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Acute liver failure following immune checkpoint inhibitors

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A B S T R A C T

We report the case of a 64-year-old man admitted to intensive care unit for liver failure secondary to immune-mediated hepatitis. This patient suffered from a progressing laryngeal squamous cell carcinoma. A treatment was started with immune checkpoint inhibitors combining anti PD-L1 plus novel anti-TIGIT or placebo (ATEZOLIZUMAB plus TIRAGOLUMAB or placebo), as part of a clinical trial. The patient then developed immune-mediated hepatitis, proven by liver biopsy. Despite 14 days of corticosteroids at 2 mg/kg the condition of the patient worsened, with the development of liver failure. The patient was admitted to intensive care unit, treated with plasma exchange, and made a complete recovery from this life-threatening condition. To our knowledge this is the case of a successful use of plasma exchange to treat ATEZOLIZUMAB +/- TIRAGOLUMAB induced liver toxicity.

Insights:

Plasma exchange could be a potential lifesaving treatment to severe immune-mediated hepatitis.

A 64-year-old man was admitted to the hepatology department for severe hepatic cytolysis. This patient was known for laryngeal squamous cell carcinoma, treated by surgery in 2009, with local recurrence in 2021. A new surgery (subtotal laryngectomy) was then performed. Unfortunately, in 2022, the patient presented lung and lymphatics node metastasis. It was decided to start a treatment with immune checkpoint inhibitors combining anti PD-L1 plus novel anti-TIGIT or placebo (ATEZOLIZUMAB plus TIRAGOLUMAB or placebo), as part of a clinical trial. The patient was admitted to the hospital for the 5th course of treatment and systematic blood tests found a previously unknown grade IV hepatic cytolysis (AST 948 UI/L, ALT 948 UI/L, PT 74%, total bilirubin 11 $\mu\text{mol/l}$). Hepatitis A, B, C, E and HIV serologies as well as autoimmune markers were negative. Oral corticosteroids at 2 mg/kg were started in the hypothesis of drug induced liver injury.

Despite 14 days of corticotherapy, liver function tests got worse (AST 1994 UI/L, ALT 3288 UI/L) and the patient developed acute liver failure (ALF) (total bilirubin 227 $\mu\text{mol/L}$, conjugated bilirubin 187 $\mu\text{mol/L}$, PT 28%, factor V 38%, lactate levels at 5.8 mmol/L, hepatic encephalopathy with flapping tremor). A computed tomography showed a non-dysmorphic liver and no vascular anomalies.

A transjugular liver biopsy found signs of acute hepatitis and a polymorphous inflammatory infiltrate with many mononucleous cells, compatible with immune-related hepatitis secondary to immune checkpoint inhibitors (Fig. 1). No underlying cirrhosis or steatosis was found.

Facing neurological state deterioration (Glasgow scale < 7), the patient was transferred to the intensive care unit. We chose to treat our patient with plasma exchange. In total, three sessions were performed every day exchanging 1.5 total plasma volume (TPV) using half 5% albumin and half donor plasma as replacement fluid.

We observed a global improvement with a regression of hepatitis, a normalization of PT and factor V. We observed disappearance of hepatic encephalopathy a few days after plasma exchange. After a rapid improvement, it took a few weeks of slow improvement for bilirubin levels to reach quasi normal range (Fig. 2). During this time, the patient was treated with oral corticosteroids at 1 mg/kg and intravenous mycophenolate mofetil (MMF) 1000 mg twice a day.

Immunotherapy with monoclonal antibodies targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA4) and the programmed death-1 receptor (PD-1) and its ligand (PD-L1) has become standard of care for an increasing number of indications. Combined treatments with new immunotherapies are being tested even now. There are 48 on-going trials on the ClinicalTrials.gov database on monoclonal antibodies targeting the novel immune checkpoint receptor TIGIT (anti-T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains). Therefore, many patients will be exposed to organ [1]. Acute hepatitis occurs in 5–10% of patients treated with immunotherapy and this incidence seems higher in patients treated with a combination of immune check-point inhibitors, with an incidence close to 25–30% of which ~15% are severe [1]. Anti-TIGIT antibodies have mainly been tested in combination and their safety profile seems acceptable although some studies report more frequent severe adverse events in case of treatments combination and on-going trials will provide additional data on the matter [2]. The first treatment of this adverse event is to stop the therapy. De Martin et al. reported 16 histologically proven cases of hepatitis after immune check-point inhibitors, 38% of hepatitis resolved after treatment cessation [3]. If no improvement is seen, corticosteroids at 1–2 mg/kg and second line immunosuppressive treatment such as MMF are required [1].

Unfortunately, immune-mediated hepatitis can lead to ALF, with a poor prognosis despite treatment with high dose corticotherapy and MMF [4]. In these cases, liver transplant is usually not an option, because of progressive metastatic cancer.

In a case report published by Riveiro-Barciela et al. [5], a patient was treated with immune checkpoint inhibitors (NIVOLUMAB) for a vulvar melanoma. She developed ALF after the 5th cure, with no response to corticotherapy and MMF. Plasma exchange (PE) were initiated when hepatic encephalopathy appeared with continuous clinical and biological improvement from there.

