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CASE REPORT

Overlapping Hepatotoxicity and Colitis Associated with Immune Checkpoint Inhibitors

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Abstract

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that are widely used for the management of many solid-organ and hematologic cancers. These agents work by inhibition of cytotoxic T-lymphocyte−associated antigen-4 (CTLA-4), programmed cell death-1 (PD-1), and PD ligand 1 (PD-L1). Hyperactivation of immune system results in ICI-associated adverse events. Simultaneous hepatotoxicity and colitis associated with ICIs is rare and potentially overlooked, as clinical symptoms are often nonspecific. A 73-year-old man with metastatic squamous cell carcinoma presented six weeks after starting pembrolizumab with abdominal discomfort and diarrhea. Pembrolizumab therapy was held, and supportive therapy with antidiarrheals provided partial relief. After initial workup, ICI-associated hepatitis (ICIH) and ICI-related colitis (ICIC) were diagnosed. Colitis resolution required corticosteroids. This case illustrates the importance of high index of clinical suspensions for gastrointestinal and hepatic adverse events associated with ICIs, which may be overlooked and result in severe complications. While isolated ICIH and ICIC are well known adverse events, overlapping ICIH and ICIC is rare. Prompt recognition, cessation of the inciting agent, and initiation of early supportive therapy are essential. Treatment may require corticosteroids or mycophenolate mofetil.

Keywords: Immunotherapy, Hepatitis, Colitis, Hepatotoxicity, Checkpoint inhibitors

1. Introduction

Immunotherapy with immune checkpoint inhibitors (ICIs) targeting cytotoxic T-lymphocyte−associated antigen-4 (CTLA-4), programmed cell death-1 (PD-1), and PD ligand 1 (PD-L1) have become the standard of care for many solid-organ and hematologic malignancies. ICIs are among the most common classes of agents to cause idiosyncratic drug-induced liver injury in the Western world, with reported incidence in 1−6% of patients.[1,2] Gastrointestinal toxicities are common side effects of ICIs that typically occur six weeks after starting ICI therapy.[3] Previous literature has described isolated gastrointestinal toxicities related to ICIs, with the incidence of colitis reported in the literature ranging from 8 to 27%.[3] Here we present a case of ICI-associated hepatitis (ICIH) and ICI-related colitis (ICIC) in a patient who was treated with corticosteroids.

2. Case description

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. His symptoms began six weeks after starting pembrolizumab (a PD-1 inhibitor) for metastatic squamous cell carcinoma of the head and neck. Initial lab work showed elevated

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Table 1. Initial laboratory tests.

Laboratory Test	Reference Range and units	Results
Liver function tests		
Alanine aminotransferase (ALT)	0–34 U/L	205 (H)
Aspartate aminotransferase (AST)	15–46 U/L	137 (H)
Alkaline phosphatase (ALP)	38–126 U/L	813 (H)
Total bilirubin	0.2–1.3 mg/dL	1.1 (N)
Total Protein	6.3–8.2 g/dL	6.1 (L)
Albumin	3.5–5.0 g/dL	3.5 (N)
Coagulation Studies		
Prothrombin time	9.0–12.0	11.4 (N)
International normalized ration	0.9–1.1	1.1 (N)
Viral serologies		
Hepatitis A, IgM	Non-reactive	Non-reactive
Hepatitis B, core IgM	Non-reactive	Non-reactive
Hepatitis B, surface antigen	Non-reactive	Non-reactive
Hepatitis C antibody	Non-reactive	Non-reactive
Hepatitis E Antibody	Non-reactive	Non-reactive
Herpes simplex virus 1 & 2, IgM	≤0.89	0.87 (N)
Cytomegalovirus, IgM	≤29.9	<8.0 (N)
Cytomegalovirus, IgG	≤0.59	<0.20 (N)
Epstein Barr virus, IgM	Not detected	Not detected
Autoimmune liver disease panel		
Antinuclear antibody (ANA) titer	<1:80	1:80
Anti-smooth muscle antibody (ASMA)	0–19 Units	6 (N)
Immunoglobulin G (IgG)	700.0–1600.0 mg/dL	699.5 (L)

