# Painless Jaundice: A Rare Case of Nivolumab Induced Hepatitis

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## Introduction

- Nivolumab is an IgG4 monoclonal antibody that works as an immune check point inhibitor (ICI) at the programmed death ligand-1 (PD-1) receptor.
- It unmasks tumor cells from immune system evasion, activating the T-cell to attack the malignant cells.
- FDA approved as 1st line treatment for metastatic melanoma and 2nd line therapy for squamous cell lung cancer and renal cell carcinoma.
- ICIs have been associated with many immune related adverse events including pneumonitis, hepatitis, dermatitis, colitis, nephritis, and hypophysitis, among others

## Case Description

A 67 year old man with metastatic squamous cell lung cancer currently on nivolumab immunotherapy presents to his oncology clinic for routine follow up and was found to have painless jaundice and elevated LFTs consistent with grade 4 hepatotoxicity.

Cancer History:

- Presented 1 year prior to admission with small volume hemoptysis and unintentional weight loss. Imaging showed a primary left upper lobe tumor with bilateral pulmonary involvement. Squamous cell carcinoma was diagnosed by endobronchial ultrasound biopsy.
- Initiated on palliative chemotherapy with carboplatin and paclitaxel every 3 weeks for 4 treatments with initial good response.
- 6 months later admitted after a GLF in the setting of dizziness/vision changes and found to have multiple brain metastases. Received dexamethasone with 5 rounds of whole brain radiation.
- 3 months prior to admission he started immunotherapy with nivolumab every two weeks.

Social History:

- Vietnam veteran, possible AO exposure
- 40 pack year smoking history, quit 2013. Remote history of heavy drinking. Now drinks 1-3 alcoholic beverages daily

Initial Labs:

AST 2797 IU/L, ALT 2170 IU/L, ALP 873 IU/L,
T-bilirubin 11.7 mg/dL, INR 1.22, PLT 170

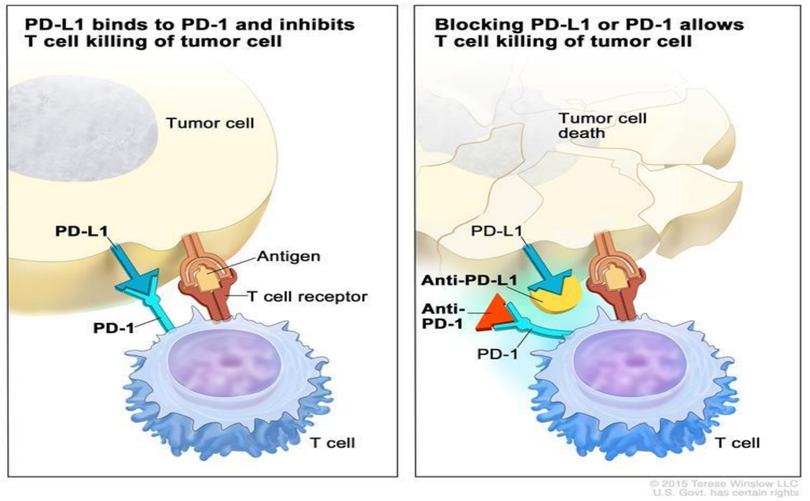
*Review of records showed elevated transaminases 3 days prior to presentation

Imaging: Abdominal CT and ultrasound showed chronic cholecystitis but no evidence of acute obstructive process.

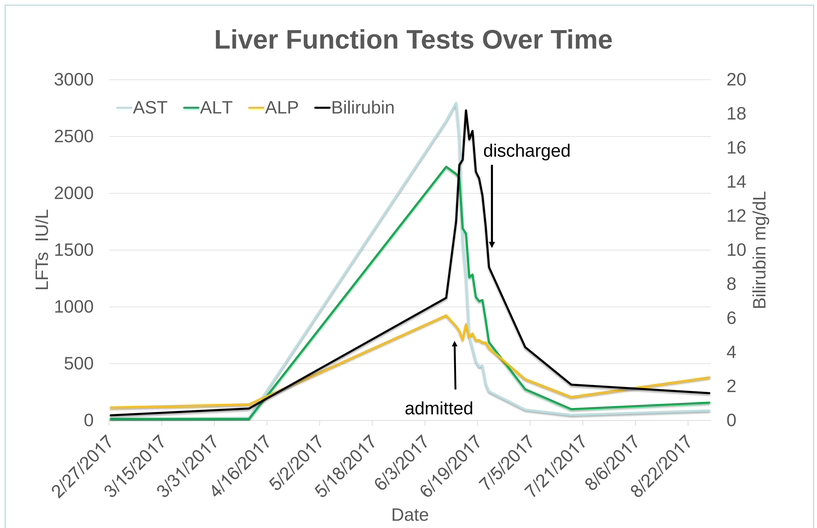
Exam: No acute distress. Jaundiced. RRR. Occasional crackles throughout. No abdominal tenderness, asterixis, or neurologic deficits.

