# Immune Checkpoint Inhibitor Therapy Induced Acute Immunologic Hepatitis: A Case Report

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## Abstract

Immune checkpoint inhibitors (ICIs) have resulted in a paradigm shift in recent cancer therapy and are becoming widely used in the treatment for advanced malignancies. ICIs harness the body's immune response to help combat malignancy; however, patients receiving ICIs are at an increased risk of immune–related adverse events. We present a 67–year–old female with metastatic melanoma on combination ipilimumab (anti–CTLA–4)/nivolumab (anti–PD–1) therapy who developed elevated liver enzymes and fever. Her liver biopsy showed panlobular hepatitis and centrilobular inflammation, confluent necrosis, histiocytic aggregates, and absence of fibrosis, features consistent with ICI–induced hepatitis. After discontinuation of the combination therapy and a course of prednisone and mycophenolate, the patient's liver enzymes improved. Patients undergoing combination therapy should be monitored by serial liver function tests to screen for ICI–induced liver injury. Furthermore, a liver biopsy is helpful in confirming the diagnosis of ICI–induced hepatitis.

## Introduction

Immune checkpoint inhibitors (ICIs) are becoming widely used for treating advanced malignancies, including but not limited to metastatic melanoma, metastatic renal cell carcinoma, microsatellite unstable colorectal carcinoma, and non–small–cell lung carcinoma.[1] ICIs improve survival of patients with metastatic disease and show a promising future for cancer treatment.

Two commonly used ICIs are nivolumab (Opdivo) and ipilimumab (Yervoy). ICIs are monoclonal antibodies targeting downregulators of the body's anti–cancer immune response, such as programmed cell death protein 1 (PD–1), its ligand programmed death ligand 1 (PD–L1), and cytotoxic T lymphocyte antigen 4 (CTLA–4), activating the patient's endogenous immune system. Nivolumab targets PD–1, found on T lymphocytes, and blocks its interaction with PD–L1 expressed on cancer cells.[1] Ipilimumab, on the other hand, targets CTLA–4 found on the surface of T lymphocytes and prevents deactivation of T lymphocytes.[2]

Given that ICIs inhibit negative immune regulation to help combat malignancy, patients are at an increased risk of immune–related adverse events. The gastrointestinal tract and liver are among the most commonly affected organs.[3] It is currently unclear why certain organ systems are preferentially affected over others; however, as more cases are reported, the pathophysiology of these adverse events may become better understood. In a safety review of 400 patients, when nivolumab and ipilimumab are combined, the risk for treatment–related grade 3-4 adverse events occurred in 55% of patients.[4] Furthermore, these effects can present earlier than when an anti–PD–1 or anti–PD–L1 antibody is used alone.

We present a case of severe drug–induced liver injury in a patient with metastatic melanoma treated with ipilimumab/nivolumab combination therapy. This is the first reported case at the Vancouver General Hospital. The purpose of this case is to illustrate the clinical and histopathologic presentation of liver injury in a patient on combination therapy and to briefly discuss its management.

## Case Presentation

A 67–year–old female with metastatic melanoma was treated with nivolumab and ipilimumab combination immunotherapy. After approximately three months of treatment, she developed a fever of 39 degrees Celsius. Although her symptoms resolved with low–dose acetaminophen, she developed elevated liver enzymes. The patient was admitted to the internal medicine unit for suspected immunotherapy–related hepatitis. The patient's serology for hepatitis A, B, and C, EBV, HIV, and CMV were negative. The patient's alpha–1 antitrypsin and ceruloplasmin were also negative. She was asymptomatic otherwise, and was discharged with a diagnosis of grade 3 immunotherapy–related hepatotoxicity. The patient was started on prednisone 80 mg daily, with subsequent improvement in her liver enzymes.

Four days following her discharge, the follow–up blood test revealed elevated liver enzymes—ALT of 990 U/L [< 50 U/L], AST of 305 U/L [< 38 U/L], and GGT of 96 U/L [< 55 U/L]—although her serum bilirubin remained within normal limits. Despite being asymptomatic, she was advised to present to the emergency department by her oncologist. She was admitted to the internal medicine unit once again to investigate the etiology of her elevated liver enzymes while being treated with high–dose prednisone. Her past medical history was pertinent for biopsy–confirmed melanoma with metastasis to the breast and suspected lung metastases, hypertension, dyslipidemia, and type 2 diabetes. On examination, she denied having abdominal pain, fevers, chills, significant weight loss, or other gastrointestinal symptoms. She denied alcohol intake and her review of systems was non–contributory. Her combination immunotherapy was discontinued on admission and she was subsequently started on mycophenolate mofetil (Cellcept) in addition to continued prednisone.

