N,N-dimethylformamide-induced acute hepatic failure: A case report and literature review

YUANLI LEI, SHASHA XIAO, SHOUQUAN CHEN, HAIYAN ZHANG, HUIPING LI and YINGRU LU

Department of Emergency Medicine, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang 325000, P.R. China

Received March 6, 2016; Accepted March 3, 2017

DOI: 10.3892/etm.2017.5213

Abstract. N,N-dimethylformamide (DMF) is a major solvent predominantly used in the chemical industry. The main toxic effects following exposure to DMF are gastric irritation, skin eruption and hepatotoxicity. However, hepatic failure induced by DMF is rare. In this report, we present a case of acute hepatic failure following exposure to a toxic dose of DMF via respiratory tract inhalation and skin absorption with detailed abdominal computed tomography scan, sequential laboratory data and polymorphisms. The patient recovered satisfactorily following artificial liver support therapy and pharmacological agents to protect the liver in addition to plasma, blood platelet and albumin transfusions. In view of the high mortality rate and rare occurrence rate of acute hepatic failure, the clinical characteristics, polymorphisms and therapeutic strategy of DMF poisoning are discussed.

Introduction

N,N-dimethylformamide (DMF) is a major solvent predominantly used in the chemical industry. Wenzhou is the largest synthetic leather-producing district in the world, producing ~70% of synthetic leather goods in the domestic market and 50% worldwide (1,2). The primary toxic effects following DMF exposure are gastric irritation, skin eruption and hepatotoxicity. DMF may be metabolized by mixed-function oxidase in the liver to toxic metabolites, including N-acetyl-S-(N-methylcarbamoyl) cysteine, which is one of the principal substances associated with liver injury (3,4).

Previous studies have reported that the severity of liver injury induced by DMF may be directly related to exposure dosage, exposure time and the patient's liver function prior to exposure (5,6). There have been previous case reports of hepatic dysfunction occurring in workers as a result of DMF alone or in combination with other organic solvents (3). DMF-induced liver toxicities include hepatitis, fibrosis, cirrhosis and cancer (3). Treatment strategies for DMF-induced hepatic dysfunction include hepatoprotection, symptomatic treatment and life support (7). However, acute hepatic failure induced by DMF is rare. The present case report describes a patient with acute hepatic failure following exposure to high DMF levels via respiratory tract inhalation and skin absorption over a short period of time. The patient recovered satisfactorily following artificial liver support therapy and other treatments. The clinical characteristics, polymorphisms and therapeutic strategy of DMF poisoning are discussed herein.

Case report

Patient information. The patient was a fit and healthy 38-year-old female who did not consume alcohol. The patient started a job at a synthetic leather factory that manufactured belts using DMF as a solvent in September, 2014. One week later, the patient had a routine physical check-up, including laboratory tests and an abdominal ultrasound, the results of which were all within normal levels.

After 2.5 months, the patient was referred to Pingyang County Hospital (Wenzhou, China) due to symptoms of fatigue, poor appetite, abdominal distention, nausea and jaundice. No specific treatment was administered at this time. The patient's condition worsened 3 days after this hospital visit. The patient subsequently visited The First Affiliated Hospital of Wenzhou Medical University (Wenzhou, China), at which point a physical examination indicated stable vital signs, consciousness, jaundiced skin and sclera, abdominal shifting dullness and edema of both lower limbs; however, there was no splenomegaly. Laboratory data are presented in Table I. The clinical data indicated a serum bile acid level of 435 μmol/l (normal range, 0-12 μmol/l) and hyaluronidase >2,000 ng/ml (normal range, 0-100 ng/ml). The patient tested negative for viral infections with hepatitis A-E. The patient exhibited polymorphisms for the glutathione S-transferase mu-1 (GSTM1)-null genotype and the glutathione S-transferase theta-1 (GSTT1)-positive genotype. The GSTM1 and GSTT1 genotypes were determined by co-amplification of both genes

Correspondence to: Professor Yingru Lu, Department of Emergency Medicine, The First Affiliated Hospital of Wenzhou Medical University, 2 Fuxue Road, Wenzhou, Zhejiang 325000, P.R. China
E-mail: yingrulu66@163.com

Key words: acute hepatic failure, N,N-dimethylformamide, artificial liver support system, case report, abdominal computed tomography scan

Table I. Sequential laboratory data for the patient.

