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A Rare Case of Immune Checkpoint Inhibitor Cholangitis

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Abstract

Immune checkpoint inhibitor cholangitis (IMC) due to its rarity poses difficulties in diagnosis and treatment. IMC includes a range of biliary tract injuries with different clinical and pathological characteristics, from small-duct to large-duct involvement. A 32-year-old man presented hospital with presyncope, nausea, and vomiting. Upon computed tomography, he was found to have multiple cryptogenic liver lesions. He had a history of lung adenocarcinoma on maintenance Keytruda. He had multiple admissions related to Keytruda complications which included pancreatitis requiring high-dose steroids, esophagitis, and gastritis (last esophagogastroduodenoscopy showing Severe hemorrhagic gastritis, gastric stenosis). A magnetic resonance cholangiopancreatography was obtained for cholestatic elevation of transaminases and showed intrahepatic and extrahepatic biliary dilatation with periductal enhancement. A liver biopsy was inconclusive. However, the findings could be associated with obstructive changes. The likely differentials were primary versus secondary sclerosing cholangitis. In the setting of prolonged use of pembrolizumab for 1.5 years and taking into consideration the timeline of symptoms, secondary sclerosing cholangitis was diagnosed. He was treated with steroids and Keytruda was discontinued with improvement in symptoms. Immune checkpoint inhibitors (ICI) can affect any organ system, including the liver, causing cholangitis, although this is less common than immune-mediated hepatitis. Steroids alone or with immunosuppression show similar results.

Keywords

Keytruda, Immune Checkpoint Inhibitors, Immune Checkpoint Inhibitor Cholangitis

1. Introduction

Cancer treatment is evolving with the introduction of immune checkpoint inhib-

itors (ICIs) that target the checkpoints cancer cells use to reduce immunity against them. ICIs include programmed cell death-1 (PD-1-nivolumab and pembrolizumab), programmed cell death ligand 1 (PDL-1-atezolizumab and avelumab), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4-ipilimumab) inhibitors. However, immune-related adverse events (irAEs) caused by cancer immunotherapy have been increasing in parallelly as well. The exact pathogenesis of irAEs remains unknown, but compared to conventional chemotherapy-induced cytotoxicity, irAEs take longer to manifest. Amongst the adverse effects, hepatotoxicity is a major AE with 9% incidence.

In a study by Coukos *et al.*, three patterns of Immune checkpoint inhibitor-induced liver injuries were defined—hepatic, cholangitis, and mixed [1]. In a multicenter study of 117 patients who underwent liver biopsy, cholestatic forms were seen in 37%, which was higher than anticipated. Immune-mediated cholangitis (IMC), includes a range of biliary tract injuries with different clinical and pathological characteristics, from small-duct to large-duct involvement [2]-[4]. Recently, Pi *et al.* compiled 53 cases of ICI-induced cholangitis in their review with a distribution of 12 with small-ducts involvement, 29 with large-ducts involvement, and 12 with mixed involvement [5].

There are many obstacles in managing IMC since immunosuppressive medication is not always effective. It is also essential to differentiate IMC from other biliary tract conditions such as cholangiocarcinoma and other drug-induced liver injury to choose the best course of treatment.

Here, we present a case of a 32-year-old male on PD-L1 inhibitor for non-small cell lung cancer (NSCLC) with good response, suffering from a myriad of side effects including but not limited to esophagitis, pancreatitis, and ultimately, cholangitis. Despite the side effect profile, the patient's insistence on continuing the treatment was met with repeated adverse effects. Whether the emergence of one side effect predisposes a patient to further side effects is unclear, but this case demonstrates rare side effects of the newer agent in one patient and more interestingly even rarer cholangitis.

2. Case

A 32-year-old male with a history of lung adenocarcinoma presented to hospital due to a presyncopal episode associated with nausea and vomiting. Intake vitals were stable. Abdomen was soft and nontender. Upon CT imaging, he was found to have multiple cryptogenic liver lesions.

He had a history of lung adenocarcinoma post-chemoradiation therapy followed by maintenance Keytruda. He had multiple admissions related to Keytruda complications which included pancreatitis requiring high-dose steroids (prednisone 75mg with a taper), esophagitis, and hemorrhagic gastritis leading to cessation of Keytruda treatment 3 months ago.

The patient had previously presented similarly with a cholestatic pattern of transaminase elevation. An MRCP at the time demonstrated both intrahepatic

and extrahepatic biliary dilatation with periductal enhancement. The autoimmune panel, including anti-mitochondrial antibodies, anti-neutrophil cytoplasmic antibodies, and anti-smooth muscle antibodies, was negative. Further, HIV antigen/antibody was negative, and IgG4 levels were within normal limits too. His ALT and AST trended down at that time from 102 U/L and 122 U/L, respectively to 32 U/L and 34 U/L, but ALP remained elevated around 750 U/L despite management as drug-induced acute cholangitis with steroids.

Since discharge, he was again treated for mild acute cholangitis three months after the previous episode. CT showed diffuse metastatic disease throughout the liver, prompting a liver biopsy which showed cholestatic changes with interspersed lymphocytes in the portal triads. The patient was still on the proposed offending agent, Keytruda, and hence diagnosed with drug-induced cholangitis. However, it was not treated with steroids at the time due to the presence of newly diagnosed hemorrhagic gastritis in this episode, per hematology recommendation. However, Keytruda was discontinued.

On this subsequent readmission, with ALP 606 U/L. ALT/AST bilirubin was within normal range. CT of the abdomen with intravenous contrast demonstrated multiple liver lesions and subsequent MRCP showing similar changes as before despite discontinuation of Keytruda, and a trial of immunosuppressant versus observation was considered with the decision for observation taken at the end.

Informed consent from the patient was obtained for reporting this case.

