CLINICAL VIGNETTE

Immune Checkpoint-Inhibitor Induced Cholangiopathy

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A 68-year-old woman was diagnosed with advanced stage 4 non-small cell lung cancer. Baseline FDG PET CT scan showed bilateral lung masses involving left upper lobe (LUL) and right lower lobe (RLL), mediastinal adenopathy of right hilum as well as increased FDG uptake along right posterior pleural. CT guided biopsy of LUL mass demonstrated lung squamous cell carcinoma. PD-L1 immunohistochemistry assay testing showed 50% expression. Next generation sequencing (NGS) panel revealed a tumor mutation burden (TMB) of 2.6 somatic mutations per million coding base pairs as well as KRAS pG12D exon 2 mutation. No actionable mutations were noted in the following genes: EGFR, BRAF, ALK, ROS1, RET, MET, and ERBB2.

Due to high PD-L1 expression, patient was started on systemic therapy with intravenous pembrolizumab every 3 weeks. Serial CT scans of chest abdomen pelvis showed partial and persistent response to checkpoint inhibitor with decreased size of bilateral lung masses as well as mediastinal adenopathy. Patient was continued on this treatment for nearly three years until onset of significant Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grade 3 transaminitis with AST 470 (normal 13-62 U/L), ALT 540 (normal 8-70 U/L) in conjunction with normal total bilirubin and alkaline phosphatase level 493 (normal 37-113 U/L). Further treatment with pembrolizumab was held, and patient was referred to Hepatology for further evaluation.

The patient had not received potentially hepatotoxic medications or taken over-the-counter supplements. Viral hepatitis panel was negative as well as serologies for smooth muscle and mitochondrial antibodies. The transaminitis gradually resolved but alkaline phosphate continued to rise to a peak level of 807 U/L. MR cholangiopancreatogram with and without contrast revealed diffuse periportal edema with mural thickening as well as hyperenhancement of common bile duct and intrahepatic bile duct. There were no ductal strictures or intraluminal filling defects noted. An ultrasound-guided core needle biopsy of right liver lobe was performed. Histologic evaluation showed no evidence of hepatocyte necrosis or ballooning. There was a mild mixed infiltrate of both neutrophils and lymphocytes within ducts and lobules. Pathologic findings were thought to be most consistent with checkpoint inhibitor cholangiopathy.

Until recently platinum-based chemotherapy doublets were held as the standard of care for advanced stage 4 non-small cell lung cancer regardless of histology. A large meta-analysis showed an absolute improvement in one-year survival of 10% and an increased median survival of 1.5 months.[1] The advent of immune-checkpoint inhibitors (ICIs) ushered in a revolution in the treatment of advanced, metastatic solid malignant tumors. In particular, ICIs have consistently shown an improvement in overall survival as first line treatment of non-small cell lung cancer.[2] Taking into consideration clinically significant 5-year overall survival (OS) exceeding 25%,[3] clinicians must remain vigilant for recognition of early immune-related adverse events (irAEs). These systemic toxicities associated with ICIs can be effectively managed with a multidisciplinary approach.

Immune-checkpoint inhibitors are commonly associated with development of inflammatory changes and end-organ dysfunction. Common pathologic alterations can be dermatologic, endocrinopathies, pulmonary, rheumatologic, and gastrointestinal including hepatic toxicity. In particular, immune-checkpoint inhibitor (ICI)-related hepatotoxicity can occur at any time during treatment, although it is most commonly seen 6 to 12 weeks after the onset of treatment.[4] The incidence of ICI-related hepatotoxicity is dependent on the type of checkpoint inhibitor. Cytotoxic T-lymphocyte associated protein-4 (CTLA-4) inhibitors are associated with an all-grades incidence of 3 to 9 % of autoimmune hepatotoxicity. Conversely, programmed cell death protein-1 (PD1) inhibitors have a lower associated incidence of 1 to 3%. These two mechanistically different ICIs are currently used in combination for the treatment of certain advanced malignancies such as cutaneous melanoma and non-small cell lung cancer. In this these patients, combined ICIs therapy is associated with a higher incidence of autoimmune hepatotoxicity, up to 11 to 20%.

