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Case Report

Multiple Immunosuppressants for Immune-related Acholia in a Patient with Metastatic Colorectal Cancer

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Abstract

Immunotherapy-related adverse events (irAEs) such as hepatitis or cholestasis have been well recognized. In contrast, acholia was not previously reported as an irAE with a lack of standard treatment. We presented a case of a 68-year-old man with metastatic colon cancer that progressed after several chemotherapy sessions with targeted agents. He received nivolumab plus regorafenib (REGONIVO) as salvage treatment. However, he reported clay-colored stools and jaundice after 3 months of REGONIVO treatment. Computed tomography (CT) revealed no significant biliary tract dilation. Laboratory tests ruled out viral hepatitis or autoimmune hepatitis. Endoscopic retrograde cholangiopancreatography showed multiple filling defects of blood clot formation, and endoscopic retrograde biliary drainage was ineffective. An irAE presenting as acholia and hyperbilirubinemia was diagnosed. Subsequently, the patient was initially administered a corticosteroid only, with an equivalent dose of prednisone (1 mg/kg/day); however, this treatment had only limited effect. After the addition of multiple immunosuppressants, including mycophenolate mofetil and tacrolimus, the severity of hyperbilirubinemia declined and acholia was resolved. This case demonstrated that irAEs can present as acholia and hyperbilirubinemia without significant biliary obstruction. Although the mechanism of such an unusual irAE remains unclear, it seems to be refractory to corticosteroid treatment alone. A more aggressive strategy, such as multiple immunosuppressants, may be advisable.

Keywords: Acholia, immune-related adverse event, multiple immunosuppressants, mycophenolate mofetil, tacrolimus

Introduction

Immune checkpoint inhibitors targeting programmed death-1 (PD-1) and PD-1 ligand have improved the overall survival of patients with multiple cancers and have been

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established as one of the standard treatments for such cancers.[1-3] However, these agents could lead to immune-related adverse events (irAEs), such as hepatic irAEs. The incidence of hepatic irAEs varies from <5% to 17%, depending on the cancer type and immunotherapy combination.[3-5] The exact mechanisms of hepatic irAEs are unclear. Several reported hepatic irAE pathophysiologies included: hepatitis with lobular inflammation, periportal inflammation, and ductal injury.[6] The predominant clinical manifestation is transaminitis. Hepatic irAEs presenting as cholestasis have rarely been reported, and to the best of our knowledge, irAEs presenting as acholia have not yet been reported. Herein, we report a unique case of an irAE presenting as acholia and hyperbilirubinemia that successfully resolved after treatment with multiple immunosuppressants. We present the following case in accordance with the CARE reporting checklist.

Case Report

A 68-year-old man was diagnosed as having sigmoid colon cancer with peritoneal, liver, and lung metastases at National Taiwan University Hospital (NTUH) in August 2018. Immunohistochemical staining revealed proficient mismatch repair enzymes and KRAS G12D mutation. The patient denied past medical history or relevant family history. This patient had been treated with targeted therapies with bevacizumab and ramucirumab and chemotherapies with 5-fluorouracil plus leucovorin, irinotecan, oxaliplatin, and trifluridine/tipiracil (TAS-102). Computed tomography (CT) performed in August 2020 revealed progressive disease, especially diffuse peritoneal metastases and malignant ascites. The patient received regorafenib plus nivolumab (REGONIVO) regimen as salvage treatment.[7]

The patient exhibited disease stability for the next 3 months. However, after four sessions of nivolumab, he began passing clay-colored stools and developed jaundice soon after. His vital signs were within the normal ranges. Physical examination revealed icteric sclera and jaundice from his face to the lower trunk. Serum biochemistry revealed an abrupt hyperbilirubinemia (from baseline 0.6 to 6.0 mg/dL, normal range <1.0 mg/dL) along with elevated aminotransferase levels (aspartate transaminase [AST]: 86 U/L, normal range: 8–31 U/L; alanine aminotransferase [ALT]: 97 U/L, normal range: 0–41 U/L). Complete blood count, renal function, and electrolytes were all within normal ranges. Emergent CT on November 25, 2020, revealed progressive liver metastases with mild dilation of the left intrahepatic duct (IHD). The first impression was progressive disease complicated with hyperbilirubinemia. The patient received the 5th nivolumab treatment on November 26, 2020, as treatment beyond progression. We closely follow up his clinical condition and laboratory tests after this treatment [Figure 1].

