recipients reported 42% of gastrointestinal symptoms.[4] Maybe immunosuppression alters the clinical presentation and course of the disease, making them more susceptible to gastrointestinal symptoms. After these cases, we considered that we should be alert to search for the virus even in the absence of respiratory complaints. We changed our policy of outpatient screening for SARS-CoV-2 infection, and included diarrhea, besides respiratory symptoms, as a feature for proceeding with precaution measures and diagnostic investigation.

Other important finding was that 2 out of 4 cases were initially discharged and returned 48 hours later due to worsening symptoms, and one case presented desaturation even after 13 days of symptoms (case 2), which led us to adopt more careful criteria for follow-up, hospitalization, and discharge.

All patients had lymphopenia, which is common in COVID-19, related to severity and mortality, and this finding reinforces the recommendations of American Association for Study of Liver Diseases (AASLD) to withdrawal antimetabolite during hospitalization for COVID-19.[5] All patients had elevated C-RP and LDH at admission with a progressive drop in both of them and increase of lymphocyte count, coincidental with clinical improvement. The patient who required oxygen supplementation had one of the greatest levels of C-RP and D-dimer and drop in platelet count, with clinical improvement after increasing the dose of enoxaparin and switching prednisone to methylprednisolone. Disease severity has been linked to markers of coagulation disturbances, including thrombocytopenia and elevated D-dimer and fibrin degradation products, and autopsy findings show relation between thromboembolic phenomena and clinical outcomes.[6] The use of heparin in therapeutic doses tailored to clinical severity resulted in significant increase in PaO_2/FiO_2 ratio in a series of 27 cases, which allowed us to adopt this measure to deal with this patient.[7]

Despite the presence of risk factors for severe disease, all patients were discharged without ICU admission and only one patient required oxygen supplementation. Our series of cases demonstrates that long-term LT recipients may have an atypical initial clinical presentation and disease progression. It appears that immunosuppression has no protective effect and age and comorbidities could worsen the prognosis of disease, such as in general population. It is important to closely monitor these patients if one proposes an outpatient follow-up.

AUTHOR CONTRIBUTION

Débora Raquel Benedita Terrabuio, Luciana Haddad, and Liliana Ducatti designed the manuscript, reviewed the literature, and drafted the initial manuscript. Edson Abdala supervised the study, reviewed the literature, and reviewed and edited the manuscript. Larissa Gouveia, Vinicius Rocha-Santos, Renee Mignolo Tanaka Ferreira, George Felipe Darce, and Ana Julia Andrade Cardoso acquired data and wrote the table. Flair José Carrilho, Wellington Andraus, and Luiz Augusto Carneiro D´Albuquerque reviewed and edited the manuscript.

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TABLE 1 Clinical and laboratorial data of four long-term liver transplant recipients with COVID-19