In regard to global immune-related hepatotoxicity, less is known about the adverse effects of ICI's on the biliary system. In general, the biliary tract provides an outlet for the transport of bile into the gastrointestinal tract.[5] Anatomically, the biliary tract is composed of intra-hepatic bile ducts running parallel to the portal venous and hepatic arterial supply. The extra-hepatic compartment of the biliary tract encompasses the gallbladder and a system of extra-hepatic bile ducts which converge distally as the common bile duct (CBD). The CBD combines with the main pancreatic duct (PD) to form the hepatopancreatic ampulla of Vater, which opens on the major duodenal papilla distal to pylorus.[6]

At the microscopic level, the connection of bile canaliculi from hepatocytes to bile ductules and interlobular bile ducts by

canals of Hering marks the beginning of the intra-hepatic biliary tract.[7] Interlobular bile ducts continue in sequence as a triad of septal, area, and segmental bile ducts, which are differentiated based on diameter size. Interlobular and septal ducts are considered small intrahepatic ducts (ie. <300 μm in diameter). Area and segmental bile ducts are large intrahepatic ducts (>300 μm in diameter). Histologically, small intrahepatic ducts are lined with small, cuboidal-shaped cholangiocytes, whereas large intrahepatic ducts are composed of tall, cylindric cholangiocytes. The main function of cholangiocytes is the modification of bile derived from hepatocytes.[8]

As the largest organ in the human body, the liver has prominent physiologic functions as well as notable and essential immune capabilities. It was long believed that lymphocytes circulate in and out of peripheral organs via lymphatic channels. It is now well understood that tissue-resident lymphocytes exist such as tissue-resident memory T cells, innate lymphoid cells (ILCs), and tissue-resident natural killer (NK) cells.[9] These types of immune cells play a major role in the recruitment of circulating immune cells to tissues. Cholangiocytes are a type of intra-luminal epithelial cells lining the intrahepatic and extrahepatic biliary tract. Cholangiocytes can be activated by various pathological triggers into a complex proinflammatory cascade known as a ductular reaction. In this abnormal milieu, with increased production of proinflammatory cytokines, cholangiocytes crosstalk with adjacent immune cells and cholangiocyte proliferation. Cholestasis and fibrosis are the end results of this proinflammatory cascade.

About 25% of patients receiving treatment with ICIs will develop checkpoint inhibitor-induced liver injury (CHILI).[10] The clinical presentation of CHILI can vary based on the biochemical findings of drug-induced liver injury (DILI). In general patients can present with a cholestatic, hepatocellular, or mixed injury pattern. A retrospective, observational study by Hountondji, Lina et al, reported 117 patients with CHILI: 36.8% with cholestatic pattern; 38.5% hepatocellular, and 24.8% with mixed findings. In this cohort, 20 patients within the cholestatic group underwent liver biopsy, with noted biliary injury with lymphocytic cholangitis, granulomatous cholangitis, and/or ductal dystrophy.

The medical treatment of CHILI and in particular the therapeutic management of checkpoint inhibitor-induced cholestasis (CHIC) requires a multidisciplinary approach and close collaboration between Hepatology and Medical Oncology. A small percentage of patients with CHILI will experience spontaneous resolution without therapeutic intervention. Nevertheless, patients with bile duct injury may experience a delay in resolution of CHIC. Systemic glucocorticoids are considered first line treatment for checkpoint-induced hepatocellular hepatitis.[11] Pi et al retrospectively studied 53 patients with immune-mediated cholangitis (IMC), including evaluation of biochemical response to immuno-suppressive therapy.[12] In this study 4 patients had complete biochemical response, 33 with partial biochemical response, and 10 had poor biochemical responses.

Therapies managing these patients varied, and included glucocorticoid monotherapy in 32 patients. Combined therapy involved the use of glucorticoids with ursodeoxycholic acid as well as other immunosuppressive medications such as mycophenolate mofetil, azathioprine and tacrolimus. In some cases, immunomodulators of tocilizumab and plasmapheresis were also used.

Immune-checkpoint inhibitors have transformed the therapeutic landscape in malignant hematology and oncology. Physicians involved in the day-to-day medical care of patients with neoplastic malignancies must remain vigilant for immune-related adverse effects that can be associated with significant morbidity and mortality. Fortunately, temporary cessation of immune therapy, and in some cases institution of immune suppressive therapy can mitigate immune-related toxicity, while preserving therapeutic benefit.

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