In immune-mediated hepatitis with liver failure, there seems to be some clinical and physiological arguments in favor of plasma exchange. First, plasma exchange is the treatment of choice for immune-mediated diseases, by removal antibodies and restoring a well-balanced immune regulation [6]. Second, a prospective multicenter study shows a potential improvement on survival in patients with ALF by attenuation of immune activation [7]. Third, plasma exchange could help by quickly removing ATEZOLIZUMAB and TIRAGOLUMAB which have a high molecular weight (144 356 Da and 149 000 Da, respectively) and a prolonged plasma half-life (27 days for ATEZOLIZUMAB).

To our knowledge, it is the first time that PE is used to treat toxic hepatitis secondary to these particular immune checkpoint inhibitors. Immune checkpoint inhibitors carry a lot of hopes for the treatment of a large number of pathologies and patients. Health practitioners involved in the management of these patients should be aware of these adverse events and of the potential therapeutic role of plasma exchange. In the context of liver failure, time is running out and sometimes we cannot afford to wait for the effects of corticotherapy and second line immunosuppressive treatment. Future studies are needed to assess efficacy and safety of plasma exchange in this indication.

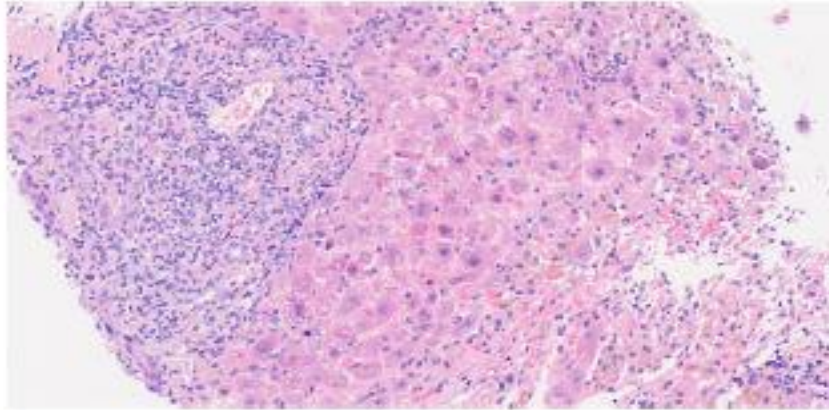


Fig. 1. Transjugular liver biopsy.
This image shows an acute hepatitis with panlobular necrosis and bridging necrosis, and a polymorphous inflammatory infiltrate with a majority of mononucleous cells.
Optical microscopy (x20).

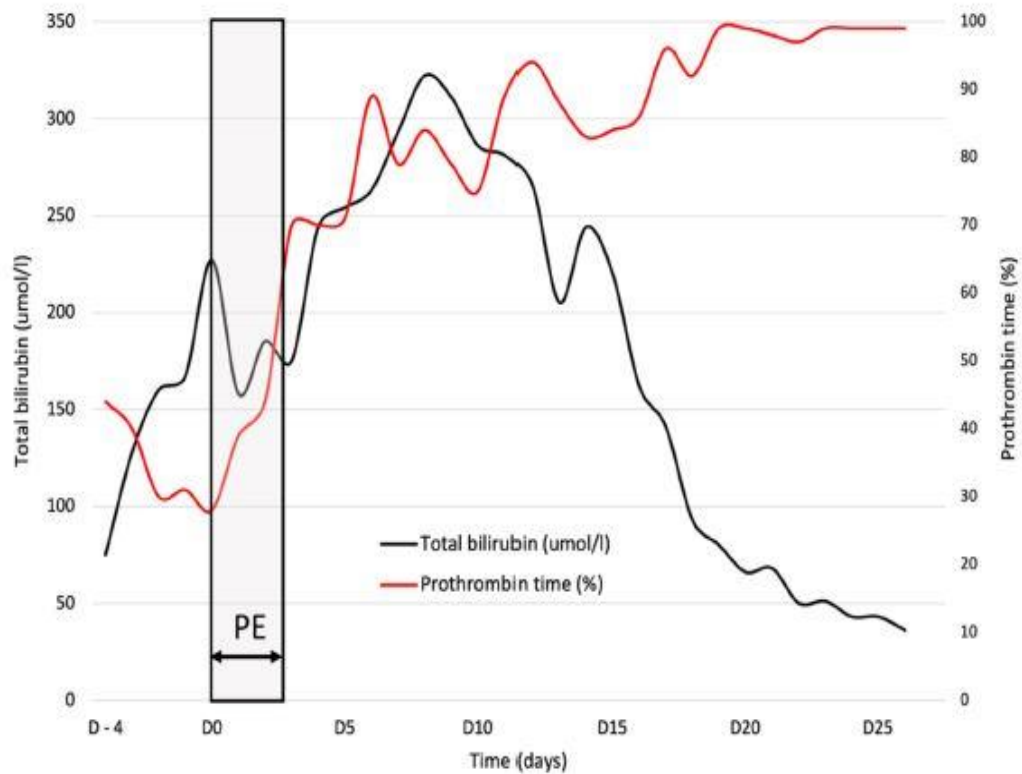


Fig. 2. Evolution of total bilirubin and prothrombin time from 4 days before plasma exchange to 25 days after.
D0 to D2: plasma exchange (PE).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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