Anesthesia and surgical procedures can lead to abnormalities in liver function. The effects of volatile anesthetic drug-induced liver injury (VA-DILI) can range from asymptomatic abnormal liver function tests to fatal hepatic failure [1-3]. Although modern volatile anesthetics have significantly reduced the incidence of hepatic toxicity, the risk of VA-DILI has not completely disappeared, even with the use of agents like sevoflurane and desflurane. Most hypotheses on the mechanism of VA-DILI are based on the production of metabolites causing immunoallergic reactions in patients [4,5]. Diagnosing VA-DILI involves ruling out the other common causes of hepatic failure. Here, we present a case that strongly suggests sevoflurane-related DILI. This study was exempted from review by the Institutional Review Board.

### CASE REPORT

A 69-year-old male patient underwent surgery under local anesthesia for a right breast mass a month earlier. He was hospitalized for nipple-sparing total mastectomy under general anesthesia due to suspicion of malignancy on the excisional mass biopsy and positron emission tomography-computed tomography (CT). He was diagnosed with diabetes 5 years earlier, and it was well-controlled with medication without complications. The patient had a history of knee surgery 15 years ago but did not remember the anes-
thetic method used at that time. The patient was 167 cm tall, weighed 70 kg, had a body mass index of 25.09 kg/m², and was considered slightly overweight. He had no history of atopy or allergies and no kidney dysfunction. The patient did not undergo chemotherapy before surgery, but chemotherapy and/or radiation therapy were planned depending on the surgical results. The preoperative laboratory findings were normal, including liver function tests (aspartate aminotransferase [AST] 37 IU/L, alanine aminotransferase [ALT] 28 IU/L, and total bilirubin 0.8 mg/dl) (Table 1). Cefbuperazone sodium 1,000 mg (Tomiporane 500 mg, one vial) was administered intravenously as a preoperative antibiotic before entering the operating room. Blood pressure (left upper arm) at the operating room was 130/76 mmHg. Pulse rate (67 beats/min) and O₂ saturation (100%) were also assessed.

Anesthesia induction was performed with propofol 120 mg, fentanyl 50 mcg, rocuronium 50 mg, sevoflurane 3 vol%, and mask ventilation for 1–2 min, followed by 7.5 mm inner diameter endotracheal tube intubation. The patient’s vital signs after induction were blood pressure 140/90 mmHg, pulse 83 beats/min, end-tidal CO₂ (ETCO₂) 37 mmHg, and oxygen saturation 100%. After intubation, the tidal volume and respiratory rate were adjusted to achieve an ETCO₂ of 30–35 mmHg, and the fresh gas flow rates of O₂ and air were each set to 1.5 L/min. Blood pressure was measured every 5 min using a noninvasive blood pressure (NIBP) monitor. After inducing anesthesia, the surgeon adjusted the patient’s position for right breast surgery and proceeded with the surgical preparation. During this process, blood pressure, which was set to be automatically measured again after 5 min, went unchecked. We suspected an error in the blood pressure measurement due to the movement of the patient’s body for proper surgical positioning. However, oxygen saturation was maintained at 100%, ETCO₂ was 34 mmHg, and the heart rate was stable at 63 beats/min without significant fluctuation. After positioning the patient appropriately for surgery, blood pressure was measured using the NIBP monitor. Blood pressure was 75/50 mmHg, and ephedrine 5 mg was injected intravenously. During this period, no hemodynamic instabilities, such as tachycardia or desaturation, were observed. A subsequent blood pressure measurement was 89/60 mmHg (Table 2). The operation was started 30 min after anesthesia induction. Intraoperative blood pressure was stably maintained between 130–95/70–60 mmHg and the heart rate between 60–80 beats/min. The total duration of sevoflurane anesthesia was 80 min. The dose of sevoflurane was adjusted to keep the bispectral index of the patient between 40 and 60. The mean alveolar concentration (MAC)

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**Table 1. Liver Function Test Results**

