Clinical Case Report

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Acute liver failure caused by occupational exposure to HCFC-123

Two case reports

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Abstract

Rationale: Hydrochlorofluorocarbon 123 (HCFC-123, Freon123; 2,2-dichloro-1,1,1-trifluoroethane) has been widely used in refrigeration and heat-transfer applications as a substitute for chlorofluorocarbons due to its lower ozone-depleting potentials. Occupational exposure to HCFC-123 may cause mild reversible hepatoxicity, but no fatal cases have been reported yet.

Patient concerns: In this report, we present cases of severe hepatitis with fatal outcome by HCFC-123. Two industrial workers from a manufacturing factory of fire extinguishers which use HCFC-123 were presented with diarrhea, fever, myalgia, and jaundice. Patients had been repeatedly exposed to the liquid form of HCFC-123 for the past three weeks before flare of symptoms.

Diagnosis: The blood biochemistry tests showed acute cholestatic hepatitis and liver biopsy findings indicated inflammatory hepatocellular injury. The diagnosis of HCFC-123 induced hepatitis was made.

Interventions: The treatment for both patients were generally supportive. The second patient went through hemodialysis, ventilatory care, and artificial liver support therapy (molecular adsorbent recirculating system) at intensive care unit.

Outcomes: One patient recovered uneventfully, whereas the other patient showed rapid deterioration leading to acute liver failure complicated with cerebral edema, subdural hemorrhage, and death on hospital day 10.

Lessons: The HCFC-123-induced hepatitis showed similarities with halothane hepatitis, both of which may share pathophysiologic mechanisms. Exposure to HCFC-123 needs to be listed as a potential cause of acute liver failure, and to be considered in patients with acute hepatitis of uncertain etiology and negative viral serology.

Abbreviations: AEL = acceptable exposure limit, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CFCs = chlorofluorocarbons, eGFR-CKD-EPI = estimated Glomerular Filtration Rate – Chronic Kidney Disease - Epidemiology Collaboration, HCFC-123 = 2,2-dichloro-1,1,1-trifluoroethane, aka hydrochlorofluorocarbon 123 (HCFC-123), HCFC-123 = Hydrochlorofluorocarbon 123, LOAEL = lowest-observed-adverse-effect level, MARS = molecular adsorbent recirculating system, SDH = subdural hematoma, TWA = time-weighted average.

Keywords: acute liver failure, HCFC-123, toxic hepatitis

Editor: N/A.

There are no prior publications or submissions with any overlapping information, including studies and patients.

Data sharing is not applicable to this article, because no datasets were generated or analyzed during the present study.

Written informed consent was obtained from the patient 1 and the parent of patient 2 for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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1. Introduction

2,2-dichloro-1,1,1-trifluoroethane, aka hydrochlorofluorocarbon 123 (HCFC-123) or Freon-123, has been widely used for a solvent, refrigerant, and aerosol propellant as a substitute for chlorofluorocarbons (CFCs) due to its relatively shorter atmospheric half-life and lower ozone-depleting potentials than CFCs.[1] However, repeated occupational exposures to HCFC-123 vapors may cause liver injuries.[2] Previous reports of HCFC-123-associated acute hepatotoxicity showed benign course with complete recovery,[3–6] and grave hepatic outcome has not been reported yet.[7,8] Recently, we had 2 cases of industrial workers who presented with severe acute liver injury mimicking viral hepatitis after exposure to HCFC-123, and 1 of the patients died of acute liver failure and cerebral edema. This report presents the clinical courses and discusses the potential of severe hepatic injury caused by HCFC-123.

