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Desflurane Hepatitis Associated with Hapten and Autoantigen-Specific IgG4 Antibodies

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Abstract

BACKGROUND—Three cases of drug-induced liver injury (DILI) have been reported after desflurane anesthesia. However, no previous reports have detected serum autoantibodies such as that reported with DILI from halothane or isoflurane.

METHODS AND RESULTS—We describe the first documentation of cytochrome P450 2E1 IgG4 autoantibodies, as well as 58 kDa endoplasmic reticulum protein and trifluoroacetyl chloride hapten-specific IgG4 antibodies, in a patient who developed DILI after desflurane anesthesia.

CONCLUSIONS—These findings suggest that allergic and autoimmune mechanisms have critical roles in the development of desflurane DILI.

We describe the first documentation of cytochrome P450 2E1 IgG4 autoantibodies, as well as 58 kDa endoplasmic reticulum protein and trifluoroacetyl chloride hapten-specific IgG4 antibodies in a patient who developed hepatitis after desflurane anesthesia. These findings suggest that allergic and autoimmune mechanisms have critical roles in the development of desflurane-induced liver injury.

CASE REPORT

A 22-yr-old female patient weighing 56 kg and 156 cm tall underwent an uneventful exploratory laparotomy and left oophorectomy for ovarian cysts and adnexal torsion. After administration of oxygen, general anesthesia was induced IV with propofol (175 mg), fentanyl (150 micrograms), and rocuronium (35 mg) and maintained with 6%–8% desflurane in air plus oxygen for approximately 85 min. The patient was discharged home the next day.

Sixteen days later, the patient developed fever and nausea. On postoperative day 17 she developed dark urine, followed by 2–3 days of pruritis, severe nausea, vomiting, and dehydration. On postoperative day 21 she developed jaundice and was admitted to the

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Conflicts of Interest: Dr. Eger is a paid consultant to Baxter Healthcare Corporation, the manufacturer of desflurane.

hospital. Her only medication was oral contraceptives. She had no history of blood transfusions, a negative human immunodeficiency virus test and had received the hepatitis A vaccine. She had had a tonsillectomy and adenoidectomy under general anesthesia six years before. The details of the anesthetic are unknown.

The patient was presumptively diagnosed with jaundice from cholecystitis. She had an unremarkable abdominal ultrasound wherein no gall stones were visualized, a normal lipase 245 U/L (normal 114–286) but abnormal liver function tests: aspartate aminotransferase 167 U/L (normal 15–37), alanine amino-transferase 347 U/L (normal 30–65), alkaline phosphatase 376 U/L (normal 50–136), and total bilirubin 6.2 mg/mL (normal 0.2–1). Infectious and autoimmune hepatitis screens were negative for hepatitis A IgM, hepatitis B core IgM, hepatitis B surface antigen, hepatitis C antigen, antinuclear antibody, antimitochondrial antibody, antimicrosomal antibody, and antismooth muscle antibody. She received IV rehydration, diphenhydramine for pruritis, and ursodiol for cholestasis. She was discharged on hospital day 3.

The patient's serum was tested in three enzyme-linked immunosorbent assays to detect 58 kDa endoplasmic reticulum protein (ERp58), cytochrome P450 2E1 (CYP2E1), and trifluoroacetyl chloride (TFA)-specific IgG4 antibodies, as previously described for volatile anesthetic-induced hepatitis (1). The serum contained significantly increased IgG4 subclass autoantibodies to ERp58 (0.329 OD) and CYP2E1 (0.730 OD), as well as increased TFA antibodies (1.029 OD) more than two standard deviations above control values (0.310, 0.654, and 0.279 OD, respectively). These results support the diagnosis of desflurane drug-induced liver injury (DILI).

DISCUSSION

Idiosyncratic DILI is the third most common cause of acute liver failure in the United States. Volatile anesthetics are a relatively rare cause (2,3). Nonetheless, a type of DILI develops in susceptible individuals from one to three weeks after exposure to volatile anesthetics, most commonly halothane or isoflurane, with rare reports after desflurane (4,5). Certain risk factors have been associated with DILI: previous exposure to volatile anesthetics, female gender, and history of autoimmune diseases (6). Anesthetic DILI is diagnosed only after infectious and autoimmune liver diseases have been excluded. The presentation of our patient 16 days after desflurane exposure, female gender, and absence of infectious or primary autoimmune liver disease supports the diagnosis of desflurane DILI.

One constant challenge with reports of desflurane DILI has been the absence of circulating TFA antibodies or autoantibodies to native proteins (4,5), such as those associated with halothane or isoflurane DILI (1,7,8). One previous report of suspected desflurane DILI was associated with antibodies to liver proteins from halothane-treated rats (9), but no previous report has demonstrated CYP2E1 and ERp58 autoantibodies.

The concept of IgG autoantibodies as confirmation of anesthetic DILI has been questioned (10) and CYP2E1 IgG autoantibodies can develop in anesthesiologists exposed to volatile anesthetics without DILI (10,11). A recent study (1) clarifies this apparent controversy, showing that DILI patients develop IgG4 autoantibodies to CYP2E1, whereas asymptomatic exposed anesthesiologists develop IgG1 autoantibodies. These data suggest that IgG4 autoantibodies are specifically associated with active liver disease. Moreover, IgG4 subclass antibodies are typically the least abundant of all of the immunoglobulin subclasses and are intimately associated with signaling of IgE in hypersensitivity reactions and autoimmune diseases. Increased IgG4 subclass antibodies have been associated with inhalant allergies and asthma (12), and autoimmune thyroiditis (13). This strongly suggests that finding

CYP2E1, ERp58, and TFA IgG4 subclass autoantibodies in our patient indicates that allergic and autoimmune mechanisms have critical roles in the development of DILI.

Volatile anesthetic DILI may be an autoimmune response triggered by native hepatic proteins, such as ERp58 (8) and CYP2E1 (7–11), covalently coupled to the TFA hapten formed after oxidative metabolism of volatile anesthetics by CYP2E1 (14,15). A recently described (16) model of TFA hapten-induced hepatitis in mice supports the importance of this mechanism in the development of anesthetic DILI. Moreover, a recent clinical study (1) suggests that CYP2E1 IgG4 autoantibodies in persons with halothane and isoflurane DILI can induce hepatitis through small pathogenic immune complexes that escape detection and clearance by the complement system. Our report supports these findings and suggests that IgG4 autoantibodies to CYP2E1, ERp58, and TFA may result in heterogeneous immune complexes in DILI. In summary, we describe the fourth case of desflurane DILI and provide the first documentation of IgG4 subclass-specific CYP2E1 and ERp58 autoantibodies as well as TFA antibodies.

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