Drug-Induced Liver Injury by Checkpoint Inhibitors: Benefit of a Causality Assessment Tool

TO THE EDITOR:

As recently reported in this journal, hepatoxicity during therapy with immune checkpoint inhibitors (ICIs) is a diagnostic challenge with major clinical implications.[1] Other causes of liver injury, such as increasing hepatic tumor burden or drug-induced liver injury (DILI) caused by comedication, need to be excluded. To address this issue, we used an *in vitro* test based on blood monocyte-derived hepatocyte-like (MH) cells[2,3] to support causality assessment in 6 patients with acute liver injury after ICI. The MH cell test was performed as described previously.[4] Briefly, monocytes are isolated from patients' blood and cultivated under proprietary conditions for 10 days, yielding cells with individual hepatocyte features such as CYP450 activities. These MH cells are incubated for 48 hours with the drugs the respective patient was exposed to, then the individual toxicity was calculated based on the release of lactate dehydrogenase. The MH cell test was validated in patients with re-exposure.[3] The patients were recruited for our prospective study on hepatotoxic drugs (NCT 02353455). DILI diagnosis was based on clinical and laboratory findings, the Roussel Uclaf Causality Assessment Method, and expert opinion supported by the MH cell test. The administered ICIs were pembrolizumab, nivolumab and ipilimumab, respectively. Characteristics of patients and liver injury are summarized in Supporting Table S1. All but 1 patient had received several comedications at the time of liver injury; 2 patients also took supplementary herbal products. Every patient had normal liver functions tests before ICI treatment. Imaging did not reveal progression or new occurrence of liver metastasis in any patient.

ICI-induced liver injury was considered the most likely diagnosis in all patients. In 5 patients, the MH cell test was positive for the ICI only, not for the comedications, as illustrated in Fig. 1A. The remaining patient, with acute liver injury during pembrolizumab and concomitant herbal supplements, tested negative for pembrolizumab, but positive for an herbal component (Fig. 1B). After discontinuation of the herbal supplement and prednisolone for 37 days, transaminases normalized. Pembrolizumab was resumed without recurrent liver injury.

Liver injury associated with ICI therapy does not necessarily reflect causality, as other causes such as hepatic tumor spread and comedication DILI need to be considered. This small case series suggests that the MH cell test could be useful to support causality assessment in complex cases of presumed ICI-induced liver injury. If confirmed in larger cohorts, this could benefit the patients by supporting the continuation of ICI treatment.

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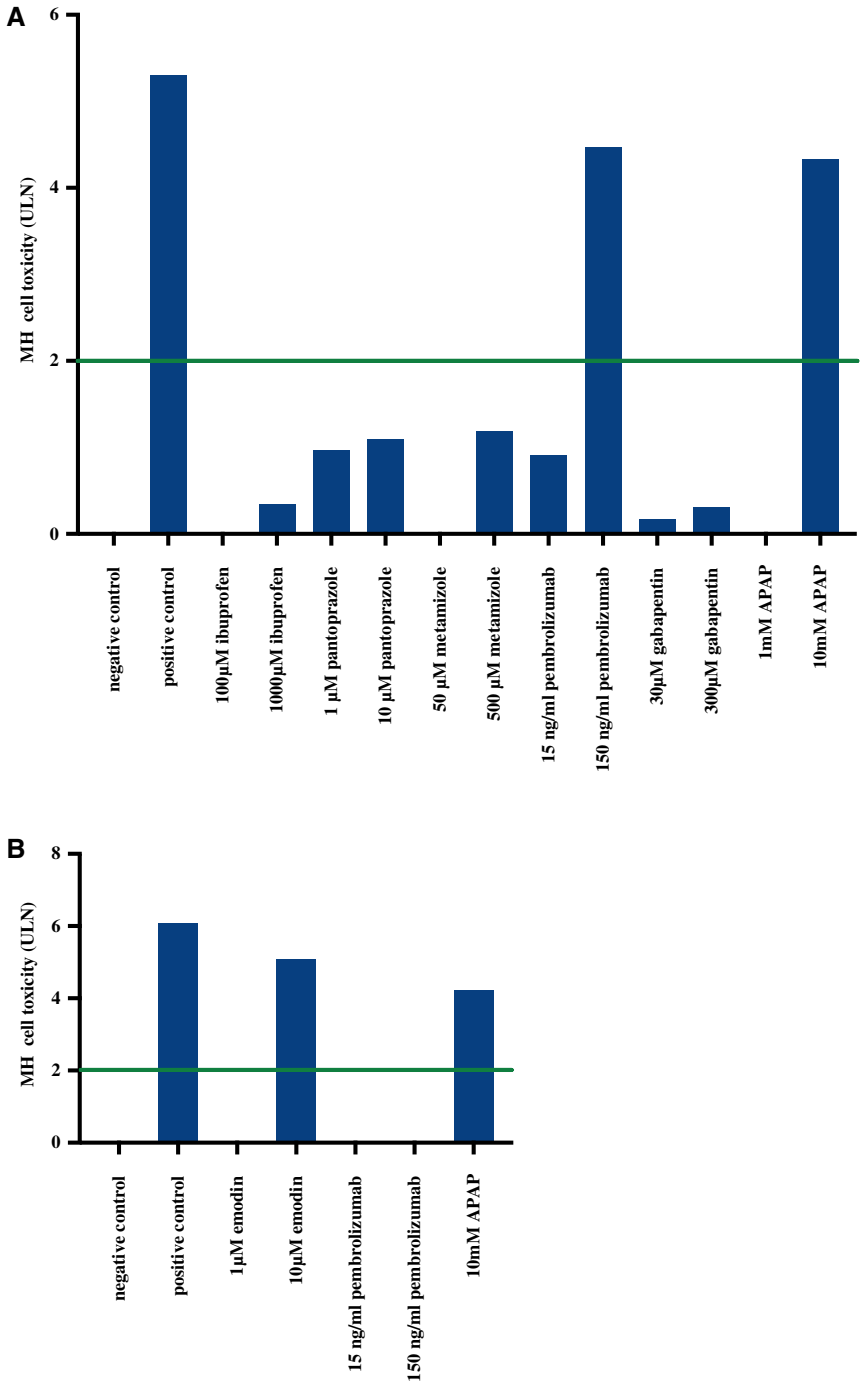

FIG. 1. Results of the MH cell test in 2 patients with presumed pembrolizumab-induced liver injury. (A) MH cell test showing a positive result for pembrolizumab and negative results for the patient's other four medications. (B) MH cell test exhibiting a positive result for emodin and a negative result for pembrolizumab. The green line indicates the test cutoff of 2. APAP (acetaminophen) is a standard part of the test, demonstrating dose-dependent toxicity. Abbreviation: ULN, upper limit of normal.

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Informed Consent in Studies with Human Subjects: All procedures were in accordance with the requirements of the responsible committee on human experimentation (Faculty of Medicine, LMU Munich; project number 55-13) and with the Declaration of Helsinki. Informed consent was obtained from all patients.

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Potential conflict of interest: Dr. Benesic owns stock in, was employed by, and owns intellectual property rights in MetaHeps GmbH. Prof. Gerbes owns stock and intellectual property rights in MetaHeps GmbH.

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