2. Case report

2.1. Case 1

A 21-year old male was referred to the emergency room for symptomatic acute hepatitis. He had been working at a fire extinguisher manufacturer for three weeks prior to admission. He

was involved in the manufacturing process for 8 hours a day, 5 days a week. Specifically, the work involved putting fire extinguisher tank on the conveyer belt and charging with nitrogen gas. He began to experience mild abdominal discomfort and intermittent diarrhea during the first week at work. Four days before admission, sudden fever developed up to 39°C with chill, myalgia, abdominal bloating, nausea, and headache. The history of alcohol and drug abuse was denied. The body mass index was 21.6 kg/m^2 and body temperature was 39.1°C. Physical examination showed diffuse tender hepatomegaly. The initial test revealed high aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels (2491 IU/L and 2335 IU/L, respectively). Total and direct bilirubin levels were 3.4 and 2.3 mg/dL, respectively, and PT INR was 1.51. BUN and creatinine levels were 10 and 0.83 mg/dL, respectively. Serology for hepatitis A, B, C, E, Herpes Simplex virus, Varicella Zoster virus, Rubella, Treponema antigen, Hantaan virus antibody, Leptospira Ab, *R. tsutsugamushi* Ab were all negative. His liver function further deteriorated during the subsequent 2 days, with AST and ALT level reaching up to 3108 and 3265 IU/L, respectively, and then spontaneously improved (Fig. 1A, upper panel). Transjugular liver biopsy performed on hospital day 6 showed lobular disarray, multifocal spotty and confluent necrosis. Mixed inflammatory cells infiltrated portal tracts and lobules, especially with abundant eosinophils (Fig. 2). All symptoms resolved gradually, and the patient was discharged uneventfully on hospital day 8.

Informed consent for the publication of the case details was obtained from the patient after recovery.

2.2. Case 2

The second patient was 21-year old male patient who had started working at the same facility 4 days earlier than patient 1. His job and working hours were similar to that of patient 1, except that the patient 2 did more work of valve assembly, which is located closer to the automatic HCFC-123 injector. The patient also experienced intermittent diarrhea for 3 weeks, followed by fever, nausea and vomiting 5 days before admission. The history of alcohol and drug abuse was denied. The body mass index was 27.1 kg/m^2 and body temperature was 37.5°C. Physical examination showed diffuse tender hepatomegaly. The con-