3. Discussion

The likely differentials for this patient were primary biliary cholangitis (PBC) versus primary versus secondary sclerosing cholangitis (PSC v/s SSC). With negative antimitochondrial antibodies and existing co-morbidities, PBC was unlikely. Common causes of SSC including HIV and IgG4 disease were ruled out by their respective serum testing. Further liver biopsy was done to look for uncommon causes including malignancy, eosinophilic cholangitis or chronic bacterial cholangitis, however presence of nonspecific cholestatic changes and ductal reaction resembled drug-induced biliary injury. In the setting of prolonged use of pembrolizumab for 1.5 years and taking into consideration the timeline of symptoms, secondary sclerosing cholangitis from pembrolizumab toxicity seemed more likely to be persistent despite cessation of treatment 3 months ago.

Immune-related mediators can affect any organ system producing immune-related adverse events (irAEs) [6]. The pathophysiology of irAEs is unclear. Hypotheses include cross-reactivity of T cells with normal tissue, an increase in levels of pre-existing autoantibodies, or direct toxicity [6]. The incidence of gastrointestinal side effects is more common with combination therapy followed by anti-CTLA-4 agents and then the PD1/PDL1 inhibitors [7]. Side effects occur 6–8 weeks after the start of treatment but can persist months after the drug is discontinued. This is because the molecular effects are maintained after drug clearance [8]. In our patient, side effects started later than the proposed 6 - 8 weeks but as stated in the

literature, drug cessation predated the duration of side effects.

As for the side effects, the incidence of ICI-related pancreatitis is 1.2% - 2.1%, with presentations ranging from asymptomatic lipase elevation to acute pancreatitis to chronic endocrine or exocrine insufficiency [9]. ICI-mediated mucosal inflammation has been well-described in the colon but infrequently so in the stomach.

With hepatic manifestations, immune-mediated hepatitis is fairly more common compared to its biliary counterpart. The cases reported by Kawakami *et al.* showed extrahepatic bile duct dilatation and hypertrophy. However, the pathology did not show small duct involvement, but liver biopsies performed by Gelsominon *et al.* showed intraductal microabscesses and ductular proliferation, whereas imaging suggested that there were no changes to the intra- or extrahepatic bile duct [2]-[4].

IMC can be categorized into three categories based on the architecture of the biliary system. (1) Small duct (2) Large-duct type: lesions were observed at the segmental ducts, left and right hepatic ducts, and common bile and hepatic ducts. (3) Mixed type: both the big and small bile ducts were impacted as in our patient. Based on current literature, the incidence of IMC with large-ducts type has been estimated to be between 0.05 and 0.7% [3] [4]. The incidence of IMC with small-duct type is likely underestimated because a liver biopsy is necessary for diagnosis. Retrospective pathological analysis done in Boston between 2014 and 2018 revealed that patients with biopsies for elevated transaminases primarily had cholangitis patterns in 27% of cases, small-duct types in 20%, and mixed types in 7% of cases [10].

Like the biliary damage in DILI, the histology results of IMC were often imprecise. Common changes include portal inflammation with a predominance of CD8+ T cell infiltration, CD8+/CD4+ T cells, ratio of 12 times compared to 3 in AI hepatitis and 5 in DILI. Small bile duct injuries, with intraepithelial or periductal lymphocytosis, periductal fibrosis, proliferative ductular reaction or bile duct loss, and lastly, cholestasis [11] [12]. Our patient exhibited a cholestatic pattern, with lymphocytic predominance and ductal reaction. The onset from injury to pathological changes is not clearly defined in the literature, and hence, the duration of biliary changes was unclear.

Common clinical symptoms include intermittent fevers, right upper quadrant pain, and jaundice. Some cases are however asymptomatic. Investigations include CT and MRCP. Koya *et al.*, McClure *et al.*, and Hirasawa *et al.* had a magnetic resonance cholangiopancreatography (MRCP) revelation of an irregularly narrowed intrahepatic bile duct resembling beading sign similar to IgG4-related cholangitis or Primary Sclerosing Cholangitis [13]-[15].

For treatment, as per a systematic review, the Barcelona criterion has been used where ALP normalization was the criterion for complete resolution, a decrease of 40% partial response and less than 40% as an unsatisfactory response. In the review, steroids, and steroids with immunosuppression were compared with similar

results. Imaging and histology-wise, results were mixed, with some patients showing progression as well [16].

Our patient was treated with steroids, but the ALP decrease demonstrated a dissatisfactory response. Ultimately, steroids were contraindicated due to coexisting gastritis, and a conservative approach of waiting after discontinuation was taken. However, the patient succumbed to the complications of malignancy, and further follow-up was not possible. Treatment with ursodeoxycholic acid (UDCA) is generally done to facilitate biliary drainage and arrest the ductal inflammation.

Apart from diagnosis and treatment, it is important to differentiate it from cholangiocarcinoma which might present similarly but will not show response to steroids. IgG4-related disease can also present similarly and would respond to steroids as well. Lastly, taxanes can produce similar picture and might need to be discontinued if ICI related cholangitis is suspected [16].

4. Conclusions

With ICI-related treatment, any organ system involvement can be involved. Prompt recognition, and differentiation from more common etiologies are required to halt the offending agent and start treatment.

ICI-related complications are getting more common with more recent use and would require more research for further guidelines regarding diagnosis and treatment.

ICI-cholangitis is a rare complication and has varied presentations including small and large duct involvement either in isolation or together. The clinical and radiological picture resembles other biliary pathologies and requires a high suspicion if there is a temporal association.

Treatment guidelines and the definition of remission are unclear. However, based on present data, steroids, and immunosuppression have not yielded good results. UDCA and ICI cessation are the cornerstones of therapy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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