Severe Immune-Related Hepatitis Treated With Plasma Exchange

To the Editor:
A 77-year-old man diagnosed with stage IV lung adenocarcinoma had a tumor proportion score for programmed cell death-ligand 1 (PD-L1) of 0% (clone 22C3), manifested disease progression after four courses of carboplatin and pemetrexed, and then underwent treatment with atezolizumab. Thirteen days after the onset of atezolizumab treatment, he was admitted to our hospital with fever and elevated liver enzymes. He was diagnosed with grade 3 hepatitis (aspartate aminotransferase level, 760 U/L; alanine aminotransferase level, 441 U/L), with a liver biopsy revealing severe hepatitis with centrilobular necrosis associated with CD8+ lymphocytes (Fig. 1). He was closely monitored, and these abnormalities normalized in 2 weeks. Six days later, laboratory tests revealed aspartate aminotransferase, alanine aminotransferase, creatinine, amylase, and C-reactive protein levels of 2172 U/L, 1153 U/L, 4.43 mg/dL, 1246 U/L, and 23.7 mg/dL, respectively. Computed tomography revealed swelling of the kidneys and pancreas. On the basis of these clinical features, the patient was diagnosed with immune-mediated organ injury associated with acute liver failure (ALF) induced by atezolizumab. Methylprednisolone (1000 mg/d) was administered followed by plasma exchange (PE), with 40 units of plasma administered as replacement fluid for three consecutive days. The patient experienced a gradual clinical improvement and was switched to oral prednisolone. As relapse of liver enzyme elevation became apparent during steroid tapering, azathioprine was added to his treatment regimen (Fig. 2). He was discharged with prednisolone (15 mg/d) and azathioprine (50 mg/d) treatment.

Currently, there are no clinical recommendations regarding the management of immune-related hepatitis beyond the administration of steroids and immunosuppressive agents such as mycophenolate mofetil.1 In general, multorgan dysfunction in ALF is thought to be attributable to a systemic inflammatory response triggered by the release of cytokines and damage-associated molecular patterns,2 with PE being a therapeutic option to attenuate innate immune activation by removing plasma cytokines and adhesion molecules.2 A recent prospective, multicenter study has indicated that PE removes cytokines and consequently improves survival in patients with ALF.3 Nevertheless, there is little evidence regarding the role or benefit of PE in the management of severe immune-related hepatitis. PE has been reported to improve steroid- and mycophenolate mofetil-refractory immune-related hepatitis caused by anti–cytotoxic T-lymphocyte-associated protein 4 therapy.4 To the best of our knowledge, the present case is the first of immune-related hepatitis caused by anti–PD-L1 therapy that has been managed with PE.

Serum analysis revealed that the levels of tumor necrosis factor-α, interferon-γ, and interleukin-6 were greatly increased before PE and declined after PE in association with clinical improvement (Table 1).5 These findings support the notion that the severe immune-related hepatitis developed as a result of the release of inflammatory cytokines and that the removal of these cytokines by PE contributed to the therapeutic effect; however, steroid therapy might also have had an impact on cytokine production.

References
5. Chen L, Xun S, Shao Y, et al. Comparison of ALK detection of Medical Oncology, Faculty of Medicine, Kindai University, 377-2 Ohno-higashi, Osaka-Sayama, Osaka 589-8511, Japan. E-mail: hidet31@med.kindai.ac.jp
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The present case suggests that PE might be a feasible treatment option for patients with immune-related hepatitis, although further evaluation is needed to understand the role and benefit of PE in the management of this condition.

Figure 1. Microscopic findings of liver specimens obtained from biopsy. (A) Hematoxylin-eosin staining revealed centrilobular hepatocellular loss associated with T-cell and macrophage infiltration. (B-E) Immunohistochemical staining for CD3 (B), CD4 (C), CD8 (D), and CD68 (E) revealed positivity of most T cells to CD8, macrophages and sinusoidal endothelium to CD4, and macrophages to CD68. *Centrilobular vein. Scale bars, 100 μm. HE, hematoxylin and eosin.

Satoru Hagiwara, MD, PhD
Department of Gastroenterology and Hepatology
Faculty of Medicine
Kindai University
Osaka-Sayama, Osaka, Japan

Tomoyuki Otani, MD
Department of Pathology
Faculty of Medicine
Kindai University
Osaka-Sayama, Osaka, Japan

Hiroaki Kanemura, MD, MPH
Hidetoshi Hayashi, MD, PhD
Department of Medical Oncology
Faculty of Medicine
Kindai University
Osaka-Sayama, Osaka, Japan
Figure 2. Clinical course of the present case and serum cytokine levels (pg/mL). On day 6, laboratory tests revealed an AST level of 2172 U/L, an ALT level of 1153 U/L, a CRNN level of 4.43 mg/dL, an AMY level of 1246 U/L, and a CRP level of 23.7 mg/dL. Methylprednisolone (1000 mg/d) was administered, and plasma exchange was performed on days 7 to 9. On day 17, the patient was switched to oral prednisolone (40 mg/d). On day 23, AST and ALT levels were elevated at 62 and 128 U/L, respectively; thus, azathioprine (50 mg/d) was added. The patient was discharged on day 52 with prednisolone (15 mg/d) and azathioprine treatment (50 mg/d). Arrowheads indicate collection of serum for cytokine measurements. ALT, alanine aminotransferase; AMY, amylase; AST, aspartate aminotransferase; CRNN, creatinine; CRP, C-reactive protein.

