Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Liver damage associated with Covid-19: A direct causality is difficult to establish

Commentary

In this first issue of the Journal of Liver Transplantation, Pishgar et al. [1], from Iran, are publishing the case of a 42-year-old man that underwent liver transplantation for acute liver failure (ALF) attributed to SARS-CoV-2 infection. Indeed, this man without any pre-existing liver condition developed liver tests abnormalities two days after admission for acute respiratory symptoms due to COVID-19. Jaundice and a decrease of the INR rapidly occurred, without improvement over time, even though respiratory symptoms resolved. Common causes of ALF were excluded. A liver biopsy was performed showing severe inflammation and intra hepatic cholestasis. These features were however not specific of any aetiology. He finally received a liver transplantation because of end stage liver failure around two months after his first admission to the hospital. According to the authors, the final diagnosis was acute cholestatic liver failure due du Covid-19. This interesting case description must lead to several considerations.

Since the beginning of the Covid-19 pandemic one year ago, the involvement of several organs including the liver has been described [2]. There are however very few cases of ALF attributed to Covid-19. Haji Esmaeil Memar et al. [3] reported the case of an 11-year-old boy presenting with jaundice and abdominal pain, concomitantly with a positive nasopharyngeal SARS-CoV-2 PCR. He subsequently died due to fulminant hepatitis, without any aetiology retrieved except Covid-19. Melquist et al. [4] reported the case of a 35-year-old woman that developed fulminant hepatitis in the context of Covid-19. Fortunately, liver function improved and liver transplantation was not necessary. As this patient had a history of systemic lupus erythematous and a raise in the title of antinuclear antibodies, she was treated with steroids and hydroxychloroquine. The event of an autoimmune hepatitis could thus neither be confirmed nor excluded. Vujaklija Brajkovic et al. [5] described the case of a previously healthy 22 years old man who presented with ALF and cardiac failure. He showed signs of sepsis attributed to Covid-19 but respiratory symptoms were mild. Liver function improved in parallel with the recovery of a normal left ventricular function, suggesting the diagnosis of hypoxic ALF. Off notes, no other causes of cardiac failure except Covid-19 infection were found. Yohanatan et al. [6] described the case of an 18-year-old women who received a liver transplant for ALF. She was initially admitted for respiratory symptoms due to Covid-19. She rapidly developed multi organ failure and required vasopressors, mechanical ventilation and renal replacement therapy. Liver failure with hyperammonemia and encephalopathy persisted in spite of the improvement of respiratory and hemodynamic failures. She was thus listed and fortunately received a liver transplantation (LT). Wilson's disease was diagnosed only after transplantation as quantitative copper dosage on the explanted liver was elevated and genetic testing was positive. In the latter case, COVID 19 probably acts as an aggravating factor leading to liver decompensation. Last, the results of large cohort of 2073 hospitalized COVID 19 patients [7] showed that only 0,5% of patients developed Acute Liver Injury (ALI). The authors pointed that 8/10 patients with ALI were sedated under mechanical ventilation, making the diagnosis of hepatic encephalopathy and thus fulminant hepatitis very difficult. It is also likely that in this context of severe SARS-CoV-2 infection, a combination of factors, such as hypoxia, sepsis, shock, renal failure and drug-induced liver injury (DILI) may lead to liver damage and potentially liver failure, highlighting that a direct causality between SARS CoV2 and liver injury is difficult to establish [8]. In summary, ALF associated with COVID19 can either be related to the decompensation of a pre-existing liver disease [6], or to another cause of liver failure related to ARDS and sepsis such as heart failure [5]. DILI may also be an aggravating factor. More specifically, exposure to ketamine for prolonged sedation for mechanical ventilation should be examined. Indeed, cholestatic liver injury potentially leading to LT or death has been described in patients who had received high-cumulated doses of ketamine in several contexts including Covid-19 during the first wave of the pandemic [9]. Finally, a direct involvement of SARS-Cov2 in the pathophysiology of liver damage in these patients must be considered as viral replication in liver cells and especially cholangiocytes may occur [2,10].