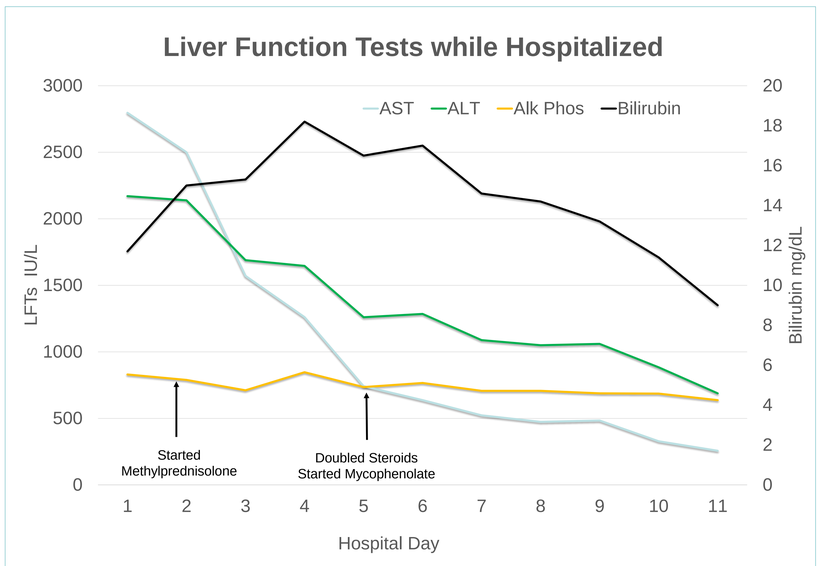
### National Cancer Institute Classification of Hepatotoxic Adverse Events

| Lab Test | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Alk Phos/ AST, ALT | ULN - 2.5xULN | 2.6 - 5.0 x ULN | 5.1 - 20 x ULN | >20 x ULN |
| Bilirubin | ULN - 1.5xULN | 1.6 - 3.0 x ULN | 3.1 - 10 x ULN | >10 x ULN |
| Level of severity | observation only, no intervention required | minimal or noninvasive intervention | severe but not immediately life threatening | urgent intervention required |




www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=772606




## Clinical Course

- Initially held steroids to rule out viral hepatitis
- The morning after admission started immunosuppressive therapy with methylprednisolone 0.8 mg/kg intravenous daily
- 5 days of stagnant liver function tests (LFTs) and up-trending bilirubin
- On hospital day 6, methylprednisolone was increased to 1.6 mg/kg and mycophenolate 1g twice daily was added.
- Liver biopsy was considered but decided against given good mentation and intact synthetic function.
- 3 days of slow improvement before LFTs dramatically improved
- Alternative etiologies for hepatitis, including toxic ingestion, infection, and portal vein thrombosis were ruled out.
- Smooth muscle antibody titer came back positive at 1:160, but other autoimmune markers were negative.
- Discharged on a 30 day oral immunosuppressive taper.
- LFTs 30 days after discharge returned as AST 49, ALT 99, alkaline phosphatase 207, and total bilirubin of 2.1
- 1 month after discharge a small rise in LFTs required restarting low dose steroids

## Discussion

- Grade 3-4 immune related toxicities occur in 15-25% of individuals taking immune checkpoint inhibitors and up to 50% when two are combined.[1]
- Ipilimumab, an ICI that acts at a different receptor, has caused hepatitis requiring treatment with mycophenolate[2] and antithymocyte globulin.[3]
- Approximately 1% of patients on nivolumab have grade 2-3 hepatitis reactions.[4]
- Nivolumab has previously induced grade 4 hepatitis responsive to high dose steroids[5] but no reports of ever requiring secondary immunosuppression as in our case.
- Other case reports have also described patients with recurrent LFT abnormalities after treatment with ICIs.
- Could our patient's positive smooth muscle antibody titer or alcohol use predisposed him to liver injury?
- More research is needed on long term effects of treatment with ICIs and if certain patients are more predisposed to adverse events.

## Teaching Points

- The frequency of adverse events with ICIs underscore the importance of close oncology follow-up and laboratory monitoring in these patients.
- Although patients with ICI induced hepatitis often present with impressive LFT abnormalities, they usually initially respond well to immunosuppressive therapy.
- Many of these patients have reoccurrences of their hepatitis after treatment even without restarting the offending agent.

References

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