Brazilian Journal of TRANSPLANTATION

https://doi.org/10.53855/bjt.v28i1.656_ENG

CASE REPORT

Liver Transplantation in a Patient with Fulminant Hepatic Failure Associated with Leptospirosis

Tércio Genzini[1], Mariana Kobata Caio[2], Fernando Kruglensky Lerner[2*], Thaís Franco Dias[2], Philipe Ho[2], Tiago Genzini de Miranda[1], Yasmin Ciamaricone Moukbel[1], Juliana Ferreira Ferranti[1], Juan Raphael Branez Pereira[1] Fernanda Ribeiro Danziere[1]

1.Hospital Leforte – Departamento de Transplantes – São Paulo (SP) – Brazil.

2.Faculdade de Ciências Médicas da Santa Casa São Paulo – São Paulo (SP) – Brazil.

*Corresponding author: feklerner@gmail.com

Seccion editor: Ilka de Fátima Santana F. Boin

Received: Dec. 22, 2024 | Approved: Feb. 21, 2025

ABSTRACT

Leptospirosis is a zoonosis that can progress to severe forms, such as Weil's syndrome, characterized by jaundice and liver failure. This report describes the case of a 13-year-old female patient who initially presented with epigastric pain, myalgia, fever, and jaundice, later progressing to fulminant hepatitis. Serology confirmed leptospirosis with positive IgM, and the patient underwent an emergency liver transplant due to severe hepatic failure, with complications including ascites, coagulopathy, and the need for dialysis. The liver explant revealed submassive necrosis and advanced fibrosis. The favorable postoperative outcome highlights the importance of early disease recognition and a multidisciplinary approach in critical cases. This report significantly contributes to the limited literature on liver transplantation associated with leptospirosis.

Descriptors: Case Report; Liver Transplant; Leptospirosis; Weil's Disease, Fulminant Hepatitis.

Transplante de Fígado em Paciente com Insuficiência Hepática Fulminante Associada à Leptospirose

RESUMO

A leptospirose é uma zoonose que pode evoluir para formas graves, como a síndrome de Weil, com icterícia e insuficiência hepática. Este relato descreve o caso de uma paciente de 13 anos com quadro inicial de epigastralgia, mialgia, febre e icterícia, evoluindo para hepatite fulminante. A sorologia confirmou leptospirose com IgM positivo e a paciente foi submetida ao transplante hepático emergencial devido à insuficiência hepática grave, com complicações como ascite, coagulopatia e necessidade de diálise. O explante hepático revelou necrose submaciça e fibrose avançada. A boa evolução pós-operatória reforça a necessidade de reconhecimento rápido da doença e intervenção multidisciplinar em casos críticos. Este relato contribui significativamente para a literatura limitada sobre transplantes hepáticos associados à leptospirose.

Descritores: Relato de Caso; Transplante de Fígado; Leptospirose; Doença de Weil, Hepatite Fulminante.

INTRODUCTION

Leptospirosis is a febrile zoonosis of abrupt onset caused by the bacterium *Leptospira* spp., transmitted by direct or indirect exposure to the urine of synanthropic domestic and wild animals, mainly rats, which are the reservoir of the disease. Humans are the definitive hosts of the bacteria and manifest the disease when *Leptospira* penetrates through intact or lesioned skin and is in prolonged contact with the source of contamination[1,2]. Weil's triad is a late symptom of the disease that indicates liver involvement. This condition suggests a worsening pathology and can progress to the progressive deterioration in the patient's condition.

A national geoprocessing study found 42,310 cases in Brazil between 2007 and 2017, demonstrating the importance of addressing this disease[3]. According to the study by Marteli[3], the annual prevalence of leptospirosis is 1.9 per 100,000 inhabitants in the country,

while the South and North regions have the highest prevalence. The disease demands attention because it is linked to social and economic issues and is endemic in distribution, concentrated in areas with poor conditions and flooding. Worldwide, this pathology affects more than 500,000 people[1], with a fatality rate of approximately 10%, which can reach 50% when pulmonary hemorrhage syndrome occurs[2].

Despite the high incidence of this disease and its wide distribution throughout the country and worldwide, there is still little literature on the relationship between leptospirosis and severe liver involvement, which can lead to transplantation since this condition is rare. Thus, this report aims to record and study the correlation between leptospirosis and liver failure by describing the case of a young patient who developed severe liver failure due to leptospirosis and underwent liver transplantation.