Table 1. Serum Cytokine Levels (pg/mL) in the Study Patient and in Healthy Subjects or Patients With NSCLC

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TNF-α</th>
<th>IFN-γ</th>
<th>IL-6</th>
<th>IL-10</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;1.79</td>
<td>&lt;20.6</td>
<td>&lt;15.6</td>
<td>&lt;2.03</td>
<td></td>
</tr>
<tr>
<td>Current case before PE</td>
<td>139</td>
<td>60.6</td>
<td>235</td>
<td>20.2</td>
<td></td>
</tr>
<tr>
<td>Current case after PE</td>
<td>12.8</td>
<td>&lt;1.56</td>
<td>14.5</td>
<td>2.16</td>
<td></td>
</tr>
<tr>
<td>Healthy subjects (n = 33)</td>
<td>40 (9–190)</td>
<td>25 (8–118)</td>
<td>37 (12–89)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Patients with NSCLC (n = 86)</td>
<td>42 (1–302)</td>
<td>27 (1–341)</td>
<td>39 (4–348)</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Cytokine levels in the present case were determined by enzyme-linked immunosorbent assay (R&D Systems or Thermo Fisher Scientific) or chemiluminescent enzyme immunoassay (R&D Systems). Data from the literature are presented as medians (ranges).

IL-6, interleukin-6; IL-10, interleukin-10; IFN-γ, interleukin-γ; PE, plasma exchange; TNF-α, tumor necrosis factor-α.
PD-1 Blockers: Staying Long in the Body and Delayed Toxicity Risks

To the Editor:

The programmed death-1 (PD-1) blockers, nivolumab and pembrolizumab, confer long-term survival benefits in various types of cancer. However, these drugs can induce immune-related adverse events, including those with late onset (Supplementary Table 1). Intriguingly, durable complete response, even after withdrawal of anti-PD-1 therapy, has been reported. In clinical trials, pharmacokinetic monitoring is not frequently conducted after treatment cessation; therefore, it remains unclear how long and how many anti-PD-1 antibodies remain beyond discontinuation. We have been conducting a clinical study to evaluate the pharmacokinetics of PD-1 blockers (methodological details are provided in Supplementary Appendix). So far, 205 patients receiving nivolumab or pembrolizumab have been enrolled, and one patient with lung cancer with sustained nivolumab exposure developed secondary adrenal insufficiency long after discontinuation of treatment, which is described as follows (Fig. 1A).

This 72-year-old man was diagnosed with stage IV lung adenocarcinoma. He was treated with six cycles of nivolumab (3 mg/kg every 2 weeks) as second-line treatment until disease progression, at which point he began treatment with docetaxel plus ramucirumab. After four doses, the patient’s performance status had considerably improved, and a complete response of hepatic metastases and partial responses of the primary lesion and lymph node metastases were confirmed by computed tomography scan. On the ninth infusion (335 days after the start of nivolumab treatment), the patient presented with fatigue, nausea, and anorexia, which resulted in discontinuation of chemotherapy. The next day, the patient visited the emergency room because of severe muscle weakness in the lower limbs, with worsening of the aforementioned symptoms. He was admitted to the hospital, and laboratory tests revealed hypokalemia (5.8 mmol/L), hyponatremia (131 mmol/L), and hypoglycemia (79 mg/dL). Magnetic resonance imaging revealed no pituitary abnormalities. On the ninth day of hospitalization, he was diagnosed with secondary adrenal insufficiency 8.6 months after nivolumab discontinuation. He received intravenous betamethasone (8 mg/day for 6 days) followed by oral dexamethasone (8 mg/day) with subsequent tapering. His symptoms and eosinophilia rapidly resolved with glucocorticoid replacement. He was discharged after 16 days of hospitalization and palliative care was given to the patient.

The peak (55.3 μg/mL) and trough (~60 μg/mL) plasma concentrations of nivolumab were similar to those reported in previous clinical trials (Fig. 1A). Nivolumab concentrations after discontinuation seemed to decline log-linearly with a slow elimination half-life (T1/2, 40.3 d; Fig. 1B, Supplementary Fig. 1). Notably, nivolumab (0.2 μg/mL) was still detectable at diagnosis. Anti-nivolumab antibody was negative throughout follow-up.

Our overall study population of patients who had discontinued treatment demonstrated persistent drug

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References