<table>
<thead>
<tr>
<th>Time of test</th>
<th>AST (IU/L)</th>
<th>ALT (IU/L)</th>
<th>ALP (IU/L)</th>
<th>T. Bilirubin (mg/dl)</th>
<th>r-GTP (IU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Op</td>
<td>37</td>
<td>28</td>
<td>82</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>5 h after surgery</td>
<td>1,417</td>
<td>2,176</td>
<td>231</td>
<td>3,8</td>
<td></td>
</tr>
<tr>
<td>7 h after surgery</td>
<td>1,501</td>
<td>2,556</td>
<td>254</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>POD 1</td>
<td>922</td>
<td>1,869</td>
<td>247</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>POD 3</td>
<td>786</td>
<td>1,770</td>
<td>241</td>
<td>3.9</td>
<td>560</td>
</tr>
<tr>
<td>POD 5</td>
<td>761</td>
<td>1,629</td>
<td>217</td>
<td>4.4</td>
<td>473</td>
</tr>
<tr>
<td>POD 10</td>
<td>537</td>
<td>786</td>
<td>187</td>
<td>2.5</td>
<td>306</td>
</tr>
<tr>
<td>POD 20 (discharge)</td>
<td>94</td>
<td>67</td>
<td>132</td>
<td>1.0</td>
<td>138</td>
</tr>
</tbody>
</table>


**Table 2. Hemodynamic Changes**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-induction</th>
<th>After induction</th>
<th>Post-induction</th>
<th>After iv. E. injection</th>
<th>5 min after iv. E. injection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 min</td>
<td>10 min</td>
<td>15 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP (mmHg)</td>
<td>130/70</td>
<td>140/90</td>
<td>110/70</td>
<td>NC</td>
<td>89/60</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>67</td>
<td>83</td>
<td>69</td>
<td>63</td>
<td>62</td>
</tr>
<tr>
<td>ETCO₂ (mmHg)</td>
<td>NC</td>
<td>37</td>
<td>34</td>
<td>34</td>
<td>35</td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

was maintained between 0.9 and 1.1 during the entire procedure. During surgery, 600 ml of plasma solution was intravenously administered, and the amount of bleeding was small (200–300 ml).

After 20 min of observation in the postanesthesia care unit, the patient was moved to the ward. No problems occurred other than complaints of mild surgical site pain. Routine laboratory examinations conducted 5 h after surgery revealed abnormal liver function test results, including elevated AST at 1,417 IU/L, ALT at 2,176 IU/L, and total bilirubin at 3.8 mg/dl (Table 1). Consequently, the administration of antibiotics or painkillers that might affect liver function was immediately discontinued, and the liver function tests were repeated. The reexamination revealed even higher levels (AST, 1,501; ALT, 2,556 IU/L; and total bilirubin 4.1 mg/dl), leading to the administration of hepatotonics both intravenously and orally. At the same time, the blood urea nitrogen, creatinine, and blood coagulation test results (prothrombin time/international normalized ratio and activated partial thromboplastin time) were within the normal ranges. On the third day after surgery, the liver values were still elevated (AST/ALT 786/1,770 IU/L, total bilirubin 3.9 mg/dl, and gamma-glutamyl transferase 560 IU/L) (Table 1), and the patient presented with symptoms of mild icteric sclera, fatigue, and pruritus. The patient was transferred to the hepatology department for accurate cause identification and treatment. Laboratory investigations (virology, serology, and autoimmunity) were negative for the common etiologies of acute hepatitis. Ultrasound examination and abdominal CT findings were unspecific except for multiple hepatic cysts and renal cysts. If the AST, ALT, and bilirubin levels continued to rise, magnetic resonance cholangiopancreatography or other interventions, including liver biopsy, were considered. However, the patient’s general condition was not serious, and the liver function test results improved steadily (10 days after surgery the AST/ALT ratio was 537/786 IU/L) (Table 1). Also, the patient desired outpatient treatment after discharge, so no further evaluations were performed. He was discharged on the 20th day after surgery. After discharge, the patient underwent radiotherapy for breast cancer and also visited the internal medicine clinic for regular liver function monitoring. Medical treatment and follow-up liver function examinations were terminated 6 months after surgery. In our patient’s case, after excluding other causes that may lead to postoperative hepatic dysfunction, VA-DILI due to sevoflurane was concluded.

