Overlapping Hepatotoxicity and Colitis Associated With Immune Checkpoint Inhibitors

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Objectives

- We acknowledge the increased use of immunotherapy in the management of solid-organ and hematologic malignancies.
- We review standardized diagnostic criteria for gastrointestinal toxicities related to immune checkpoint inhibitors (ICIs).
- We highlight the potential for more than one GI toxicity to simultaneously affect a patient on ICI therapy.

Introduction

- Immunotherapy with ICIs has become the standard of care for many solid-organ and hematologic malignancies.
- Gastrointestinal toxicities are common side effects of ICIs that typically occur 6 weeks after starting ICI therapy [1].
- ICIs are among the most common classes of agents to cause idiosyncratic drug-induced liver injury in the Western world [2].
- Overlapping hepatotoxicity and colitis associated with ICIs is rare and may be overlooked, resulting in high morbidity and mortality.

Case Description

Presenting history:

- A 73-year-old man presented to his oncology clinic with complaints of intermittent, diffuse abdominal discomfort, bloating and painless non-bloody diarrhea triggered by meals.
- Symptom onset: 6 weeks after starting Pembrolizumab for metastatic squamous cell carcinoma of the head and neck.

Diagnostic Workup

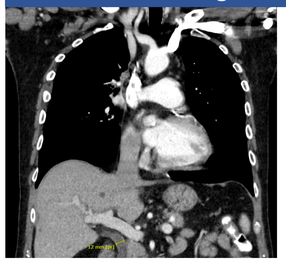

Figure 1.
CT chest/abdomen with contrast (coronal view) showing common bile duct dilation of 1.2cm (yellow calipers) status post cholecystectomy

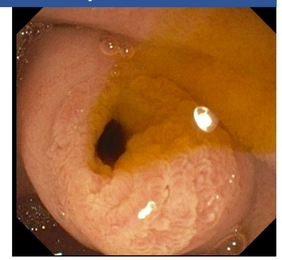

Figure 2.
Upper endoscopy showing prominent ampulla with free-flowing bile

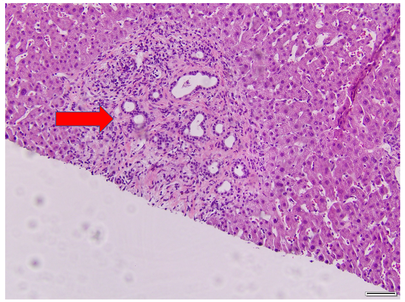

Figure 3. Histology of percutaneous, ultrasound-guided liver biopsy with H&E staining (10x) shows preserved lobular hepatic architecture with mixed inflammatory infiltrate including lymphocytes, histiocytes, and scattered eosinophils expanding the portal tracts.

Table 1. Immune Checkpoint Inhibitor Associated Hepatitis Grades [1]

Grade	Criteria
1	Asymptomatic (AST or ALT > ULN to 3.0 X ULN and/or total bilirubin > ULN to 1.5 X ULN)
2	Asymptomatic (AST or ALT > 3.0 to ≤ 5 X ULN and/or total bilirubin > 1.5 to ≤ 3 X ULN)
3	AST or ALT 5-20 X ULN and/or total bilirubin 3-10 X ULN, OR symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; and reactivation of chronic hepatitis
4	AST or ALT > 20 X ULN and/or total bilirubin > 10 X ULN OR decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, and coma)

Diagnostic Workup

- Liver enzymes were elevated with AST 132 U/L, ALT 220 U/L, ALP 851 U/L and normal TB, PT/INR
- Negative serologies for anti-smooth muscle antibody, CMV, EBV, HSV, viral hepatitis and unremarkable total IgG (699.5 mg/dL) with ANA titer 1:80.
- Diagnostic criteria for grade-2 ICI-associated hepatitis (ICIH) was met (Table 1) and Pembrolizumab was held.
- Conservative therapy was initiated with a proton pump inhibitor, antacids and antidiarrheal agents.
- CT chest/abdomen with contrast revealed dilated common bile duct (CBD) of 12mm and a new curvilinear filling defect in the distal CBD, without choledocholithiasis.
- MRCP revealed mildly dilated intrahepatic biliary ducts, CBD dilation (13mm), and an ovoid 8mm soft tissue nodule in the periampullary region.
- Upper endoscopy was nondiagnostic.
- Percutaneous liver biopsy showed interlobular bile duct injury with intraepithelial lymphocytes, neutrophils and a neutrophilic ductular reaction consistent with ICIH.
- Liver enzymes gradually improved, with AST 77 U/L, ALT 69 U/L and ALP 667 U/L at 60 days.
- Diarrhea resumed, up to 6 episodes per day, consistent with the Common Terminology Criteria for Adverse Events diagnosis of ICI-related colitis (ICIC).
- Initial supportive therapy failed to improve his diarrhea; thus, a prednisone taper was started, resolving the colitis.

Case Description

- He declined the option to resume immunotherapy with a different agent and transitioned to comfort care.

Discussion

- Clinical presentation of ICIH and ICIC are nonspecific, requiring thorough clinical evaluation, medical reconciliation, serial labs, appropriate abdominal/pelvic imaging when appropriate, and consideration of upper/lower endoscopies and liver biopsy.
- Patients who do not experience resolution of ICIC with corticosteroids should be considered for early biologic therapy [3].
- Concomitant ICIH with ICIC poses an additional challenge as infliximab is contraindicated in the setting of hepatitis [4].
- Patients who experience resolution of GI toxicities after withdrawing from a given ICI can be offered a different agent within the class of ICIs. This option was offered to the patient, but his wishes to pursue comfort care were respected.

Conclusions

- Overlapping ICIH and ICIC is rare and may have discordance between symptomatology and lab findings.
- Early recognition of overlapping ICIH and ICIC, supportive treatment, permanent cessation of the inciting ICI and switching it with alternative immunosuppressive therapy may improve patient outcomes and quality of life.

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References

1. Schneider BJ, Naidoo J, Santomasso BD, Lacchetti C, Adkins S, Anadkat M, Atkins MB, Brassil KJ, Caterino JM, Chau I, Davies MJ, Ernstoff MS, Fecher L, Ghosh M, Jaiyesimi I, Mammen JS, Naing A, Nastoupil LJ, Phillips T, Porter LD, Reichner CA, Seigel C, Song J-M, Spira A, Suarez-Almazor M, Swami U, Thompson JA, Vikas P, Wang Y, Weber JS, Funchain P, Bollin K. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update. JCO. 2021;39:4073-4126.
2. Chalasani NP, Maddur H, Russo MW, Wong RJ, Reddy KR. American College of Gastroenterology Clinical Guideline: Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury. The American Journal of Gastroenterology: May 2021 - Volume 116 - Issue 5 - p 878-898 doi: 10.14309/ajg.0000000000001259
3. Rampersad A, Abrams G, Bauer C. Immune Checkpoint Inhibitor Colitis in a Community-Based Hospital System. The American Journal of Gastroenterology: December 2021 - Volume 116 - Issue - p S17-S18 doi: 10.14309/01.ajg.0000798868.27587.86
4. American College of Rheumatology. Infliximab (Remicade). Available at: https://www.rheumatology.org/Learning-Center/Medication-Guides/Medication-Guide-Infliximab-Remicade. Accessed August 16, 2022.