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# Immunotherapy-Related Liver Toxicity in Neoadjuvant Therapy for Triple-Negative Breast Cancer: A Case Report and Literature Review

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**Abstract**

**Background**: The emergence of immune checkpoint inhibitors (ICI) in localized and advanced cancer has been a major development in the last decade. With this increased use, side effects, including immune checkpoint inhibitor-related hepatotoxicity (ICH) have emerged as a significant clinical complication.

**Case Presentation**: Herein, we report a case of 62-years Caucasian women with pembrolizumab-related hepatic toxicity in the setting of neoadjuvant chemotherapy for a triple-negative breast cancer. Through this case report, we will discuss optimal strategies for early recognition and management of checkpoint ICH and the particularity of the anatomopathological aspect characterized by the presence of eosinophils.

**Conclusion**: ICI-induced liver toxicity is a rare complication of cancer immunotherapy. This case report describes the different clinical, biological and pathological characteristics in order to incriminate an ICH and managing it effectively.

**Keywords**: Immune checkpoint inhibitors; Hepatitis; Drug-induced liver injury; Case report

## Background

Immune checkpoint inhibitors (ICI) improve clinical outcomes in patients suffering from different types of cancer including breast cancer. The KEYNOTE-522 trial was the first prospective phase III study to explore the efficacy of pembrolizumab in neoadjuvant chemotherapy in patients with early-stage triple negative breast cancer [1]. The addition of pembrolizumab to platinum-containing neoadjuvant chemotherapy resulted in a significant increase in the percentage of patients who had a pathological complete response (64% vs 51 %) also an event free survival at 18 months were 91.3% (95% CI, 88.8 to 93.3) in the pembrolizumab–chemotherapy group and 85.3% (95% CI, 80.3 to 89.1) in the placebo–chemotherapy group and elevated grade 3 or 4 alanine aminotransferase was observed in 5.2% of patients with pembrolizumab - chemotherapy group [1]. Liver toxicity is an immune-related adverse events associated with immunotherapy; although not common, its management still challenging, as it is heterogeneous in terms of presentation and severity. Unfortunately, the overactive immune response can lead to some immune-related adverse effects [2,3]. The skin, endocrine, respiratory, and the gastrointestinal organs are the most frequently affected. PD-1 and PD-L1 inhibitors are mostly associated with fatigue, rash, hypothyroidism, pneumonitis, and colitis [4,5]. Cutaneous adverse effects are described as a very common immune adverse event of anti-CTL-4 followed by colitis and hypophysitis. However, hepatitis is a rare side effect of all three classes of ICIs, as its occurrence often leads to the discontinuation of therapy and might require treatment. The prevalence of grade 3/4 hepatic toxicity related to immunotherapy range from 1.7% to 4.1% [6]. Herein, we present a case of grade 3 pembrolizumab-induced liver toxicity associated with an excellent treatment response. Through this case report we aim to provide a comprehensive review of ICI-induced liver toxicity and highlight several clinical issues that need to be addressed in the future.

## Case Presentation

A 62-years caucasian women, with a history of Hodgkin's disease at 21 years old and mediastinal radiotherapy and splenectomy with no alcohol and smoking history, consulted for a control visit regarding to her localized triple negative breast cancer. Mammography revealed a 19 mm nodule without visible lymph node involvement in the upper outer quadrant of the right breast (Figure 1).