However, progressive jaundice was noted on December 1, 2020, and we arranged admission for further investigations (day 1 = December 2, 2020). Abdominal sonography revealed multiple metastatic hepatic lesions and stationary minimal dilation of the left IHD. Follow-up serum biochemistry showed progressive hyperbilirubinemia (9.8 mg/dL), transaminitis (AST: 121 U/L, ALT: 150 U/L), and coagulopathy (INR: 1.29, normal range: 0.92–1.09). A complete blood count revealed mild anemia (Hb: 12.4 g/dL, normal range >13.1 g/dL) and leukocytosis (white blood cell: 13.2 K/μL, normal range: 3.3–9.6 K/μL). Changes in the patient's liver function and stool color are illustrated in [Figure 2].

The disproportionate increase in the patient's serum bilirubin level compared with the mild dilation of the left IHD led to the suspicion of nonobstructive cholestasis. Subsequently, the hepatitis profile of the patient was retested, yielding the following results: HBsAg: negative, anti-HBs antibody: positive, anti-HBc antibody: positive, HBeAg: negative, and anti-HCV antibody: negative. Screening for atypical infections and autoimmune hepatitis also produced negative results [Table 1]. Viral hepatitis and autoimmune hepatitis were excluded based on these test results. An immune-mediated biliary disease, possibly related to an immune checkpoint inhibitor (i.e., the combination REGONIVO regimen), was thus highly suspected. Accordingly, the patient immediately underwent intravenous corticosteroid treatment (equivalent dose of prednisone 1 mg/kg/day). The empiric antibiotic cefepime was also administered because a superimposed biliary tract infection could not be completely excluded.

A repeat CT scan performed on day 3 after admission indicated mildly dilated left IHD, confirming nonobstructive cholestasis [Figure 3], and the images were comparable to those obtained from a CT scan 6 days before admission [Figure 3]. The patient's serum bilirubin and transaminase levels stabilized during the 1st few days of steroid treatment but deteriorated again on day 7 (total bilirubin = 12.7 mg/dL, AST = 155 U/L, ALT = 279 U/L, INR = 1.29). A diagnosis of an uncontrolled irAE was considered; consequently, mycophenolate mofetil (MMF; 250 mg Q12H) was added as the second immunosuppressant on day 7.

Table 1: Investigation of the etiology of abnormal liver function

Atypical infections	Autoimmune diseases
EBV-EA IgG: Positive	Mitochondrial Ab: 1:40 (−)
EBV-VCA IgG: Positive	Smooth muscle Ab: 1:40 (−)
EBV-VCA IgM: Negative	LKM: 1:10 (−)
EBNA Ab: Negative	Anti-nuclear antibody: 1:40 (−)
HSV IgM: Negative	Anti-ENA: Negative (0.11)
Cytomegalovirus IgM: Negative	C4 quantitation (mg/dL): 27.5
Varicella-Zoster virus IgM: Negative	C3 quantitation (mg/dL): 98.3
	IgG (mg/dL): 589.0
	IgM (mg/dL): 81.20
	IgA (mg/dL): 237.00

EBV: Epstein–Barr virus, EA: Early antigen, VCA: Viral capsid antigen, EBNA: EBV viral nuclear antigen, Ab: Antibody, HSV: Herpes simplex virus, ENA: Extractable nuclear antigen, LKM: Liver kidney microsomal