(N): Data is within limits of normal.
(L): Data is abnormally low.
(H): Data is abnormally high.

liver enzymes including aspartate transaminase (AST) 132 U/L, alanine transaminase (ALT) 220 U/L, alkaline phosphatase (ALP) 851 U/L; normal total bilirubin, antinuclear antibodies (ANA) titer 1:80, normal anti-smooth muscle antibody (ASMA), normal total immunoglobulin-G (IgG) 699.5 mg/dL, and normal international normalized ratio (INR). Serologies for Cytomegalovirus (CMV), Epstein Barr virus (EBV), herpes simplex virus (HSV), and viral hepatitis were negative (Table 1). Diagnostic criteria for grade-2 ICIH were met (Table 2A) and pembrolizumab was held. Conservative therapy was initiated with oral anti-diarrheal agents. Computed topography (CT) imaging of the chest and abdomen with contrast was obtained due to persistent abdominal discomfort, despite conservative management. CT revealed a dilated common bile duct (CBD) of 12 mm and a new curvilinear filling defect

Table 2. American society of clinical oncology diagnostic criteria for immune-related adverse events.

Table 2A: Criteria for Grading of Immune Checkpoint Inhibitor Associated Hepatitis [3]

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)

Table 2B: Criteria for Grading of Immune Checkpoint Inhibitors Associated Colitis [3]Table 2B: Criteria for Grading of Immune Checkpoint Inhibitors Associated Colitis [3]

Grade	Criteria
1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline
2	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared with baseline
3	Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared with baseline; and limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated

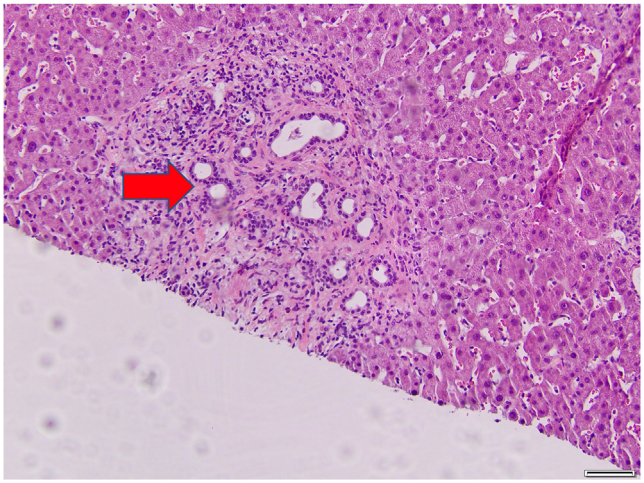

Fig. 1. Histology of percutaneous, ultrasound-guided liver biopsy with H&E staining (10x) shows preserved lobular hepatic architecture with mixed inflammatory infiltrate including lymphocytes, histiocytes, and scattered eosinophils expanding the portal tracts (red arrow).

in the distal CBD, without choledocholithiasis. Magnetic resonance cholangiopancreatography (MRCP) revealed mildly dilated intrahepatic biliary ducts, CBD dilation (13 mm), and an ovoid 8 mm soft tissue nodule in the periampullary duodenum. Upper endoscopy was nondiagnostic, and free-flowing bile was observed from the ampulla. Percutaneous liver biopsy showed interlobular bile duct injury with intraepithelial lymphocytes and neutrophils and a neutrophilic ductular reaction consistent with ICIH (Fig. 1). Serial lab work demonstrated improvement of liver enzymes, with AST 77 U/L, ALT 69 U/L and ALP 667 U/L at 57 days after initial labs. He had persistent watery diarrhea, up to seven episodes per day. Abdominopelvic CT demonstrated nonspecific wall thickening of the descending colon, sigmoid colon, and rectum. After ruling out other causes of diarrhea, the clinical diagnosis of grade-2 ICIC was made (Table 2B). Initial supportive therapy failed to improve his diarrhea. Subsequent endoscopic procedures including colonoscopy were offered but differed by the patient. A prednisone taper was started, which led to resolution of his colitis. Following improvement of his symptoms and discussions with his gastroenterologist and oncologist, he was given the option to resume immunotherapy with a different agent. However, he chose to defer further immunotherapy and transitioned to comfort care.