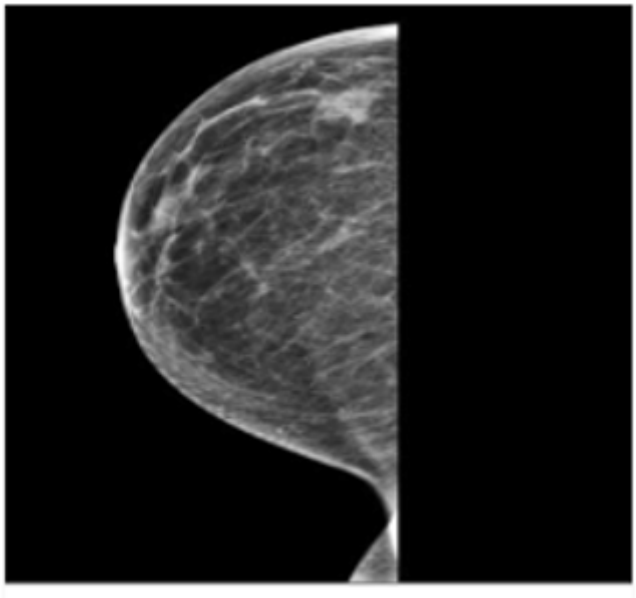

**Figure 1**: Right breast mammogram: showing a nodule in the upper outer quadrant of the right breast.

The biopsy showed in June 2022, a poorly differentiated infiltrating carcinoma, SBR grade 3, RH negative, HERB2 negative (0) and Ki-67 at 80%. Positron Emission Tomography confirmed intense hypermetabolism of the nodule in the upper outer quadrant of the right breast without any other suspicious regional or distant metabolic abnormality. Multidisciplinary team meetings validated the indication of neoadjuvant chemotherapy with pembrolizumab compliant with no indication for adjuvant radiotherapy because of the radiation history. After 3 cycles of the antineoplasic association in September 2022 (Paclitaxel and Carboplatin once weekly and Pembrolizulab once every 3 weeks), the patient experienced hepatocytolysis with liver function tests: (aspartate transaminase (AST): 105 UI/L, alanine transaminase (ALT): 166 UI/L, gamma-glutamyl transferase ( GGT ): 862 UI/L, alkaline phosphatase (ALP): 376 UI/L, total bilirubin (BT): 8 umol/l). Despite the various postponements (one month delay), and the initiation of corticosteroid therapy (1mg/kg) and ursodeoxycholic acid (UDCA) (15mg/kg/jr), hepatocytolysis was increased (AST: 480 UI/L, ALT: 771 UI/L, GGT: 1856 UI/L, ALP: 552 UI/L, a total bilirubin was always normal) with negative serologies (hepatitis B and C, Epstein Barr, Herpes simplex ½). The patient was asymptomatic, no immunosuppressive treatment was indicated. A hepatic echography was then performed and was perfectly normal. Liver biopsy

showed cholestatic and cytolytic chronic hepatitis lesions with moderate activity and mild peri sinusoidal and peri portal fibrosis, associated with an inflammatory infiltrate rich in eosinophils and histiocytes with lobular necrotic lesions, perisinusoidal fibrosis with thickening of the wall of the centrilobular vein (Figure 2). The clinical history and histopathological aspects were compatible with drug hepatotoxicity probably post immunotherapy because of the presence of eosinophils and histiocytes in the inflammatory infiltrate and the topography of the centrilobular lesions. Given the grade III liver toxicity which is more related to immunotherapy, and the impossibility to restart either immunotherapy or chemotherapy, and the good clinical response (non-palpable breast mass), the patient was referred for surgery (right total mastectomy associated with sentinel node). After surgery in November 2022, hepatocytolysis remained stable, until a re-increase in AST to 943 UI/L and ALT to 964 UI/L at the end of December 2022. New liver exploration showed positive Epstein Barr virus with an average viral load requiring no antiviral treatment after advice from infectious disease specialists since the patient is still asymptomatic. To date, the patient is under surveillance.

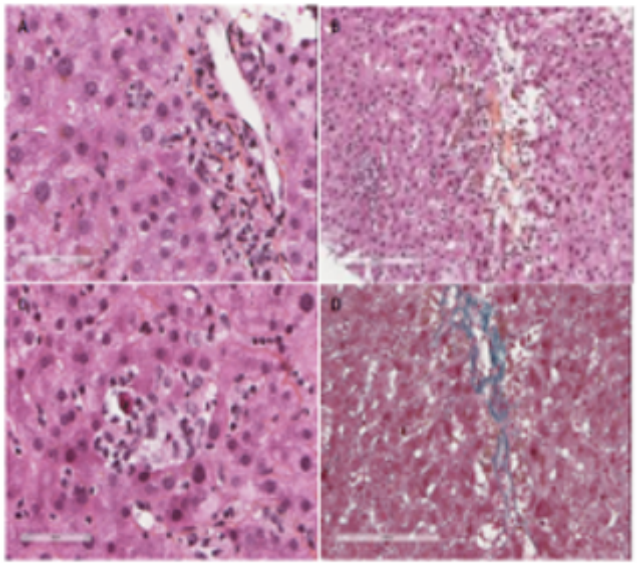

**Figure 2**: Pathological examination (A) HES x 400: a minimal inflammatory infiltrate in a portal space, rich in PNE (polynuclear eosinophils); (B) HES x 100: centrilobular vein with thickened wall and centrilobular hepatocyte necrosis with cholestasis; (C) (HESx100): parenchymal inflammatory infiltrate; (D) Masson's trichrome x 100: centrilobular vein with thickened wall and centrilobular hepatocyte necrosis.