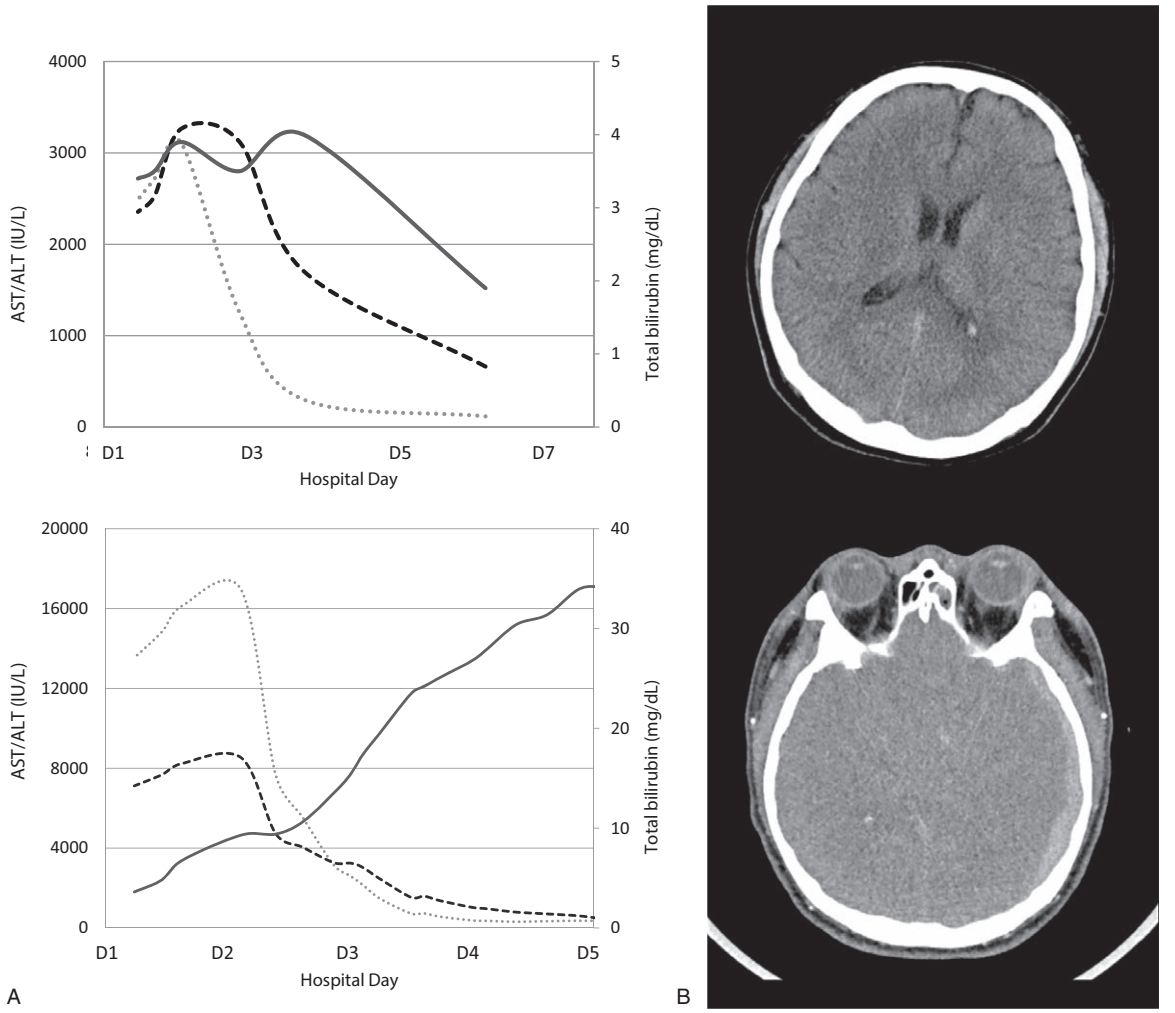

Figure 1. Clinical courses and laboratory findings of two patients who were exposed to HCFC-123 at the same workplace. (A) Clinical courses of liver function tests of 2 patients. *Gray, dotted line* represents AST, *black jagged line* represents ALT, and *solid line* represents the level of total bilirubin. AST and ALT level declined after the acute toxic phase, however total bilirubin level of the patient 2 continued to rise to 34.1 mg/dL. (B) Brain CT of Patient 2 showed slight degree of swelling on Hospital day 3 (upper panel), and CT scans on day 5 revealed diffuse brain edema with subdural hemorrhage (lower panel). ALT = Alanine transferase, AST = Aspartate transferase.