CASE REPORT

The 13-year-old patient was admitted to our service after being transferred from another institution with a suspected diagnosis of fulminant hepatitis and was already on dialysis. The patient had a history of epigastric pain, headache, and myalgia, accompanied by sporadic fever spikes for 7 days, without prior use of hepatotoxic medications, nor history of viral hepatitis or other etiologies. The father reported the presence of rats in the residence.

She had creatine phosphokinase (CPK) of 339 U/L at 6:47 am and 293.72 U/L at 4:35 pm on March 22, 2024. She progressed to jaundice with a total bilirubin of 37.9 mg/dL, prothrombin time of 42 seconds, and coagulopathy [international normalized ratio (INR) = 4.36] and was admitted to the intensive care unit (ICU) on April 4, 2024. She was medicated with piperacillin-tazobactam, metronidazole, meropenem, and teicoplanin, in addition to three doses of albendazole. She required a transfusion of packed red blood cells and plasma in addition to the administration of vitamin K to control coagulopathy. She progressed to ascites, need for paracentesis, mental confusion, and agitation. A computed tomography (CT) scan of the skull was performed, and no changes were observed. Given this situation, a liver transplant was indicated.

The recipient authorized the preparation and publication of this case report.

Serologies

After medication use, hemolytic anemia was ruled out by negative Coombs and less than three schistocytes/field in peripheral blood. The diagnosis of leptospirosis was confirmed with evidence of IgM antibodies for this disease and acute liver failure. Serum, urinary copper and ceruloplasmin tests were not performed to investigate Wilson's disease. Non-reactive for hepatitis B (April 3); anti-HBS + anti-AgHBS+; non-reactive for hepatitis C (April 3); IgG- and IgM-; non-reactive for syphilis (April 3). ANA and other autoantibody markers were not tested; April 14, PCR for CMV = 0. Research into metabolic disease was not performed.

The day after admission to our service, laboratory tests were conducted, revealing a platelet count of 50,000 cells/L, creatinine of 0.88 mg/dL, sodium of 152 mmol/dL, total bilirubin of 37.90 mg/dL (direct bilirubin of 27.23 mg/dL and indirect bilirubin of 10.67 mg/dL), prothrombin time (PT) of 42.00 s (INR = 4.36), and activated partial thromboplastin time (aPTT) of 54.30 s.

Therapeutic intervention

The patient underwent a liver transplant.

Donor data

Eleven years old, brain death due to subarachnoid hemorrhage (SAH) with ischemic stroke (IS). Blood typing O- IgG+ antibodies for toxoplasmosis and cytomegalovirus (CMV). On the day of liver collection: AST 67, ALT 45, alkaline phosphatase 119, gamma GT 15, total bilirubin 0.45 and direct bilirubin 0.2.

Recipient intraoperative data

The liver was multinodular and hardened, with areas of parenchymal collapse suggestive of severe acute hepatitis. The transplantation technique used was piggyback with good graft reperfusion. Immunosuppression was performed with tacrolimus and prednisolone. The patient had a good evolution 10 months after transplantation and standard liver function tests.

Anatomopathological

The liver explant weighed 1,144 g, measured 22.0 × 15.5 × 7.2 cm, and was diagnosed with submassive hepatic necrosis (fulminant hepatitis) associated with chronic liver disease (Fig. 1).

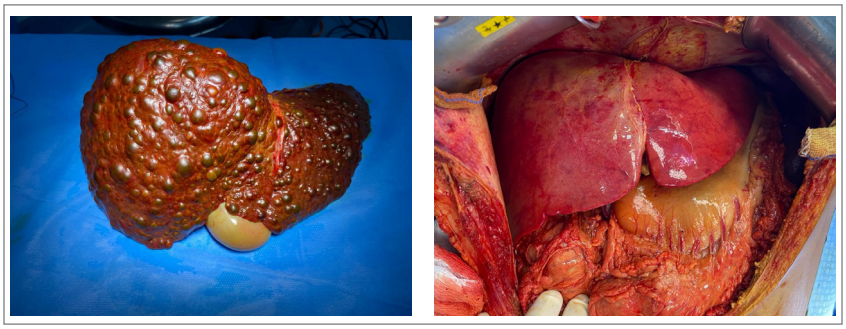

Figure 1. Explant on the left and graft after reperfusion on the right.

Source: Prepared by the authors.