## Discussion

ICI have become a part of cancer treatment, and demonstrated impressive survival results in several malignancies compared to chemotherapy by improving the host antitumor activity and blocking immune checkpoints, which in turn leads to a series of cellular-level steps which promote pro-inflammatory events (7). There are three main classes of ICI, anti-programmed cell death receptor-1 (PD-1) antibody, anti-programmed cell death ligand-1 (PDL-1) antibody, and anti-programmed cell death molecule-4 cytotoxic T-lymphocyte-associated (CTL-4) antibodies. All three classes block the inhibitory effects that immune checkpoints exert on the immune system and therefore allow for a less regulated and heightened immune response from a variety of immune cells. Unfortunately, due to an overactive immune response these molecules are known to induce immune-related adverse events [2,3]. Immunotherapy-induced hepatotoxicity can range from little elevation of liver aminotransferases to rarely, fulminant liver failure [8]. The reported incidence of immunotherapy-induced hepatitis varies considerably. Most clinical trials reported a low rate of ICH approximatively around 5.8% [9]. However, some retrospective studies reported higher rates of this adverse effect, up to 64% [10]. Moreover, the management of hepatotoxicity recommended by various societies differs among professional, and some studies have suggested clinical approaches that diverge from the guidelines (11–13). Liver toxicity associated with ICI is characterized by elevated liver parameter values, usually those of AST and ALT. Drug-induced liver toxicity is classified according to the pattern of elevation of liver enzymes based on the first set of laboratory tests in relation to the clinical event. This pattern is defined by the increase of ALT or ALP alone above a specific threshold or by the ratio of serum ALT to ALP levels (R value = [ALT/upper limit of normal (ULN)] / [ALP/ULN]) and can be categorized as hepatocellular (ALT ≥5-fold above ULN or R >5), mixed (R >2 to <5), or cholestatic (ALP ≥2-fold above ULN or R <2) [14,15]. In our case, liver toxicity was revealed by hepatic cytolysis and cholestasis. In the literature, it is mostly a simple cytolysis. Our patient remained asymptomatic, which is often described in the studies. The pattern of ICI-induced liver toxicity is heterogeneous; it may be cytolytic, mixed or cholestatic, although the incidence of cholestasis seems to be lower. Liver toxicity depends on the type of immunotherapy, the dose and baseline liver status. Overall, the incidence of liver toxicity is higher in patients who receive combination therapy than in those under monotherapy, but it remains lower compared to other organ toxicities. Patients with liver toxicity on ICI are usually asymptomatic and the symptoms, when present, are particularly non-specific; fever, skin rash and, in rare cases, jaundice can be observed [15,16]. No male or female preponderance has been described and age does not appear to constitute a risk factor for the development of liver toxicity. The interval elapsing between the initiation of therapy and the beginning of liver toxicity varies widely, and toxicity may even occur after treatment discontinuation. A study from the VigiBase, the World Health Organization database for individual

safety case reports, highlighted a significant earlier onset of hepatitis in patients having melanoma and non- small cell lung cancer treated with anti-CTLA-4 antibodies (34 [25-46.5] days) compared to those receiving anti-PD-1/PD-L1 antibodies (48 [27-118] days) (p = 0.04) [17]. Riveiro-Barciela et al. found that the interval between ICI initiation and liver toxicity was shorter in patients (who had cervical cancer and melanoma) treated with anti-CTLA-4 than in those receiving anti-PD-1/PD-L1 antibodies (having urothelial cancer and non-small cell lung cancer), although the difference was not statistically significant [16,18]. In this case, hepatic cytolysis started after 03 cycles of treatment. The time between the introduction of immunotherapy and the appearance of ICH was also in the majority of studies after 03 or 04 cycles of treatment. In most patients, the profile of liver injury is usually hepatocellular, but cases of cholestatic presentation have been described [14,15,17,19]. It should be pointed out that the immune-mediated hepatitis induced by ICI is an entity that is completely different from autoimmune hepatitis (AIH). This was shown in a recent study where patients with AIH were younger (median of 55 vs. 63 years, p = 0.02), presented more frequently with previous autoimmune disorders, and had cirrhosis, a lower platelet count, higher bilirubin levels and higher gamma globulin levels than patients with liver toxicity. Patients with a diagnosis of AIH were also more numerous in needing a second immunosuppressive drug and their liver test values took longer to normalize than those with ICH [16]. Moreover, liver histological features were also completely different between the 2 groups, as described in Table 1. Cases of acute liver failure with hepatic encephalopathy remain rare (20-22). Indeed, Vigilyze-VigiBase, reported an incidence of fulminant hepatitis at 0.4%. A liver biopsy can confirm a suspected diagnosis of immune-mediated hepatitis and may be used to evaluate the features and severity of liver tissue damage, as well as to rule out any underlying misdiagnosed chronic liver disease. There are few data on the histological appearance of the liver during the acute phase of hepatotoxicity, as most patients do not undergo liver biopsy. Results from case reports described a panlobular hepatitis with foci of confluent necrosis, periportal inflammation and prominent perivenous infiltrate with endothelialitis and, rarely, cholestatic lesion [23,24]. Inflammatory cells consist primarily of lymphocytes, with a predominance of CD8+ T lymphocytes, and less frequently CD4+ T-lymphocytes and B-lymphocytes. Interestingly, the presence of eosinophils and plasma cells are rare. Granulomatous hepatitis has also been reported [19].