To conclude, it is important to consider the specificity of ALF in the context of Covid-19. It remains a rare event that must be carefully investigated in order to diagnose an underlying liver disease and look for aggravating factors such as sepsis, heart failure or DILI. When possible, the treatment of such aggravating factors may prevent further deterioration of the liver function. Whether SARS-CoV-2 is a direct cause of liver failure in the case described by Pishgar et al. [1] remains uncertain. Nevertheless, in cases when liver failure is not associated with multiple organ failure, the indication of liver transplantation must be evaluated, as it is a lifesaving procedure.

References

[1] Pishgar E, Zamani F, Mansoorian M, Sahraei R, Rahimian N, Alibeik N. Successful liver transplant in a patient with acute cholestatic liver failure due to COVID-19 infection. A case report. J Liver Transp 2021.

[2] Marjot T, Webb G, Barritt T, Moon A, Stamataki Z, Wong V, Barnes E. COVID-19 and liver disease: mechanistic and clinical perspectives. Nat Rev Gastroenterol Hepatol 2021 May;18(5):348–64.

[3] Haji Esmaeil Memar E, Mamishi S, Sharifzadeh Ekbatani M, Alimadadi H, Yaghmaei B, VChegini V, et al. Fulminant hepatic failure: a rare and devastating manifestation of Coronavirus disease 2019 in an 11-year-old boy. Arch Pediatr 2020 Nov;27(8):502–5 Epub 2020 Sep 29. doi: 10.1016/j.arcped.2020.09.009.

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https://doi.org/10.1016/j.liver.2021.100011

[4] Melquist S, Estepp K, Aleksandrovich Y, Lee A, Beiseker A, Saei Hamedani F, et al. COVID-19 presenting as fulminant hepatic failure: a case report. Medicine (Baltimore) 2020 Oct 23;99(43):e22818.
[5] Vujaklija Brajković A, Zlopaša O, Gubarev Vrdoljak N, Goran T, Lovrić D, Radonić R. Acute liver and cardiac failure in multisystem inflammatory syndrome in adults after COVID-19. Clin Res Hepatol Gastroenterol 2021 Mar 11;45(3):101678. doi: 10.1016/j.clinre.2021.101678.
[6] Yohanathan L, Corsini Campioli C, Mousa OY, Watt K, Friedman DZP, Shah V, Ramkissoon R, Hines AS, Kamath PS, Razonable RR, Badley AD, DeMartino ES, Joyner MJ, Graham R, Vergidis P, Simonetto DA, Sanchez W, Taner T, Heimbach JK, Beam E, Leise MD. Liver transplantation for acute liver failure in a SARS-CoV-2PCR-positive patient. Am J Transplant 2021 Mar 31. doi: 10.1111/ajt.16582.
[7] Ding ZY, Li GX, Chen L, Shu C, Song J, Wang W, Wang YW, Chen Q, Jin GN, Liu TT, Liang JN, Zhu P, Zhu W, Li Y, Zhang BH, Feng H, Zhang WG, Yin ZY, Yu WK, Yang Y, Zhang HQ, Tang ZP, Wang H, Hu JB, Liu JH, Yin P, Chen XP, Zhang B, Tongji Multidisciplinary Team for Treating COVID-19 (TTTC). Association of liver abnormalities with in-hospital mortality in patients with COVID-19. J Hepatol 2020 Dec 19 S0168-8278(20)33885-X. doi: 10.1016/j.jhep.2020.12.012.
[8] Singh A, Premkumar M, Singh V. Liver Injury in COVID-19 - The culprit may not be COVID-19!. J Hepatol 2021 Mar 19 S0168-8278(21)00182-3. doi: 10.1016/j.jhep.2021.03.010.
[9] Keta-Cov research group. Electronic address: vincent.mallet@aphp.fr; Keta-Cov research group. Intravenous ketamine and progressive cholangiopathy in COVID-19 patient. J Hepatol 2021 May;74(5):1243–4. doi: 10.1016/j.jhep.2021.02.007.
[10] Nayagam J, Jeyaraj R, Mitchell T, Walder D, Al-Agil M, Shek A, Barker R, Teo J, Maharaj R, Agarwal K, Vlachos S, Joshi D, McPhail M. Patterns and prediction of liver injury with persistent cholestasis in survivors of severe SARS-CoV-2 infection. J Infect 2021 Apr 4. doi: 10.1016/j.jinf.2021.03.029.

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