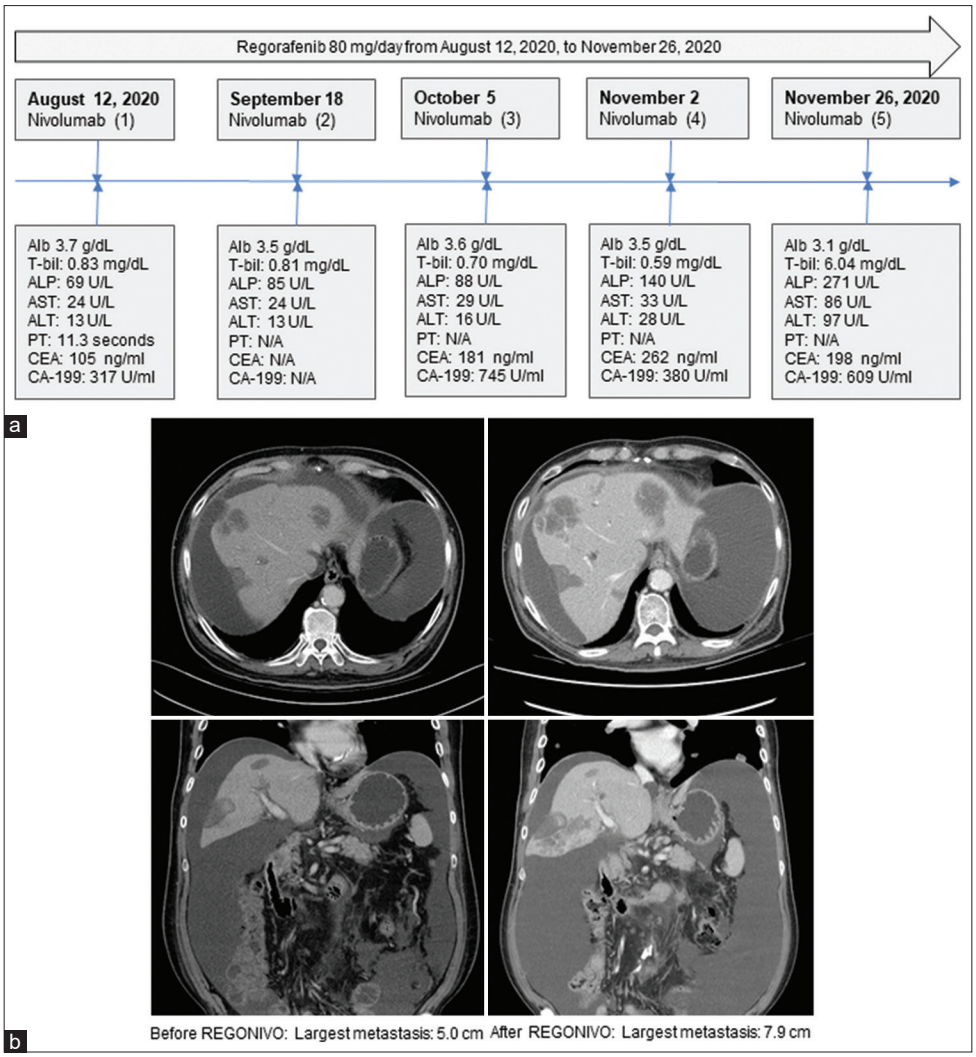

Figure 1: Patient condition before and after REGONIVO treatment. (a) Timeline of the nivolumab infusion and the trend of liver function laboratory tests. (b) CT scans of this patient showed multiple liver metastases and ascites. CT scan after REGONIVO treatment showed enlarged hepatic masses. T-bil: Total bilirubin, D-bil: Direct bilirubin, CT: Computed tomography

To confirm the etiology of cholestasis, the patient was recommended for liver biopsy for pathohistological investigation; however, he refused due to concerns regarding the risk of major bleeding related to the persistent presence of a moderate amount of ascites. Subsequently, a gastroenterologist was consulted for endoscopic retrograde cholangiopancreatography (ERCP) evaluation. Endoscopic examination on day 8 confirmed a mildly dilated left IHD and multiple filling defects over the common bile duct and right IHD. The silhouettes of these defects suggested hemobilia with blood clot formations rather than liver metastases, indicating biliary tract inflammation [Figure 4]. Endoscopic retrograde biliary drainage (ERBD) was performed for bilateral IHD to relieve the hyperbilirubinemia.

Despite ERBD, the patient's serum bilirubin level continued to increase until it reached 14.0 mg/dL on day 9. A follow-up abdominal sonography showed no progression of IHD dilation; hence, an uncontrolled irAE was still suspected. The MMF dosage was accordingly titrated to 500 mg Q12H. After 2 days (day 11), the patient's bilirubin level had decreased to 11.4 mg/dL; however, the patient continued to pass clay-colored stools. To enhance the treatment effect, tacrolimus (1 mg Q12H) was added as a combination therapy on day 16. Subsequently, the patient's stool color quickly returned to brown and yellowish by day 17, and his serum bilirubin level had decreased to 8.0 mg/dL by day 18 [Figure 2]. In addition, the patient's serum transaminase and INR levels returned to normal ranges. The quick and favorable response of his hyperbilirubinemia to multiple immunosuppressants and the lack of evidence of other etiologies of intrahepatic cholestasis confirmed the diagnosis of acholia as an unusual manifestation of a hepatic irAE.