Description

Advanced fibrotic phase. Associated necrotic bands (in organization) and intense ductular reaction (with bile casts). Marked bilirubinostasis and areas with moderate siderosis. Moderate inflammatory changes, mixed pattern, lymphomononuclear predominance areas, participation of frequent plasma cells (including clusters), and many neutrophils. In approximately 10% of cases, there is steatosis, multiple Mallory-Denk bodies (with irregular distribution), and hepatocellular ballooning: lobular necroinflammatory foci, oncocytic hepatocytes, apoptotic bodies, and hepatocyte anisonucleosis. Regenerative macronodules.

DISCUSSION

Leptospirosis has three clinical manifestation phases: early, late, and convalescent. The early phase is the most common form and initially presents with nonspecific and sudden-onset symptoms, such as fever, headache, and myalgia[4,5]. This stage of the disease tends to be self-limiting and regresses within 3 to 7 days, a period consistent with the beginning of the immunogenic phase, with the development of antibodies[4,5]. After 1 week of contamination, approximately 10 to 15% of patients progress to the late phase[5], with the classic manifestation of Weil's syndrome: jaundice, renal failure and hemorrhages, with pulmonary hemorrhage being the most common. Finally, in the convalescent phase, the patient may continue to have asthenia and anemia and eliminate leptospires in the urine. The jaundice gradually disappears, and the antibodies reduce[2].

The pathophysiology of hemorrhage in this syndrome is associated with the pathogen binding to cadherins, proteins present in the intercellular junctions of the vascular endothelium. This alters the permeability of the endothelium and results in the extravasation of blood in the vessels. In addition, leptospira is responsible for vessel wall inflammation, which damages the endothelial cells[6]. Clinical signs resulting from hemorrhage are skin with petechiae, ecchymoses, and bleeding at venipuncture sites, conjunctivae, and other mucous membranes or internal organs, including the central nervous system[2].

Regarding renal failure (which occurs in 16 to 40% of patients), bacteria stimulate the release of pro-inflammatory cytokines, such as interleukin (IL)-1 and IL-18, which leads to inflammation of the renal tubular cells. The acute increase in cytokines and chemokines in leptospirosis-infected individuals may progress to renal ischemia resulting from sepsis[6]. These cases may not respond to intravascular fluid replacement, requiring immediate initiation of dialysis[2].

In Weil's syndrome, jaundice is typically orange and reveals liver dysfunction[2]. Although the mechanism of this dysfunction is not yet fully understood, experimental studies have shown that leptospiral infection induces the separation of the intercellular junctions of hepatocytes, causing the passage of bile into the blood vessels[7].

The main hepatic changes in Weil syndrome are irregular necrosis with regenerative changes of hepatocytes, hyperplasia of Kupffer cells, infiltration of cells in portal areas, and cholestasis[8]. Biomarkers can observe a significant increase in serum bile and a moderate elevation of transaminases and alkaline phosphatase. The cytokine IL-8 may also increase in most patients with leptospirosis-induced hepatitis, and there is an association between this increase and the severe form of the disease.

Elevating *tumor necrosis* factor (TNF)-alpha is associated with a worse prognosis of the disease since low levels may be responsible for the non-development of Weil syndrome[9].

The patient was completely asymptomatic and had not been treated for liver disease before the clinical picture was compatible with leptospirosis, confirmed by serology. She was transferred to our service with a hypothesis of fulminant hepatitis and a diagnosis confirmed by IgM antibodies for leptospirosis. The young woman's symptoms included fulminant febrile illness with jaundice, myalgia, sporadic fever spikes, epigastric pain and headache. The patient's serum bilirubin, as described in Weil's syndrome, was elevated (47.47 mg/dL), as were the serum transaminases (Table 1). The cytokines IL-8 and TNF-alpha were not

evaluated in this case. The patient had chronic hepatitis, evidenced by the presence of fibrosis on histology, whose condition was aggravated by necrosis, cholestasis, and inflammatory infiltrates caused by leptospirosis. The severity of the liver failure required a liver transplant.

Table 1. Markers before and after surgery performed on April 7, 2024.

Day	AST	ALT	GGT	ALP
3/April	145	85	65	52
6/April	149	91	0	52
7/April	159	107	34	68
8/April	1,113	1,088	29	28
12/April	43	139	255	41
17/April	23	68	146	66
22/April	15	55	67	56
27/April	16	43	62	50
21/May	16	32	37	56

Source: Elaborated by the Author.