### DISCUSSION

Several factors may play a role in the development of post-anesthetic hepatic dysfunction, including a decrease in oxygen supply to the liver as a result of hypoxia and/or hypoperfusion, direct liver compression during surgery, viral hepatitis, transfusion, preexisting hepatic dysfunction, and the use of hepatotoxic drugs [3,4]. A diagnosis of VA-DILI requires the exclusion of other common causes of hepatic dysfunction after surgery. In our case, there were no episodes of transfusion, surgical handling of the liver, or preexisting hepatic dysfunction. The patient had no history of viral hepatitis, and no signs of hepatic dysfunction were found in the routine preoperative assessments. Laboratory findings were negative for the common etiologies of acute hepatitis.

Cefbuperazone sodium, a type of cephalosporin antibiotic, was administered intravenously as a preoperative antibiotic before entering the operating room. Cephalosporin antibiotics comprise an important proportion of drugs leading to DILI. However, DILI from cephalosporin is uncommon and characteristically manifests as a cholestatic abnormal liver biochemistry pattern that occurs at least one week after drug administration [6]. Therefore, the possibility of antibiotic-induced hepatotoxicity was ruled out in our case. During the induction of anesthesia, the patient was administered 50 mcg of fentanyl intravenously, and an additional 50 mcg of fentanyl was administered in the recovery room due to complaints of pain. The patient was prescribed an intravenous administration of ketorolac thromethamine 30 mg as needed for pain management, but it was not administered as the patient did not complain of pain. For antibiotics, cefbuperazone sodium was prescribed after surgery, but it was not administered before the laboratory tests.

Initially, the cause of postoperative hepatic dysfunction in our patient was assumed to be hypoxic hepatopathy (variably termed shock liver or ischemic hepatitis) or VA-DILI, and each was examined accordingly.

Hypoxic hepatopathy is a frequent cause of marked serum aminotransferase elevations and most commonly occurs as a result of arterial hypoxemia and insufficient hepatic perfusion [7-9]. The development of hypoxic hepatopathy seems to follow a “two-hit” process. First, the liver is already at risk—typically due to passive congestion—then, it undergoes a second hit when it experiences hemodynamic compromise, a situation where the blood flow and pressure are abnormal [7]. The diagnosis is usually based on biochemical findings due to the absence of symptoms and signs. A rea-
sonable clinical definition is as follows: a syndrome with rapid and transient (5–25 days) increases in either AST or ALT to levels more than 10 times the upper limit of normal with or without LDH elevations in the setting of cardiac, circulatory, or respiratory failure [7–9]. It has been suggested that AST concentrations are higher in zone 3, resulting in greater AST level elevations in ischemic hepatitis compared with ALT levels [7]. These findings are different from those in our patient. A diagnosis of hypoxic hepatopathy is made from characteristic biochemical findings and histological evidence of centrilobular necrosis, rapid resolution of pathology (within 7–10 days) and exclusion of other hepatic pathologies. In the case of this patient, we first suspected hypoxic hepatopathy because the liver enzyme levels increased rapidly immediately after surgery. In our case, the patient underwent surgery without experiencing excessive bleeding, which would necessitate large volumes of fluids or transfusions. Additionally, there were no signs of hemodynamic instability during surgery. Although there was a time when blood pressure was not checked for about 10 min, no symptoms indicative of hemodynamic instability were present (Table 2). Aside from well-controlled diabetes, the patient had no serious cardiac disease, respiratory disease, or events that could cause hypotension. Therefore, sustained hypotension during the periods when blood pressure was not monitored was unlikely. Considering these factors, we determined that the possibility of hypoxic hepatopathy was very low.