Item	Normal range	Weeks after the patient started her job									
		10.7	10.9	11.3	11.4	12.1	13	14.6	16	18.1	19.3
TBil (μmol/l)	0-20	Admitted to Pingyang	289	Admitted to EICU of	350	344	206	Transferred to	135	63	Discharged from
ALT (U/l)	7-40	County Hospital	621	The First Affiliated	231	58	21	general ward	17	26	hospital
AST (U/l)	13-35		572	Hospital of Wenzhou	150	53	34		32	42	
Alb (g/l)	40-55		29.4	Medical University	25.5	30.8	40.8		33.3	29.6	
PT (sec)	11.7-14.8		28.4		28.8	24.4	21.9		19.9	17.3	

TBil, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Alb, albumin; PT, prothrombin time; EICU, emergency intensive care unit.

using polymerase chain reaction (PCR). DNA was extracted from whole peripheral blood using a whole blood genomic DNA extraction kit (Tiangen Biotech Co., Ltd., Beijing, China) according to the manufacturer's protocol. PCR was performed in a 25 μl mixture containing 100 ng genomic DNA and 1 μl each of forward and reverse primers as previously described (8). Primers were as follows: GSTM1 forward, 5'-GAACTCCCTG AAAAGCTAAAGC-3' and reverse, 5'-GTTGGGCTCAAAT ATACGGTGG-3'; GSTT1 forward, 5'-TTCCTTACTGGTCC TCACATCTC-3' and reverse, 5'-TCACCGGATCATGGCCA GCA-3'. Thermocycling conditions were as follows: 94˚C for 4 min followed by 35 cycles of 94˚C for 40 sec, 62˚C for 30 sec and 72˚C for 40 sec, with a final extension at 72˚C for 10 min. The PCR products were determined by electrophoresis using 2% agarose gels. The amplified fragment length of GSTM1 was 219 bp and the amplified fragment length of GSTT1 was 459 bp (Fig. 1). The Child-Pugh score was 13, which was categorized as class C (9). An abdominal computed tomography (CT) scan was performed on admission, and the results are shown in Fig. 2A. On day 7 after admission, abdominal ultrasound indicated shrinkage of the liver, echogenicity, ascites and splenomegaly.

Following admission, the treatment for this patient included daily intravenous infusions of liver protection agents [magnesium isoglycyrrhizinate (200 mg; Jiangsu Chia Tai Tianqing Pharmaceutical Co., Ltd., Jiangsu, China), polyene phosphatidyl choline injection (10 mg; Chengdu Tiantaishan Pharmaceutical Co., Ltd., Chengdu, China) and ademetionine injection (1,000 mg; Pfizer, Inc., New York, NY, USA)] to alleviate hepatic dysfunction in addition to plasma, blood platelet and albumin transfusions for support and symptomatic treatment. Vital signs and liver function were monitored. The patient's liver function deteriorated despite supportive treatment. On days 8, 12 and 16, an artificial liver support system (ALSS) was implemented. On day 17, the Child-Pugh score was 9, which was categorized as class B (9). From day 9, the patient exhibited a fever, and blood culture and empiric antimicrobial therapy with piperacillin-tazobactam were initiated. The patient reported feeling better on day 22. Her temperature was reduced and liver function had markedly improved. CT re-examination showed an improvement compared with the initial scan (Fig. 2A and B). During hospitalization, the presence of viral infections, including hepatitis A-C was excluded, as were other medication-related causes of hepatitis. At 1 month following the last CT, CT re-examination revealed the low-density shadow had decreased and its border was clear (Fig. 2C). The low-density shadow did not appear on a contrast-enhanced CT scan (Fig. 2D). The patient was discharged 2 months after admission.