| ICI-induced liver toxicity | | Autoimmune hepatitis |
|---|---|---|
| **Clinical symptoms** | Non specific<br>Possibly<br>Asymptomatic | Non Present |
| **Biology** | | |
| AST/ALT elevatio | Present | Present |
| GGT/ALP elevation | Present | Present at lowel level than the cytolysis |
| Bilirubin elevation | Rare | Possible |
| **Immunology** | | |
| Anti-nuclear antibodies | Possibly positive (about 50% of patients) | Positive |
| Anti-smooth muscles Antibodies | Possibly positive (non anti F-actin) | Positive, high titre anti F actin |
| Anti -LKM 1 antibodies | Negative | Positive |
| IgG | Usually normal | Elevated |
| **Histology** | | |
| Plasmocytes | Absent or rare | Frequent |
| Lobular inflammation | Present | Present |
| Portal tract inflammation | Present | Present |
| Confluent necrosis | Rare | Present |

**Table 1**: Comparison of characteristics between ICI-induced liver toxicity and autoimmune hepatitis.

According to the recommendations of the European Society of Medical Oncology (ESMO) and the Society for Immunotherapy of Cancer (SITC), liver toxicity should be treated by pausing immunotherapy and administering corticosteroids from grade 2 liver injury [25,26]. In this case report, the patient had grade 3 liver toxicity. The corticosteroid dose can rise in proportion to the grade of hepatitis up to a maximum of 2 mg/kg/day. Immunotherapy should be stopped temporarily in the case of grade 2 and 3, but permanently suspended in the event of grade 4 hepatitis. The time to resolution of non-hepatic immune-related adverse events (irAEs) in patients under corticosteroids is generally around 2 weeks [27]. The time to resolution of hepatic irAEs varies considerably; it can range from 3 to 104 days in different case reports and series [28, 29]. Corticosteroids at doses higher than 60 mg/day have no benefit when compared to 1 mg/kg/day or higher regarding the time to the resolution of hepatitis. Patients whose liver function tests continue to deteriorate despite adequate corticosteroid therapy are considered refractory to this treatment. In these cases, a second immunosuppressive drug can be added, the most commonly used is mycophenolate mofetil (MMF) [28,29]. Combination therapy with azathioprine for steroid-refractory patients has also been used successfully in the absence of improvement of the liver test after initiation of corticosteroid [29]. In a few clinical observations, the use of calcineurin inhibitors (cyclosporine and tacrolimus) has proven its effectiveness in patient's refractory to corticosteroids. The use of thymoglobulin combined with methylprednisolone and MMF for refractory hepatitis has been reported in a melanoma patient after 6 months with anti PD1 treatment in an adjuvant setting [29]. It is possible to re-introduce ICIs following immune-mediated hepatitis according to ESMO guidelines; their use is left at the physician's discretion for grade 3 hepatitis but banned in grade 4 hepatitis. Different cases of re-challenge have been reported in the literature, with hepatitis recurrence rates varying from 0 to 60% [12,15,16,19,30]. However, when we analyzed all the cases reported in the literature regarding a re-challenge with ICIs after liver toxicity, among 58 retreated patients, 11 (19%) experienced a recurrence of liver toxicity. When we looked solely at patients who had experienced initial toxicity of grade ≥3; the recurrence rate rises to 40%. Herein, our management corresponded to the guidelines; we did not use immunosuppressive treatment because the patient was asymptomatic.

## Conclusion

ICI-induced liver toxicity is a rare complication of immunotherapy, which presentation and severity are extremely heterogeneous. This case report describes the different clinical, biological and pathological characteristics in order to incriminate an ICH. Any clinician must suspect it early in their patients to manage it effectively. Further studies are needed to elucidate the pathophysiological mechanisms of liver toxicity, as well as to validate predictors of resolution and recurrence.

## Abbreviations

ICI :Immune checkpoint inhibitors; ICH : immune checkpoint inhibitor-related hepatotoxicity ; PD-L1: Programmed death-ligand 1; PD-1:Programmed death-1; MMF : Mycophenolate Mofetil; ESMO: European Society of Medical Oncology; STIC: Society for Immunotherapy of Cancer; irAEs:Immune-Related Adverse Events; CTLA4 : Cytotoxic T-lymphocyte associated protein 4; AIH:autoimmune hepatitis (AIH); ULN: upper limit of normal; UCDA: ursodeoxycholic acid; AST :aspartate transaminase; ALT : alanine transaminase; GGT : gamma-glutamyl transferase

ALP: alkaline phosphatase; BT: Total bilirubin

## Declarations

### Consent for publication

Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

### Availability of data and material

Not applicable

### Ethics approval and consent to participate

Not applicable

### Competing interest

The authors declare no competing interest

### Author's contributions

All authors have contributed to realize this case report and they have read and approved the final manuscript.

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