Discussion

In this report, we present a case of a patient with unexplained hyperbilirubinemia 3 months after initiation of a REGONIVO

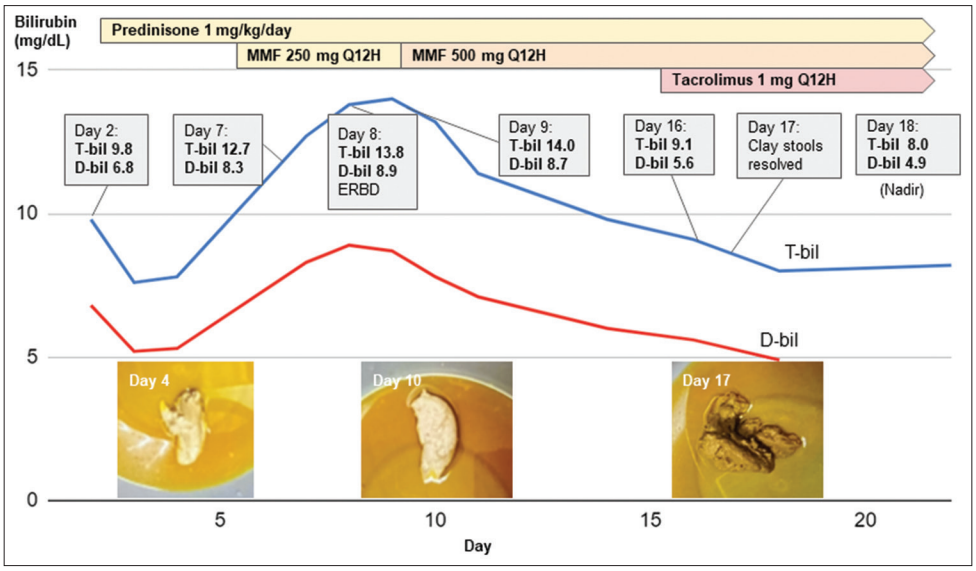

Figure 2: Timeline of the trend of serum total and direct bilirubin levels, treatment interventions, and changes in stool color over the course of treatment. ERBD: Endoscopic retrograde biliary drainage, MMF: Mycophenolate mofetil, T-bil: Total bilirubin, D-bil: Direct bilirubin (mg/dL)

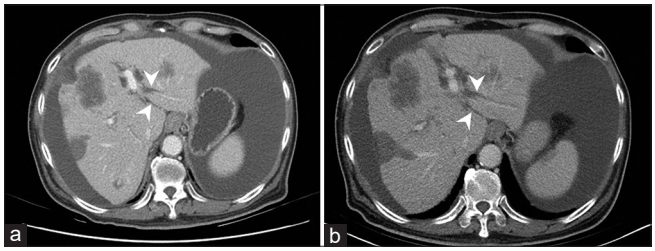

Figure 3: CT scans of the patient. CT performed (a) 6 days before admission showed mildly dilated left IHD (arrowheads) and (b) on day 3 of admission showed no obvious progression of obstruction (arrowheads). CT: Computed tomography, IHD: Intrahepatic duct

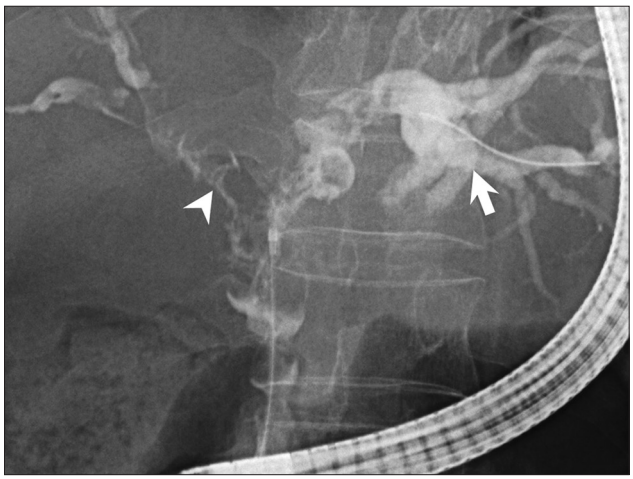

Figure 4: Endoscopic retrograde cholangiopancreatography performed on day 8 of admission indicated mild left IHD dilation (arrow) and multiple filling defects without upstream biliary dilation (arrowhead). The filling defects were possibly blood clots that had formed. IHD: Intrahepatic duct

regimen for metastatic colon cancer. Imaging studies, including CT and ERCP, revealed no evidence of biliary tract obstruction, except for stable mild left IHD dilation, which did not reflect the degree of hyperbilirubinemia. The filling defects demonstrated by the ERCP did not lead to dilation of the right IHD, suggesting a nonobstructive etiology. Moreover, the hyperbilirubinemia did not respond to ERBD but rather continued to increase over the following 2 days [Figure 2], which is unusual for biliary obstruction. Therefore, the most likely etiology was intrahepatic cholestasis resulting from either biliary canalicular injury or a decrease in the upstream transportation of bile from the hepatocytes to the canaliculi.[8] Such a decrease is often induced by medications or sepsis and often causes cholestasis but rarely causes acholia. Therefore, biliary canalicular injury was inferred.