Workplace evaluation. A visit to the patient's workplace was conducted in January, 2015. It was observed that the factory comprised a four-floor building that primarily produced raw belts. There were four major areas in the work field: A wet process line on the first floor, a dry process line on the second floor, a storage room on the third floor and a multifunctional room on the fourth floor. The patient had been employed for ~2.5 months on the wet process floor. The wet process involved using large quantities of DMF. The work areas emitted a strong odor and the room was poorly ventilated. Workers were not well

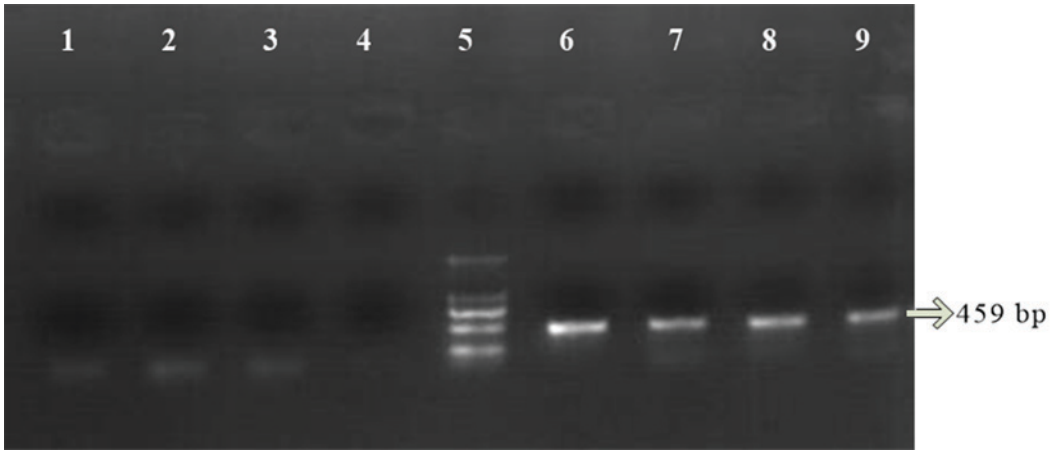

Figure 1. GSTM1 and GSTT1 gene electrophoregram. Lane 5 was the marker (dl 2000). Lanes 1-4 are amplification products of GSTM1. The amplified fragment length of GSTM1 was 219 bp. The outcome was GSTM1-null genotype. Lanes 6-9 are amplification products of GSTT1. The amplified fragment length of GSTT1 was 459 bp (arrows). The outcome was a GSTT1-positive genotype. GSTM1, glutathione S-transferase mu-1; GSTT1, glutathione S-transferase theta-1.

equipped with personal protective devices. The patient worked ~10 h per day. There were 10 workers simultaneously working at the same place. Several co-workers had similar symptoms, such as dizziness, fatigue, abdominal distention and nausea. These workers were also sent to Pingyang County Hospital, where supportive care was administered. After resting for 1 to 2 days, the workers returned to work. Policemen and officials from the Chinese Center for Disease Control and Prevention investigated the factory while the workers were hospitalized. The factory was shut down after it was found that the air DMF concentration in the workplace was 2- to 3-fold above the national standard.

Discussion

There have been several previous reports of hepatic injury from occupational exposure to DMF; however, few reports have described acute hepatic failure induced by DMF. Only 5 cases have been reported in previous articles (Table II) (10-14). In the present case, the diagnosis of DMF-induced acute hepatic failure was based on clinical history (no history of medication use or alcohol intake), symptoms and signs, abnormal liver function and negative hepatitis viral series, as well as high DMF concentrations in the work environment that exceeded legal limits. Several co-workers of the patient also suffered variable degrees of liver dysfunction. Therefore, based on the national standards for occupational disease (7,15), although the body concentration of DMF and pathology were not measured, a relationship between the acute hepatic failure and DMF intoxication was strongly suspected.

