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Early Use of Tocilizumab as an Effective Steroid-Sparing Strategy for the Treatment of Immune Checkpoint Inhibitor-Mediated Cholangiopathy: Building Foundations for Personalized Management

Hao Chi "Joseph" Zhang, M.D.[1], Ethan Miller, M.D.[1], Lan Wang, M.D.[1]
[1]University of Texas MD Anderson Cancer Center, Department of Gastroenterology, Hepatology & Nutrition, Houston, TX

Introduction

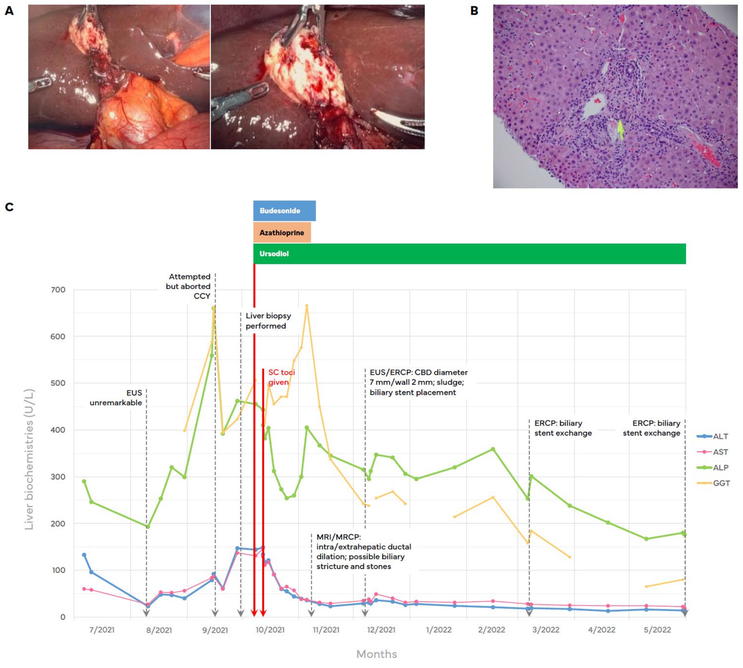
- Immune-mediated cholangiopathy (IMCp) is an increasingly recognized complication of immune checkpoint inhibitor therapy, often associated with exposure to anti-PD-1/L1 agents. Both intra- and extrahepatic manifestations can occur. Potential sequelae include biliary strictures and acute cholangitis.
- Management of IMCp remains undefined across multiple society guidelines, but published cases have offered insight into formulating effective treatment strategies.
- We present a complex case of a patient with IMCp successfully treated with budesonide and early tocilizumab, an IL-6 receptor antagonist.

Case Presentation

- A 70-year-old man with a history of urothelial carcinoma (treated with neoadjuvant carboplatin/gemcitabine, followed by 3 cycles of an anti-PD-1 agent, pembrolizumab), pre-diabetes, and no underlying liver disease, presented with abnormal liver enzymes.
- ERCP revealed some biliary sludge but no biliary stricture. Endoscopic ultrasound 3 months later was normal.
- ALT normalized, but alkaline phosphatase (ALP) remained elevated; both then increased to CTCAE grade 2. R factor was 0.5 (<2), suggesting a cholestatic-predominant pattern.
- Elective cholecystectomy was attempted but aborted: He had a firm, contracted gallbladder with dilated extrahepatic biliary ducts, and the surgeon could not demarcate borders of the cystic and common bile ducts.
- MRCP showed intrahepatic biliary ductal dilation, ductal thickening and enhancement, and CBD dilation with a new stricture. Liver biopsy showed cholestatic hepatitis with portal and lobular inflammation and hepatocyte necrosis. A diagnosis of immune-mediated cholangiohepatitis with IMCp was made.

Final Diagnosis

Immune checkpoint inhibitor-mediated cholangiopathy



(A): Intra-operative photographs revealing a white/firm contracted gallbladder and dilated extrahepatic biliary ducts, with inability to demarcate the cystic duct and common bile duct; due to distortion of the extrahepatic biliary anatomy, cholecystectomy was not performed and aborted.
(B): Histologic evaluation (hematoxylin & eosin) from liver biopsy, showing chronic cholestatic hepatitis with portal and moderate lobular inflammation, bile duct injury, bile ductular proliferation, moderate cholestasis, and scattered hepatocyte necrosis; no significant fibrosis seen.

(C): Timeline of liver biochemical tests and associated treatments. Budesonide was selected as the induction steroid, at 9 mg/day, for 5 days total, followed by 6 mg/day for 14 days, and 3 mg/day for 14 days. Azathioprine adjunct of 100 mg/day was briefly prescribed. Subcutaneous tocilizumab 162 mg was administered; serum ALT normalized at 31 days thereafter. Ursodiol was administered long-term in an attempt to address and to mitigate further cholangiopathic consequences.

Abbreviations: EUS, endoscopic ultrasound; CCY, cholecystectomy; SC, subcutaneous; toci, tocilizumab; MRI/MRCP, magnetic resonance imaging/magnetic resonance cholangiopancreatography; ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase.

Management & Clinical Course

- Oral budesonide/azathioprine/ursodiol were prescribed.
- 5 days later, subcutaneous (SC) tocilizumab 162 mg was administered without complication.
- After completion of budesonide/azathioprine, ursodiol was continued long-term for persistent elevation of ALP. Serial ERCPs for plastic biliary stent placement were performed for biliary sludge and for an unresolved CBD stricture. ALP level improved to <180 U/L about 7-8 months after tocilizumab.

Discussion

- Cases of IMCp could be potentially overlooked because ALP is not featured in the society guidelines' assessments for liver toxicity.
- Routine analysis of the R factor in cases of suspected immune-mediated hepatobiliary toxicity with ALP >1.5× upper limit of normal can aid in detection for possible biliary phenotypes.
- Although steroids can be used to initially treat IMCp, aggressive escalation to alternative treatments such as tocilizumab is important to mitigate progression to biliary sequelae that might arise.
- Choledocholithiasis and IMCp can occur simultaneously when extrahepatic biliary strictures form.
- As use of anti-PD-1/L1 agents expand, IMCp may become increasingly common, and prompt treatment is of paramount importance.
- The initial dose of tocilizumab may be given as either the intravenous (IV) route (8 mg/kg) or the SC route (162 mg).
- Our case also raises the possibility of a diagnosis of ICI-mediated cholecystitis, a rarely reported entity, for which the gross manifestations precluded surgical cholecystectomy which was otherwise the traditional management for acute calculous cholecystitis.

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