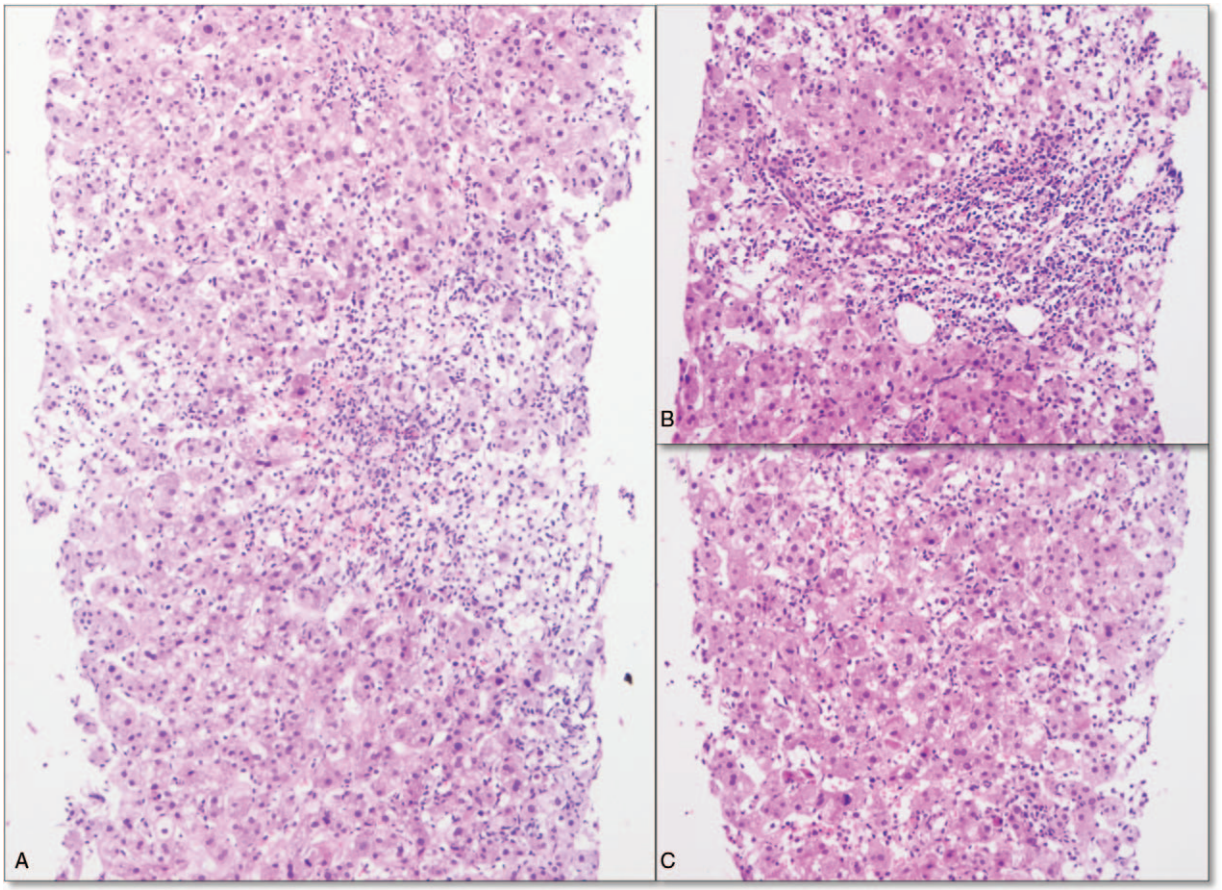

Figure 2. Microscopic findings of transjugular liver biopsy in patient 1. The core of liver biopsy shows marked lobular hepatitis with multifocal spotty and confluent necrosis (A, hematoxylin and eosin, ×100). The portal tracts are also infiltrated by mixed inflammatory cells including fair numbers of eosinophils (B, hematoxylin and eosin, ×200). The lobular architecture of the liver is distorted with parenchymal loss and hepatocytes damaging (C, hematoxylin and eosin, ×200).

sciousness was clear and neurologic examinations gave negative results at initial assessment in the emergency department. The AST and ALT levels were 13,537 and 7115 IU/L, respectively, and total and direct bilirubin levels were 3.6 and 2.4 mg/dL, respectively. PT INR was 2.29. The BUN and creatinine levels were 43 and 4.04 mg/dL, respectively, and eGFR-CKD-EPI (estimated Glomerular Filtration Rate – Chronic Kidney Disease - Epidemiology Collaboration) of 19.7 mL/min, showing acute kidney injury. Serology for hepatitis A, B, C, E, Herpes Simplex virus, Varicella Zoster virus, Rubella, Treponema antigen, Hantaan virus antibody, Leptospira Ab, *R. tsutsugamushi* Ab were all negative. His liver and kidney function deteriorated progressively (Fig. 1A, lower panel) and the patient became semi-comatose with response only to pain stimuli on hospital day 3. His brain CT showed mild cerebral edema (Fig. 1B, upper panel). He was transferred to the Medical Intensive Care Unit and managed with hyperventilation, intravenous mannitol, and continuous renal replacement therapy, without improvement of consciousness. Artificial liver support therapy (molecular adsorbent recirculating system; MARS) was applied while waiting for liver transplantation. Despite 2 sequential sessions of MARS treatment on 3 and 4 days after admission, there was no reduction in serum bilirubin or ammonia levels, suggesting treatment failure. The patient's course was further complicated by the development of subdural hematoma (SDH) on hospital day 5 (Fig. 1B, lower panel). The electroencephalogram showed very low voltage with minimal rhythm, and the patient died on hospital day 10.

Informed consent was obtained from the father of the deceased patient.