It has previously been reported that the severity of liver damage induced by DMF is directly associated with the exposure dosage and time (5,6). According to the current study (Table II), the exposure dosage of this patient was 2- to 3-fold the standard dose; however, the exposure time was relatively short. Moreover, other co-workers who worked in the same work field did not have comparable hepatic dysfunction. The contradiction between DMF-induced severe hepatic damage and low concentrations of environmental DMF and short-term exposure may be explained by individual susceptibility to DMF (6,16). It has previously been reported that

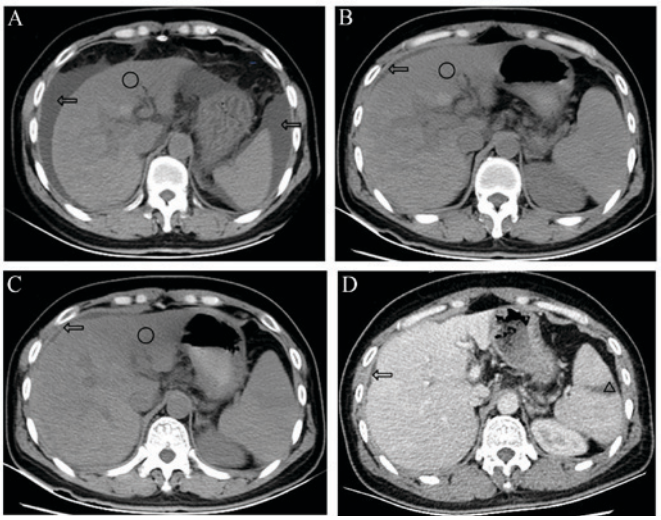

Figure 2. Abdominal CT scans of the patient. (A) Abdominal CT scan on day 5 after admission indicated liver deformation, shrinkage of the liver, border irregularity, a low-density shadow with border blurring (circle), ascites (arrows) and splenomegaly. (B) Abdominal CT scan on day 21 indicated that the size of the liver had recovered, ascites (arrows) were decreased and the low-density shadow (circle) was similar to the previous CT. (C) Abdominal CT on day 52, indicated that the low-density shadow (circle) had decreased and its border was clear, and ascites (arrows) were not present. (D) Contrast-enhanced CT scan on day 54 indicated hepatic cirrhosis, liver deformation, an infarction of the spleen (triangle) and an absence of ascites (arrows). Compared with previous CT scans, the low-density shadow was not evident. CT, computed tomography.

DMF susceptibility may be related to polymorphisms of GSTM1 and GSTT1 (5,8). In the present case, the polymorphism of GSTM1 indicated a null genotype. This was not consistent with the study by Xu *et al* (8), in which induced liver function injury in patients with the GSTM1-positive genotype was 2.3-fold as high as that of individuals with the GSTM1-null genotype in workers exposed to DMF. In the present case, the polymorphism of GSTM1 indicated a positive genotype. This was inconsistent with a previous study that demonstrated that the occurrence of induced liver function injury in patients with the GSTT1-null genotype was 4.4-fold higher compared with patients with the

Table II. Cases of DMF-induced acute hepatic failure.

Author and year	Sex (M/F)	Age (years)	Exposure time (months)	Exposure field (process line)	Air concentration of DMF (mg/m^3)	Clinical characteristics	LF recovery time (months)	ALSS	Outcome	(Refs.)
Shi *et al*, 2004	M	39	3.0	Wet	23.7	Liver dysfunction, poor appetite, jaundice, coma, abdominal distention, nausea, vomiting, and CT indicated low-density shadow in the liver and ascites	1.5	No	Survived	(10)
Liu *et al*, 2009	F	40	2.3	-	41.4-131	Liver dysfunction, fatigue, poor appetite, jaundice, coma, and CT indicated uneven liver density, splenomegaly and ascites	N/A	No	Succumbed	(11)
Ding *et al*, 2011	F	38	0.6	Dry	42	Liver dysfunction, fatigue, poor appetite, jaundice, abdominal pain	N/A	No	Succumbed	(12)
Tong *et al*, 2014	M	23	2.5	-	157.1	Liver dysfunction, fatigue, poor appetite, jaundice, disseminated intravascular coagulation, and CT indicated splenomegaly and ascites	N/A	Yes	Succumbed	(13)
Zhang *et al*, 2015	F	40	2.0	-	131	Liver dysfunction, poor appetite, nausea, fatigue, vomiting, jaundice, and CT indicated uneven liver density, splenomegaly and ascites	N/A	No	Succumbed	(14)
Present case	F	38	2.5	Wet	40-60	Liver dysfunction, fatigue, poor appetite, nausea, jaundice, abdominal distention, and CT indicated low-density shadow in the liver, spleen infarction and ascites	2	Yes	Survived	N/A

Exposure routes in all cases were the respiratory tract and skin. M, male; F, female; LF, liver function; DMF, N,N-dimethylformamide; CT, computed tomography.