On imaging, an abdominal ultrasound revealed no structural cause for elevated liver enzymes. Ultrasound–guided random core needle biopsies from the right hepatic lobe were taken for pathology assessment. Histologic sections demonstrated a panlobular hepatitis that was most severe in the centrilobular region (Figure 1A). Foci of confluent necrosis were seen in the central perivenular area (Figure 1B). Small histiocytic aggregates (Kupffer cell microgranulomas) were also present (Figure 1C). The inflammatory infiltrate consisted of lymphocytes with scattered plasma cells, neutrophils, and eosinophils,

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some of which surrounded fat vacuoles (Figure 1D). A diagnosis of grade 4 ICI–induced hepatitis was established based on these histologic findings.

During the course of her admission, the patient's ALT, AST, and LDH (normally ranging from 60-100 U/L) increased to 1411, 373, and 350 U/L respectively. The patient was discharged in stable condition with a tapering course of prednisone and mycophenolate mofetil. Seventeen days after her discharge, her ALT and AST dropped to 472 and 114 U/L, respectively. Currently, she is asymptomatic with slowly improving liver biochemistry.

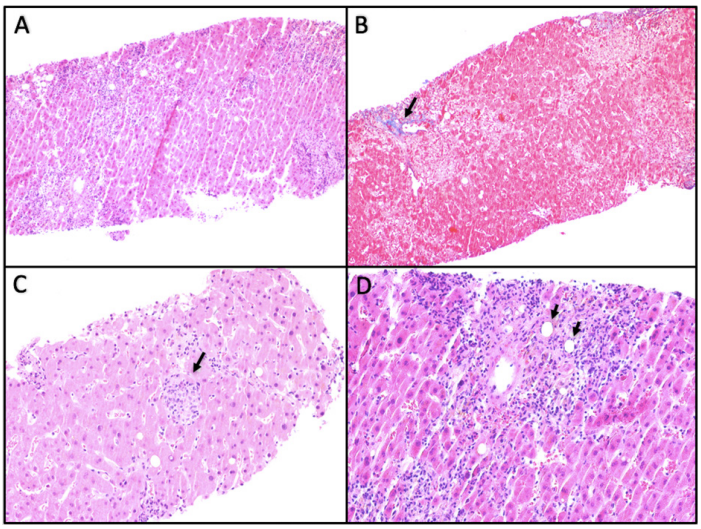


**Figure 1 | A**: Panlobular hepatitis with inflammation was most pronounced in the centrilobular region. The lymphocytic infiltration is more pronounced around central vein regions (hematoxylin–eosin, original magnification x100). **B**: Confluent necrosis is outlined by pale red areas, but no increased fibrosis was noted. Arrow indicates reticulin fibers highlighted in blue (trichrome, original magnification X100). **C**: Arrow indicates a Kupffer cell microgranuloma predominantly consisting of small histiocytic aggregates and some lymphocytes (hematoxylin–eosin, original magnification x200). **D**: The inflammatory infiltrate is composed of predominantly lymphocytes and histiocytes with scattered plasma cells, neutrophils, and eosinophils. Arrows indicate fat vacuoles with surrounding inflammatory cells (hematoxylin–eosin, original magnification x200).

## Discussion

We describe a case of combination ICI–induced hepatitis in a patient with metastatic melanoma. Combination ICI therapy has been shown to be superior to monotherapy in a double–blind, phase 3, randomized controlled trial.[5] In a pooled analysis safety profile of combination therapy versus monotherapy, severe hepatic adverse events, defined by elevated liver enzymes and total bilirubin, were more common in combination therapy.[4] To our knowledge, there are only a few studies reporting combination ICI–induced hepatitis.[4,5]

The clinical symptoms of combination ICI–induced hepatitis can vary. In a study that followed four patients who developed combination ICI–induced hepatitis, clinical symptoms ranged from fever to jaundice (Table 1).[6] In our case, the patient developed a fever after 11 weeks of combination therapy with no other clinical symptoms.