Volatile anesthetics are commonly used halogenated agents, which are a recognized cause of drug-induced liver injury. The exact mechanisms and risk factors of VA-DILI are unknown, but the possible mechanisms are likely to be immunoallergic [10–12]. After halothane, next-generation halogenated anesthetics, including enflurane, isoflurane, desflurane, and sevoflurane, were introduced. These new halogenated anesthetics have different molecular structures and are associated with less hepatotoxicity. Sevoflurane, the newest halogenated anesthetic, became available in 1995. Studies have indicated that its administration is not associated with elevated ALT and AST levels [5,13,14]. Unlike other halogenated anesthetic agents, sevoflurane is not metabolized to hepatotoxic trifluoroacetyl proteins. In addition, hexafluoroisopropanol, which consists of 85% organic metabolites, has a low binding affinity for liver macromolecules and is, therefore, rapidly converted to glucuronidates, which are excreted in the urine [5,10]. In addition to liver damage caused by metabolites, inhaled anesthetics reduce hepatic blood flow through changes in the cardiovascular system, such as decreased cardiac output, which can cause secondary liver damage [11,12]. However, sevoflurane was reported to not only be effective in preserving hepatic blood flow but also to increase hepatic blood flow in pediatric patients who had previously had significant decreases in hepatic blood flow [13,14]. Sevoflurane maintained hepatic blood flow and oxygen delivery at concentrations less than 2.0 MAC, comparable to results observed with isoflurane [13,14]. Interestingly, new studies demonstrated that sevoflurane pretreatment exerted a protective effect on hepatic ischemia/reperfusion injury, which is a common problem in hepatic surgery [14].

Contrary to these findings, some studies showed that VA-DILI is not rare, even though most cases are mild and not clinically significant [10,15]. Clinical findings show that VA-DILI typically results in elevated ALT levels within 2 to 14 days after surgery. However, in the case of this patient, liver damage occurred immediately after surgery. A prospective study reported that the type of liver injury associated with halogenated anesthetics, such as sevoflurane, is usually hepatocellular and occurs within a day or two after exposure [15]. While it varies by hospital, in cases where there are no past medical problems or events during surgery, postoperative routine laboratory tests are often not conducted immediately after surgery. Therefore, it can be surmised that liver damage may occur right after surgery but might go undetected. Additionally, it is important to note that VA-DILI is largely based on past studies with halothane, the biotransformation of these volatile anesthetics, and case reports. Little research has been conducted on modern volatile anesthetic agents. Unlike other halogenated anesthetics, sevoflurane is not metabolized to hepatotoxic metabolites. Thus, liver damage caused by other mechanisms should be considered, and further research is needed on this.

This condition can present a range of symptoms, varying from asymptomatic derangement in liver biochemistry to acute severe hepatitis, and rarely, it may lead to fatal hepatic necrosis [1,3,4]. The patients are usually asymptomatic. Thus, relying solely on clinical signs and symptoms to diagnose of DILI means that only very severe cases are detected [10,15]. Furthermore, surgery per se may cause changes in liver function regardless of the type of anesthesia [2,12,14]. Using serological tests together with clinical and epidemiological criteria would help to distinguish VA-DILI and other causes of hepatitis [14,15]. The known risk factors of VA-DILI include re-exposure, middle age, female sex, obesity, renal failure, atopy, and multiple drug allergies. However, most of
these factors were identified in studies of hepatotoxicity related to halothane exposure. More data on modern volatile anesthetic agents should be collected.

After ruling out other causes of liver injury, we concluded that this case was VA-DILI. Unlike other halogenated anesthetics, sevoflurane is not metabolized to hepatotoxic metabolites. However, very few reports have announced liver injury after sevoflurane anesthesia. We present a case of VA-DILI after sevoflurane exposure in a relatively healthy male patient. Although VA-DILI is very rare, we should be aware of VA-DILI following the use of halogenated anesthetics. More research and attention are needed regarding liver function abnormalities after anesthesia.

FUNDING

None.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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