Biliary canalicular injury has many possible etiologies, including autoimmune diseases, irAEs, infections, tumor cell infiltration, drug-related liver injury, and idiosyncrasy.[8] The definite diagnoses rely on pathological proof. However, persuading terminally ill patients to undergo invasive interventions is difficult, especially for diagnostic rather than therapeutic purposes. Furthermore, the patient's coagulopathy and moderate amount of malignant ascites increased the risk of the procedures. No evidence or indication of any autoimmune disease was observed in this patient. Although biliary tract infection could not be completely ruled out, systemic inflammatory response syndrome was not observed at any point during the hospitalization period and the patient's hyperbilirubinemia did not respond to antibiotics. A decreasing trend in his serum tumor marker level and the stable tumor size revealed by the CT scans precluded the possibility of tumor progression with hepatic infiltration. Before this episode, the patient had been treated with spironolactone, domperidone, and magnesium oxide, all of which rarely cause cholestasis.[9-11] Regorafenib-related hepatotoxicity has been reported as a rare drug complication but predominantly of the hepatocellular type

and rarely hyperbilirubinemia. The probability of grade 3 and grade 4 hyperbilirubinemia in the pivot phase 3 CORRECT study was 2% and 0%, respectively.[12,13] The administration of nivolumab and the response to MMF and tacrolimus, as observed in our patient, supported the diagnosis of an irAE with an unusual presentation of acholia. Fukuoka *et al*. reported that the REGONIVO regimen was associated with an 18% risk of developing treatment-related liver dysfunction, which is higher than the level of anti-PD1 monotherapy-induced hepatic irAE.[1,3,14] Whether anti-PD1 in combination with a multikinase inhibitor leads to more cholestatic irAEs than does PD-1 blockade alone warrants further investigation.

Immunotherapy-related cholestasis has rarely been reported. Kurokawa *et al*.[15] reported a case of a patient with non-small cell lung cancer who developed cholestasis after pembrolizumab use. Liver biopsy showed infiltration of inflammatory cells in portal tracts and destruction of the interlobular bile ducts. Thorsteinsdottir *et al*.[16] reported another patient with melanoma who developed fatal cholestatic liver injury after immunotherapy with a combination of nivolumab and ipilimumab. Pathological examination revealed portal and lobular inflammation and even loss of small bile ducts. Doherty *et al*.[14] reported three cases of irAEs with cholestasis. Liver biopsies showed different degrees of ductal injury and ductopenia, and one of the patients had vanishing bile duct syndrome. All the aforementioned patients exhibited a predominantly elevated total bilirubin level in laboratory tests, with varying degrees of transaminitis. However, no acholia was reported in any of these cases. Our case demonstrated that extensive irAE-related biliary canalicular injury can lead to acholia, without obvious biliary obstruction in CT or ERCP images.

Corticosteroids are typically used to treat hepatic irAEs in patients with a bilirubin level >1.5 times the upper limit of normal.[17] If the patient fails to respond to corticosteroid treatment in 48–72 hours, then a second immunosuppressant should be considered. However, previously reported cases of cholestatic irAEs have indicated poor response to corticosteroid treatment alone.[15,16] Infliximab, a commonly used immunosuppressant for irAEs, should be avoided in such circumstances to prevent possible additive hepatic toxicity.[17] Hence, we propose two reasonable alternatives: MMF and tacrolimus;[17] our patient responded well to a combination of these immunosuppressants. We noticed that cholestatic irAEs may require a more aggressive strategy such as additional immunosuppressant combination besides corticosteroids. Nevertheless, prolonged use of multiple immunosuppressants increases the risk of severe infection; hence, careful monitoring and timely titration are crucial for successful treatment.

In summary, we presented a rare case of a hepatic irAE presenting as acholia and hyperbilirubinemia that resolved significantly after immunosuppressant combination therapy. Because cholestatic irAEs have been reported to be refractory to corticosteroid treatment alone, we recommend a more aggressive treatment strategy against an irAE presenting as cholestasis or acholia, such as timely use of multiple immunosuppressants.

Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). This study has been approved by National Taiwan University Hospital Research Ethics Committe (approval number: 201612146RINB).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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