3. Discussion

Close coordination of care between subspecialty services (i.e., the oncologist providing ICI therapy, the gastroenterologist, and the primary care provider) is critical when addressing gastrointestinal toxicities related to ICIs. Many of the symptoms of ICIH and ICIC are nonspecific, requiring a thorough evaluation for the purposes of ruling out other causes of hepatitis and colitis.[4] The process begins with conducting a detailed medication review to identify any agents with potential side effects of hepatotoxicity and diarrhea.[5] It is important to rule out autoimmune etiologies by obtaining antinuclear antibodies, total IgG, anti-smooth muscle antibody. Testing for CMV, EBV, HSV (preferably by polymerase chain reaction) in addition to an acute viral hepatitis panel is recommended.[1] A coagulation panel should be obtained promptly as an INR value of >1.5 is indicative of impending liver failure and should prompt consideration of escalating care to a transplant unit.[5] Clinical history and physical exam findings can help guide the decision to obtain additional studies (such as iron studies, ceruloplasmin, and alpha-1-antitrypsin) and abdominal/pelvic radiological imaging when appropriate. Liver biopsy can be considered for the evaluation of ICIH of grade 2 or higher to rule out alternative etiologies, but does carry procedural risks.[2] Abdominal CT imaging can be used to examine the extent of colonic inflammation (often appearing as wall thickening or mucosal hyperenhancement) and to exclude complications related to ICIC, such as perforation, obstruction, or abscess.[6] Colonoscopy evaluation assists in establishing the diagnosis of ICIC and grading of disease severity.[3,6]

The American Society of Clinical Oncology provides guidelines discussing the diagnosis and management of ICIH and ICIC, each separately. While the diagnosis of ICIH is based on a combination of clinical features and liver chemistry values (specifically, AST, ALT, bilirubin), the diagnosis of ICIC is based on clinical symptoms alone, defined by the Common Terminology Criteria of Adverse Events related to ICI therapy.[3] The mainstay of ICIH and ICIC management involves prompt cessation of the ICI and monitoring clinical symptoms.[2,3] For ICIH, obtaining serial liver chemistry panels is recommended.[5] Recurrence of ICIH is atypical following ICI cessation.[5] Although it was not performed in the management of the present case, obtaining fecal calprotectin to monitor for resolution of ICIC is recommended. Additionally, for ICIC of grade 2 or higher, colonoscopy is highly recommended, and initiation of corticosteroids at 1–2 mg/kg is considered first-line therapy.[3] Patients with evidence of colitis on endoscopy and/or those who do not experience resolution of ICIC with corticosteroids should be considered for early biologic

therapy (infliximab or vedolizumab).[6,7] Concomitant ICIH and ICIC poses additional challenges as infliximab is contraindicated in the setting of hepatitis.[8,9] The immunomodulator, mycophenolate mofetil, can be considered for concomitant ICIH with ICIC that is refractory to corticosteroids.[3,10] However, its use may be limited due to the associated risks of gastrointestinal discomfort, cytopenias, nephrotoxicity, neurotoxicity, and metabolic derangements. Patients who experience resolution of gastrointestinal toxicities after withdrawing from a given ICI can be offered a different agent within the class of ICIs.[3,4]

4. Conclusion

Overlapping ICIH and ICIC is rare and may have discordance between symptomatology and lab findings. Early recognition of overlapping ICIH and ICIC, prompt cessation of the inciting agent, and initiation of supportive care are imperative to prevent severe complications, including liver failure and cirrhosis. Management of simultaneous ICIH and ICIC may be challenging, especially if symptoms are refractory to early treatment with steroids, where mycophenolate therapy can be beneficial. Ultimately, close communication between the patient, primary care provider, oncologist, and gastroenterologist is essential to formulating a shared decision regarding definitive management.

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Conflict of interest

There were no competing interests regarding publication of this manuscript.

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