GSTT1-positive genotype (5). Thus, severe hepatic injury may be not associated with polymorphisms of GSTM1 and GSTT1. Whether there were other susceptible factors in the current patient requires further investigation.

The clinical presentation of occupational liver disease may be acute/subacute or chronic; however, it is often insidious (17). The common clinical symptoms of DMF poisoning in patients include liver injury, fatigue, nausea, poor appetite, jaundice and ascites (10-14). However, acute hepatic failure may result in high mortality (Table II). Serum liver enzymes, including alanine transaminase, aspartate transaminase and bilirubin levels, are routinely used as indicators of hepatotoxicity (14,17). All of these parameters exhibited high serum concentrations in the current case. However, the most notable indicators in the current patient were serum bile acid and hyaluronidase levels. It has previously been reported that both of these factors are potential indicators of early hepatic fibrosis activities in occupational workers (17,18). The abdominal CT scan of the current patient indicated large, low-density shadow at admission, which markedly improved as the patient received supportive therapy (Fig. 2A-C). A contrast-enhanced CT scan indicated that the low-density shadow had been fully reduced by day 54 (Fig. 2D). It was postulated that the low-density shadow may have been due to fatty degeneration and fibrosis. Different degrees of fatty degeneration and fibrosis are characteristics of toxic hepatitis, which leads to cirrhosis (14,17).

The treatments recommended for acute hepatic failure induced by DMF are non-specific. ALSS has previously been reported to be a safe, effective and important modality for acute and acute-on-chronic liver failure via plasma exchange or absorption mechanisms (19,20). Chen *et al* (21) reported that the initiation of ALSS in patients with liver failure following acute poisoning for an average of 2.7 times every 4 to 5 days improved the survival rate (76.9 vs. 38.9%). A novel method (preconcentration method) has been proposed to increase the adsorption of protein-bound toxins onto adsorbents in ALSS, which may simultaneously reduce cost and shorten the treatment time by two-thirds (22). The combination of active supportive treatment and ALSS provided a good prognosis for the present patient.

In conclusion, DMF is a major solvent predominately used in the chemical industry. The mortality of DMF-induced acute severe hepatitis is high. There is no specific treatment for DMF-induced acute hepatic failure; however, ALSS may be an effective clinical treatment method for these patients.