	Case 1	Case 2	Case 3	Case 4
Age (y)/sex	42/female	59/female	62/female	43/male
Comorbidities	Ureterolithiasis; chronic rejection	Obesity (BMI 31.1 kg/m^2); diabetes	Obesity (BMI 36.2 kg/m); systemic arterial hypertension	Crohn's disease; PSC recurrence; nephrolithiasis
Years after liver transplantation	5	3	8	8
Symptoms	Abdominal pain; anosmia; diarrhea; and fever	Dry cough; nasal congestion; and fever	Headache; myalgia; chills; diarrhea; and fever	Headache; asthenia; diarrhea; and fever
Days of symptoms at admission	4	6	15	7
Immunosuppressive treatment at admission	FK 2 mg; MMF 1080 mg; Pd 5 mg	FK 3 mg; MMF 720 mg; Pd 5 mg	FK 4 mg; MMF 720 mg; Pd 10 mg	FK 1,5 mg; Aza 50 mg
Clinical data at admission[a]	RR = 28 bpm; HR = 150 bpm; RAOS = 96%; T = 38.4°C	1) RR = 20 bpm; HR = 94 bpm; RAOS = 96%; 2) RR = 28 bpm; HR = 100 bpm; RAOS = 94%	1) RR = 24 bpm; HR = 68 bpm; RAOS = 93% 2) RR = 23 bpm; HR = 98 bpm; RAOS = 86%	RR = 20 bpm; HR = 76 bpm; RAOS = 97%; T = 37.2°C BP = 87 × 57 mm Hg
Abnormal Laboratorial tests at admission and at discharge	Lymphocytes 0.39 0,49 at D5 2.0 at discharge Plt 138 95 at D5 279 at discharge C-RP 0.3 177 at D5 1.3 at discharge LDH 280	Lymphocytes 1.1 0.86 at D5 1.35 at discharge Creatinine 1.22 1.03 at D5 D-dimer 325 1,630 at D5 C-RP 130 124 at D5 190 at D7 LDH 283	Lymphocytes 0.44 2.63 at discharge Creatinine 1.88 (→1.32 at discharge D-dimer 710 C-RP 66.5 6.4 at discharge LDH 330	WBC 1.2 Lymphocytes 0.71 Plt 73 C-RP 36.3 Creatinine 2.16 1.25 at D2 D-dimer 16 531 656 at D2
Chest CT scan	Bilateral and multifocal ground-glass opacities—lung involvement < 50%	Admission—multiple ground-glass opacities—lung involvement 25%-50% D5—worsening—lung involvement 50%	Rare ground-glass opacities—lung involvement < 25%	Multiple ground-glass opacities—lung involvement < 50%
SARS-CoV-2 real-time PCR[b]	positive	positive	Admission—negative D3—positive	positive
Immunosuppression during hospitalization	Antimetabolite withdrawal; PD 10 → 5 mg; FK stable	Antimetabolite withdrawal; PD 5 → 10 mg; FK stable	Antimetabolite withdrawal; PD 10 → 5 mg; FK stable	Antimetabolite withdrawal; ↓ FK dosage due to renal function worsening during 3 d
Clinical treatment	Ceftriaxone (D2) Azithromycin (D2) Oseltamivir Piperacillin-tazobactam (D7) Prophylactic LMWH[d]	Ceftriaxone (D7) Azithromycin (D5) Oseltamivir Prophylactic LMWH D5 of hospitalization ↑LMWH to 1 mg/kg/d; HCQ for 5 d; MPD 1 mg/kg/d for 5 d	Ceftriaxone (D7) Azithromycin (D5) Oseltamivir Prophylactic LMWH	Ceftriaxone (D7) Azithromycin (D5) Oseltamivir Prophylactic LMWH

TABLE 1 (Continued)

	Case 1	Case 2	Case 3	Case 4
Outcomes[c]	No oxygen supplementation; discharge after 13 d of hospitalization	Clinical worsening at D5 non-invasive oxygen supplementation; discharge after 15 d of hospitalization	No oxygen supplementation; discharge after 6 d of hospitalization	No oxygen supplementation; discharge after 10 d of hospitalization

Abbreviations: Aza, azathioprine; BP, blood pressure; C-RP, C-reactive protein (<5 mg/L); d, day; D-dimer normal value < 500 ng/mL; FK, tacrolimus; HCQ, hydroxychloroquine sulfate; HCV, hepatitis C virus; HR, heart rate; LDH, lactate dehydrogenase (<214 U/l); LMWH, low molecular weight heparin (40 mg/d); MMF, sodium mycophenolate; MPD, methylprednisolone; NASH, non-alcoholic steatohepatitis; normal reference value of lymphocytes = 1.5-3.5 10^3/mm^3; Pd, prednisone; Plt, platelets (150-400 10^3/mm^3); PSC, primary sclerosing cholangitis; RAOS, room air oxygen saturation; RR, respiratory rate; T, temperature; WBC, white blood cells (4-11 10^3/mm^3).

[a]Cases 2 and 3 were discharged by the emergency room assistant team and readmitted 48 h latter due to worsening symptoms. None of the patients presented significant liver enzymes elevation or loss of graft function.

[b]All patients tested negative for influenza virus.

[c]None of the patients was admitted to intensive care unit.

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