Liver transplantation in patients with leptospirosis presents significant challenges due to the severity of the infection and the potential for postoperative complications. An annotated review elucidates the pathogenesis of leptospirosis, highlighting the occurrence of acute liver failure secondary to leptospirosis, implying the need for close monitoring and careful management during pre-and post-transplantation[10]. Another article reviewed the literature on leptospirosis and its implications for the liver, emphasizing that although the disease is rarely the primary indication for transplantation, the combination of acute hepatitis and leptospirosis may justify surgical intervention in critical cases[9]. In this context, our article contributes to the literature by describing a case of leptospirosis that evolved into severe hepatitis and was treated with liver transplantation, highlighting the scarcity of reports on this association and the importance of multidisciplinary management to optimize results in affected patients.

CONCLUSION

This case report shows the progression of leptospirosis to severe liver failure, but further studies are needed to prove the correlation with clinical relevance. Liver transplantation was the only therapeutic alternative that successfully treated the case presented.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantial scientific and intellectual contributions to the study: Genzini T, Caio MK, Lerner FK, Dias TF, Ho P, Miranda TG, Moukbel YC, Ferranti JF, Pereira JRB, Danziere FR. **Conception and design:** Genzini T, Dias TF, Caio MK, Lerner FK, Ho P. **Data analysis and interpretation:** Dias TF, Caio MK, Lerner FK, Ho P. **Conceptualization:** Genzini T, Lerner FK, Dias TF, Caio MK. **Methodology:** Genzini T, Caio MK, Lerner FK, Dias TF. **Investigation:** Genzini T, Miranda TG, Moukbel YC, Ferranti JF, Pereira JRB, Danziere FR. **Data curation:** Genzini T, Miranda TG, Moukbel YC, Ferranti JF, Pereira JRB, Danziere FR. **Supervision:** Genzini T, Miranda TG. **Article writing:** Caio MK, Lerner FK, Dias TF, Ho P. **Critical review:** Lerner FK, Dias TF Caio MK. **Final approval:** Genzini T.

DATA AVAILABILITY STATEMENT

All data were generated or analyzed in this study.

FUNDING

Not applicable.

ACKNOWLEDGEMENT

Not applicable.

REFERENCES

1. Pan American Health Organization. Leptospirosis. [access on 2 Oct 2024] Disponível em: https://www.paho.org/en/topics/leptospirosis
2. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Leptospirose: diagnóstico e manejo clínico. [access on 2 Oct 2024]. Disponível em: https://bvsms.saude.gov.br/bvs/publicacoes/leptospirose-diagnostico-manejo-clinico2.pdf
3. Marteli NA. Análise espacial da leptospirose no Brasil. Saúde debate, 2020; 44(126). https://doi.org/10.1590/0103-1104202012616
4. Rajapakse S. Leptospirosis: clinical aspects. Clin Med (Lond), 2022; 22(1): 14-7. https://doi.org/10.7861/clinmed.2021-0784
5. Bharti AR, Nally JE, Ricaldi JN, Matthias MA, Diaz MM, Lovett MA. Leptospirosis: a zoonotic disease of global importance. Lancet Infect Dis, 2003; 3(12): 757-71. https://doi.org/10.1016/s1473-3099(03)00830-2
6. 6 Petakh P, Isevych V, Kamyshnyi A, Oksenych V. Weil's disease –Immunopathogenesis, multiple organ failure, and potential role of gut microbiota. Biomolecules, 2022; 12(12): 1830. https://doi.org/10.3390/biom12121830
7. Miyahara S, Saito M, Kanemaru T, Villanueva SYZM, Gloriani NG, Yoshida S. Destruction of the hepatocyte junction by intercellular invasion of Leptospira causes jaundice in a hamster model of Weil's disease. Int J Exp Pathol, 2014; 95(4): 271-81. https://doi.org/10.1111/iep.12085
8. Shintaku M, Itoh H, Tsutsumi Y. Weil's disease (leptospirosis) manifesting as fulminant hepatic failure: report of an autopsy case. Pathol Res Pract, 2014; 210(12): 1134-7. https://doi.org/10.1016/j.prp.2014.08.011
9. Lebreton T, Aubrun F, Mabrut JY, Heyer L, Perrin C. Liver transplantation for acute liver failure attributed to leptospirosis: a report of two cases. Case Rep Crit Care, 2019; 2019: 1-4. https://doi.org/10.1155/2019/5189542
10. Ramachandran R, Almedia D, Lindo J, Vellappan N. Pathology and pathogenesis of human leptospirosis: a commented review. Rev Inst Med Trop Sao Paulo. 2018; 60: e23. https://doi.org/10.1590/S1678-9946201860023