Currently, there is no consensus on the histological diagnostic criteria of ICI–induced hepatitis. The histological differential diagnosis of ICI–induced hepatitis includes autoimmune hepatitis, acute viral hepatitis, drug–induced liver injury, and acute alcoholic liver disease.[7] Furthermore, the definitive diagnosis of ICI–induced hepatitis requires a temporal relationship with ICI therapy.[7]

Although the histology of monotherapy ICI–induced liver injury is well documented, the histological findings of combination ICI–induced hepatitis have not been well described. De Martin *et al.* reported histological findings in four patients who developed combination ICI–induced liver injury (Table 1).[6] Recently, Everet *et al.* described fibrin ring granulomas in two patients treated with combination therapy.[3] Fibrin ring granulomas are characterized histologically by central lipid vacuoles surrounded by histiocytes and a fibrin ring with an outer histiocytic layer.[7] Fibrin ring granulomas are non–specific and can be found in granulomatous hepatitis caused by infectious agents (e.g., Q fever) or medications (e.g., allopurinol).[8] In our patient's liver biopsy, there were fat vacuoles with surrounding inflammatory cells. However, special stains (Martius Scarlet Blue and trichrome) failed to demonstrate any fibrin rings.

**Table 1 |** Comparison of clinical and histological findings adapted from De Martin *et al.*[6] and this case.

| Patient | Clinical Findings | Histological Findings |
|---|---|---|
| 1 | Fever 39.0°C | Granulomatous lobular hepatitis |
| 2 | Fever 39.3°C, rash | Granulomatous lobular hepatitis + fibrin deposits |
| 3 | None | Subacute hepatitis + focal confluent necrosis |
| 4 | Jaundice | Subacute hepatitis + periportal and lobular activity |
| This case | Fever 39°C | Panlobular hepatitis with confluent necrosis in centrilobular region and Kupffer cell microgranulomas |

In patients treated with combination therapy, hepatic adverse events (transaminitis and/or elevated total bilirubin) are a relatively common occurrence.[9] In a pooled safety review consisting of over 400 patients treated with nivolumab and ipilimumab combination therapy, 17% of patients presented with treatment–related hepatic adverse events. All grade 3-4 liver injury patients required corticosteroids or mycophenolate, and symptoms resolved in 97% of these patients.[9] Furthermore, this safety review revealed that the peak incidence of hepatic events occurred at three months. In our case, the patient's onset of hepatic events occurred approximately three months after initiation of combination therapy.

The recommended workup for suspected ICI–induced hepatitis includes a complete blood count, a comprehensive metabolic panel, liver function tests, and serology to exclude infectious (e.g., viral hepatitis, cytomegalovirus, etc.) and autoimmune causes (e.g., anti–nuclear antibody, anti–smooth muscle antibody, etc.).[10] The American FDA–approved product labels recommend that patients should be evaluated for serum AST, ALT, and bilirubin before each dose, as well as after treatment completion.[11]

The management of ICI–induced hepatitis has been discussed by the Society for Immunotherapy of Cancer. Clinicians are advised to permanently discontinue ICI treatment in patients with grade 3 and 4 hepatitis (AST, ALT > 5x upper limit of normal, and/or bilirubin > 3x upper limit of normal).[12] Prednisone at 1-2 mg/kg/day can be tapered over a course of four weeks, and mycophenolate mofetil can be considered if symptoms are refractory after three days. If not already done, a liver biopsy is recommended to establish a diagnosis in patients with asymptomatic grade 3 or 4 hepatitis.[12]

In conclusion, we report a patient presenting with combination

ICI-induced hepatitis. This case illustrates the fact that patients treated with combination therapy may present with severe liver injury despite being asymptomatic, which warrants considerations to discontinue ICI therapy. Furthermore, a liver biopsy may be an essential aid in the diagnosis of ICI-induced hepatitis. Although discontinuation of ICI with the addition of potent immunosuppression (e.g., prednisone and mycophenolate mofetil) can be detrimental from an oncologic perspective, this must be balanced by the very real risk of possibly fatal acute liver failure and the fact that patients with metastatic cancer are not feasible candidates for liver transplantation.

## Statement of Ethics

Informed consent was obtained from the patient.

## Disclosure Statement

All authors state no conflicts of interest.

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