



Topical Update – The Hong Kong College of Pathologists

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Editorial note:

Immune checkpoint inhibitors revolutionize the field of immuno-oncology. They have demonstrated great potential in a wide range of adult cancers by reaching long-lasting objective responses and prolonging survival. Through completed and on-going clinical trials, their indications continue to expand among different cancer types. However, one of their limitations is immune-related adverse events, which are most frequently reported in skin, gastrointestinal tract, and endocrine organs. Immune-related adverse events in liver are less common

hepatotoxicity but still reported up to 4 to 10% of patients receiving immune checkpoint inhibitors. This Topical Update provides a concise review on the clinicopathological features of liver injury associated with immune checkpoint inhibitors. We welcome any feedback or suggestions. Please direct them to Dr. Anthony Chan (e-mail: awh_chan@alumni.cuhk.net) of Education Committee, the Hong Kong College of Pathologists. Opinions expressed are those of the authors or named individuals, and are not necessarily those of the Hong Kong College of Pathologists.

Liver injury associated with immune checkpoint inhibitors – An update on clinicopathological features

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Current applications of immune checkpoint inhibitors

Immune checkpoint inhibitors [ICPI] have been introduced as a form of targeted therapy for human cancers. They exert anti-tumor effects by

potentiating T cell functions via removing the inhibitory signals. Programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) are receptors located on T cells. Ligand-receptor interactions lead to inhibition of T cell activation, therefore

suppressing T cell activity against tumor cells (1). Currently, anti-PD1/PD-1 ligand (PD-L1) and anti-CTLA-4 are the two major forms of ICPI by exploiting an antagonistic approach using specific antibodies that target PD-1 and CTLA-4, respectively. Thus far, several ICPIs were approved by the US Food and Drug Administration for treating cancers (2). Nivolumab and pembrolizumab are FDA approved frontline anti-PD1 agents, while ipilimumab is an anti-CTLA-4 agent. These drugs are given either alone or in combination. Currently there are a number of on-going phase III/IV clinical trials with ICPI for various types of cancers (3).

Clinical features of hepatotoxicity associated with ICPI

Despite the encouraging clinical efficacy, adverse reactions related to ICPI administration have been observed, among which dermatological, gastrointestinal, endocrine manifestations were most frequently reported. These reactions are believed to result from the immune response elicited toward various organs. A meta-analysis of 17 studies revealed an increased risk of all-grade hepatotoxicity with ICPI compared with controls (pooled OR 4.10; PD-1 subgroup 1.94; CTLA-4 5.01) (4). Among all immune-related adverse reactions, hepatotoxicity was observed in a relatively small proportion of cases (up to 4-10%) in most reports (2, 5-9). Susceptibility of adverse reactions in the liver appears to be dependent on the primary cancer, regimen/dose of ICPI, and host factors. It was reported that patients receiving ICPI for HCC were at a higher risk of hepatotoxicity in terms of transaminases levels compared with lung cancer and melanoma (10). Moreover, combination therapy or a higher dose of ICPI was associated with increased risk of hepatic injury (6, 9, 11, 12). Patients may present with fever and jaundice but can also be asymptomatic (13, 14). The median time from the first dose to immune-related hepatotoxicity was 14.1 weeks (9.4–19.7) for anti-PD-1, 9.9 weeks (6.1–14.7) for anti-CTLA4, and 2.9 weeks for combined therapy (15). The biochemical derangement is usually of a hepatic or mixed hepatic/cholestatic pattern. Radiological findings

most of the time do not offer additional diagnostic information. In general, hepatotoxicity associated with ICPI is classified according to Common Terminology Criteria for Adverse Events by the National Cancer Institute (CTCAE). This system comprises grades 1-5 (with grade 5 being fatal) based on the serum levels of AST, ALT, ALP, GGT and total bilirubin. Having said that, elevated bilirubin is a less frequent phenomenon than most forms of drug-induced liver injury.

Histological features of liver injury associated with ICPI

The commonest histological features of ICPI-associated hepatotoxicity are lobular hepatitis, portal lymphoid infiltrates and variable degrees of hepatocytic necrosis (16-19). A predominant biliary pattern has been reported but is much less frequently encountered (20, 21). Cholestasis is not commonly seen, with bland cholestasis reported in 1 of 10 cases treated with pembrolizumab (22). Two cases of ICPI-induced hepatitis histologically presenting with fibrin-ring granulomas have also been reported (23). Steatosis is rare. Some histological features may be more readily observed with the use of a specific type of inhibitor. For instance, microgranulomas and central vein endotheliitis were seen in patients who received anti-CTLA4 therapy. With anti-PD1 therapy, more prominent portal tract inflammation was encountered. In contrast to autoimmune hepatitis, plasma cells are usually low in number (24), which is line with the observation that serum IgG level is mostly normal and autoimmune serological markers are negative. Likewise, in a report comparing 7 cases of ICPI-associated hepatitis versus 10 cases of AIH and 10 cases of drug-induced liver injury (DILI) (24), hepatocytic rosettes and emperipolesis were less commonly observed than AIH. When compared with DILI, bile plugs and eosinophils were less readily seen in ICPI-associated hepatitis. On immunohistochemical delineation of the lymphoid cell population in ICPI-associated hepatitis, several reports have consistently demonstrated a predominance of CD8+ lymphocytes (17, 18, 22). This could be distinguishing feature with AIH, in which CD20+ or CD4+ lymphoid cells are frequently encountered.

Diagnostic considerations and implications

The diagnosis of ICPI-liver injury can seldom be made by histology alone as there are no pathognomonic features. Before attributing the cause to ICPI, potential etiologies for liver function derangement should be considered. In particular, exclusion of hepatic involvement by tumor and viral hepatitis is needed. According to a recent report, among 491 patients treated with pembrolizumab for melanoma, lung cancer or urothelial cancer, 70 developed liver injury. Among which, a probably drug-related cause was only made in 20 cases after adjudication (25). Liver histology can help to exclude some differential diagnoses and assess the severity of liver tissue injury, which could be useful to guide management plan. The treatment options for adverse reactions would depend on the severity, and include withdrawal/discontinuation of ICPI, corticosteroids (oral or IV) +/- additional immunosuppressant e.g. mycophenolate mofetil (26). The drugs are usually permanently discontinued in cases presenting with Grade 3 or Grade 4 adverse reactions. There are no standard guidelines with reference to reintroducing ICPI after recovery from Grade 1-2 adverse reactions. As far as histology is concerned, it remains an open question whether histological parameters could offer added values in the grading of ICPI-associated hepatotoxicity. Besides, further studies are awaited to better understand the histological features associated different types of ICPI, and to depict the development and progression of fibrosis in this subset of drug-induced liver injury.

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