References

1. Zhang Q, Huang C, Wei Y, Zhu Q, Tian W and Wang C: Risk assessment of N,N-dimethylformamide on residents living near synthetic leather factories. Environ Sci Pollut Res Int 21: 3534-3539, 2014.
2. Wei YM, Tian WL, Zhang QY, Zheng YY, Yang YK, Wu ZC, Zhu Q, Zhou L and Fang SM: Evaluating population exposure to N,N-dimethylformamide in a small industrial area accounting for population movement. J Zhejiang Univ-Sci A 12: 794-806, 2011.
3. Kim TH and Kim SG: Clinical outcomes of occupational exposure to n,n-dimethylformamide: Perspectives from experimental toxicology. Saf Health Work 2: 97-104, 2011.
4. Rui D, Daojun C and Yongjian Y: Liver and heart toxicity due to 90-day oral exposure of ICR mice to N,N-dimethylformamide. Environ Toxicol Pharmacol 31: 357-363, 2011.
5. Luo JC, Cheng TJ, Kuo HW and Chang MJW: Abnormal liver function associated with occupational exposure to dimethylformamide and glutathione S-transferase polymorphisms. Biomarkers 10: 464-474, 2005.
6. Nomiyama T, Uehara M, Miyauchi H, Imamiya S, Tanaka S and Seki Y: Causal relationship between a case of severe hepatic dysfunction and low exposure concentrations of N,N-dimethylformamide in the synthetics industry. Ind Health 39: 33-36, 2001.
7. GBZ 85-2002 . Diagnostic Criteria of Occupational Acute Dimethylformamide Poisoning. Availiable online: http://www.nhfpc.gov.cn/cmsresources/zwgkzt/wsbz/zybzdbz/zyb/zyb/085.pdf (published on 8, April, 2002).
8. Xu CM, Qian YL, Zhu LJ, Xian JX, Chai JR, Ruan Z and Zhang X: Abnormal liver function associated with polymorphism of GSTT1, GSTMI and CYP2El in workers exposed to N,N-dimethylformamide. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi 27: 333-337, 2009 (In Chinese).
9. Kumbasar A, Navdar M, Ataoglu E, Uzunhasan I, Ergen K, Poturoglu S, Basinoglu F, Yilmaz F, Yenigun M, Sar F and Tanriverdi O: N-Terminal pro-B-Type natriuretic peptide levels are linked with modified child-pugh classification in patients with nonalcoholic cirrhosis [NT-ProBNP and Liver Cirrhosis]. Cell Biochem Biophys 75: 111-117, 2017.
10. Shi MG, Li L and Sui YQ: Acute DMF poisoning causes subacute hepatic necrosis: A case report. Chin J Ind Hyg Occup Dis 22: 234-234, 2004.
11. Liu Q, Du F, Tan L, Wang BW and Zhou YW: Occupational DMF poisoning causes death: A case report. Chin J Forensic Med 24: 60-61, 2009.
12. Ding YL, Ying GX and Jin LP: Occupational DMF poisoning causes death: A case report. Occup Health Emerg Rescue 29: 107-108, 2011.
13. Tong Z, Shi J, Zhu X and Zhu B: Death after exposure to dimethylformamide: A case report. Chin J Ind Hyg Occup Dis 32: 285-286, 2014.
14. Zhang H, Liu Q, Duan Y, Dong H and Zhou Y: Chronic occupational N,N-dimethylformamide poisoning induced death: A case report. Forensic Sci Med Pathol 11: 584-588, 2015.
15. GBZ 2.1-2007, 2007. Occupational Exposure Limits for Hazardous Agents in the Workplace. Part1: Chemical hazardous agents. Availiable online: http://www.nhfpc.gov.cn/zhuz/pyl/200704/38838/files/5eb946b479124c32a6ebb8c49f483c24.pdf (published on 12, April, 2007).
16. Wang C, Huang C, Wei Y, Zhu Q, Tian W and Zhang Q: Short-term exposure to dimethylformamide and the impact on digestive system disease: An outdoor study for volatile organic compound. Environ Pollut 190: 133-138, 2014.
17. Malaguarnera G, Cataudella E, Giordano M, Nunnari G, Chisari G and Malaguarnera M: Toxic hepatitis in occupational exposure to solvents. World J Gastroenterol 18: 2756-2766, 2012.
18. He J, Wang P, Zhu JQ, Wu G, Ji JM and Xue Y: Role of urinary biomarkers of N,N-dimethylformamide in the early detection of hepatic injury among occupational exposed workers. Int Arch Occup Environ Health 83: 399-406, 2010.
19. Zhang Z, Zhao YC, Cheng Y, Jian GD, Pan MX and Gao Y: Hybrid bioartificial liver support in cynomolgus monkeys with D-galactosamine-induced acute liver failure. World J Gastroenterol 20: 17399-17406, 2014.
20. Zhou PQ, Zheng SP, Yu M, He SS and Weng ZH: Prognosis of acute-on-chronic liver failure patients treated with artificial liver support system. World J Gastroenterol 21: 9614-9622, 2015.
21. Chen LG, Guleng B, Ren JL, Chen JM and Wang L: Artificial liver support system in treatment of liver failure after acute poisoning. World J Emerg Med 2: 283-286, 2011.
22. Ding W, Zou L, Sun S, Li W and Gao D: A new method to increase the adsorption of protein-bound toxins in artificial liver support systems. Artif Organs 38: 954-962, 2014.