3. Discussion

Since Hoet et al reported epidemic liver injuries by accidental exposure,[3] the potential of dose-dependent hepatotoxicity of to HCFC-123 has been increasingly recognized. The lowest-observed-adverse-effect level (LOAEL) of inhalation is reported to be 30 ppm (188 mg/m^3) and 300 ppm (1880 mg/m^3) for liver and central nervous system, respectively.[2] The manufacturer of HCFC-123 has presented the acceptable exposure limit (AEL) as 50 ppm, and prohibited the use of HCFC-123 as an uncontained flushing fluid in refrigeration work or as a general cleaning solvent.[9] American Society of Heating, Refrigerating, and Air Conditioning Engineers recommends that monitoring is required to keep the HCFC-123 concentration below 150 ppm, and that personal protective equipment be provided at a level above AEL. The personal protective equipment includes coverall chemical goggles, a face shield, steel-toe shoes, butyl rubber gloves, and accessible emergency safety showers in case of acute exposure.[10] Korean government allowed for the use of 100% HCFC-123 as fire extinguisher solvents in defiance of "The Montreal Protocol on Substances that Deplete the Ozone Layer" and exhortative

interview with the national fire agency in 2003. Moreover, the workplace of our patients was not furnished with effective local ventilation or monitoring system and none of the protective gears were provided to our case patients although the work included assembling nozzles and pouring HCFC-123 solvents into the fire extinguisher for more than 8 hours each day, during which the patients experienced liquid HCFC-123 splash over facial skin and eyes. After the death of the patient 2, assessment of the workplace was performed by the Korean Ministry of Employment and Labor. The results showed that the time-weighted average (TWA) calculated concentration was 19.1 to 20.9 ppm at the site of acute poisoning accidents, which were significantly higher than the recommended occupational limits, 10 ppm, at Finland and Japan.[11] We believe that exposure of very high concentration through skin and conjunctiva may have contributed to the fatal clinical course of our patient.

Clinical features of our cases mimic halothane hepatitis: fever, acute hepatitis, eosinophilic infiltration, and fulminant hepatic failure.[12] In addition to structural similarity, the 2 chemicals share pathophysiologic mechanisms of hepatotoxicity: the role of main metabolite trifluoroacetyl chloride, possible involvement of autoimmunity, and eosinophilic infiltration.[13,14] Therefore, it may be speculated that HCFC-123 induces 2 patterns of liver disease similar to halothane, that is, milder hepatotoxicity and rare fulminant hepatitis.[12] This hypothesis may explain the different clinical course of the two cases, although underlying fatty liver and differential induction of CYP2E1[15] may have contributed to the contrasting clinical outcomes. The direct cause of death of the patient 2 was presumed as cerebral edema and subdural hemorrhage with increased intracranial pressure as a complication of acute liver failure secondary to toxic hepatitis, but direct cytotoxic cerebral swelling by conjunctival exposure cannot be excluded as a precipitating factor.

Toxic hepatitis may be caused by organic solvents used in industrial processes.[16] Among the industrial hepatotoxins, the significance of HCFC-123 may have been underestimated despite several previous case reports.[5] Since HCFC-123 is nowadays more ubiquitous compared to halothane or carbon tetrachloride, we believe that exposure to HCFC-123 should be considered in patients with acute hepatitis of uncertain etiology. Considering potentially fatal liver injury, unauthorized use of HCFC-123 as cleaning solvents or foam-blowing agents should be strictly prohibited to prevent the exposure beyond the AEL.

In summary, we herein report 2 cases of severe acute hepatitis after occupational exposure to HCFC-123 with fatal outcome. Strict measures should be taken to prohibit unauthorized usage of HCFC-123, and the list of differential diagnosis needs to include HCFC-123 for acute hepatitis with features suggesting viral etiology but negative serology. HCFC-123 should be enlisted as a potential cause of acute liver failure.

Author contributions

HC was the major contributor to the writing of the manuscript. SA performed the histopathological examination of the liver biopsy specimen. HC, GJ, and JK were involved in treating the patients. All the authors read and approved the final manuscript.
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Writing – original draft: Hun Jee Choe.
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