Hepatitis caused by occupational chronic exposure to trichloroethylene

G. Anagnostopoulos[1], G. H. Sakorafas[2], K. Grigoriadis[3], G. Margantinis[1], P. Kostopoulos[1], S. Tsiakos[1], D. Arvanitidis[1]

(1) Department of Gastroenterology ; (2) Department of Surgery and (3) Department of Pathology, 251 Hellenic Air Force (HAF) Hospital, Athens, Greece.

Abstract

Trichloroethylene (TCE) is an organic solvent used in a variety of industries for more than 60 years. Several adverse events following acute or chronic exposure to trichloroethylene have been reported. However, TCE-induced hepatitis is very rare. We present the case of a 55-year old male who was presented with anorexia, fatigue and upper abdominal discomfort. Routine laboratory examination revealed marked elevation of liver enzyme values. All possible causes of hepatitis were ruled out. The patient has been working as a shoemaker, in a small room of a basement, with insufficient air-exchange ; during the last 5 years he used daily a glue containing 1,1,1 trichloroethylene. The diagnosis of hepatitis was confirmed by liver biopsy. The offending agent was withdrawn. Three months later, he was "feeling well" and liver enzyme values had returned to normal. Six months after the initial biopsy, a second liver biopsy was performed and histology was markedly improved. Workers exposed to hazardous chemicals, such as trichloroethylene, must have periodic follow-up examinations. Good work practices are very important when using toxic substances. In patients whose initial diagnostic workout is negative for common causes of acute or chronic hepatitis, toxic causes should be considered, with emphasis on patient's job and working conditions. (Acta gastroenterol. belg., **2004**, 67, **355-357**).

Key words : trichloroethylene, hepatitis, TCE, occupational diseases, liver.

Introduction

Trichloroethylene (TCE) is an organic chemical substance, which does not exist naturally in the environment. It is a nonflammable, colorless liquid at room temperature, used as a solvent in a variety of industries for more than 75 years (1). Nowadays, it can be found in some household products, including typewriter correction fluid, paint and adhesive removers or cleaning solutions. TCE has caused adverse health effects on the central and peripheral nervous system, the skin, the kidney, the liver, and the heart. We report the case of a 55-year-old male who presented with clinical, laboratory, and histological features of hepatitis following chronic TCE exposure. Clinical, biochemical and histological remission was observed 6 months after TCE withdrawal. The literature is briefly reviewed.

Case report

A previously healthy 55-year old male was referred to our department because of anorexia, fatigue, and upper abdominal discomfort. The patient was not "feeling well" during the last two years but he attributed his symptoms to the fact that he was working many hours every day, and he never asked for medical assistance. Clinical examination revealed a mild discomfort at palpation of the right-upper quadrant. Routine laboratory examination showed a marked elevation of liver enzymes (ALT 875 IU/L, AST 224 IU/L, ALP 284 IU/L, GGT 437 IU/L) and bilirubin (total, 3 mg/dl, and direct 2.4 mg/dl) (Table 1). Abdominal ultrasound showed heterogeneity of the hepatic parenchyma without evidence of portal hypertension, ascitic fluid, or bile duct dilatation. The patient was taking no medications. He reported no ethanol use during the weekdays, and moderate use (only 1-2 bottles of beer) during the weekend. He was heterosexual and denied any intravenous drug use. Blood tests for hepatitis A, B, and C viruses, CMV and EBV were negative, and therefore viral etiology was excluded. Tests for ANA, AMA, ASMA were also negative, and serum values of ceruloplasmin and antitrypsin were within normal limits. The patient was working as a shoemaker for about 30 years, and during the last 6 years he used a glue containing 1-1-1 TCE daily, for many hours ; moreover, air-exchange was insufficient in his working environment (a basement room 20 $\times$ 15 feet without ventilation and/or windows). Based on this information, a US-guided liver biopsy was performed with a Tru-Cut needle (18 gauge). Liver histology revealed centrilobular necrosis along with portal inflammation and moderate portal fibrosis possibly induced by TCE exposure (Fig. 1). The offending agent (TCE) was immediately withdrawn and the patient underwent monthly follow-up examinations. Three months after TCE withdrawal the patient was feeling well and liver enzymes values were within normal limits (Table 1). Six months after the initial biopsy, a second US-guided liver biopsy was performed, and hepatic histology was markedly improved (Fig. 2).

Discussion

It is generally recommended that workers who are regularly exposed to hazardous substances, such as TCE, get a complete physical examination, including an occupational and medical history, at the beginning of

Address for the correspondence : George H. Sakorafas, M.D., Arkadias 19-21, GR-115 26 Athens, Greece. E-mail : gsakoraf@hol.gr.

Table 1

Liver function tests	At presentation	3 months later
ALT	875 IU / L	40 IU / L
AST	224 IU / L	38 IU / L
ALP	284 IU / L	120 IU / L (upper normal limit 140 IU / L)
γ-GT	437 IU / L	60 IU / L (upper normal limit 75 IU / L)
Bilirubin total direct	3 mg / dl 2.4 mg / dl	1.2 mg / dl 0.8 mg / dl

their employment. They should also have periodic follow-up medical examinations. Occupational Safety and Health Administration (OSHA) sets and enforces standards for workplace chemical exposure. OSHA sets Permissible Exposure Limits (PELs) for the amounts of certain chemicals in workplace air. The PELs are intended to protect the health of a person who is exposed every day over a working lifetime. OSHA's PEL for TCE is 25 parts of TCE per million parts of air (25 parts per million, or 25 ppm) (2-3). This is equal to about 135 milligrams of TCE per cubic meter of air (135 mg/m^3). Legally, the exposure may be above 25 ppm from time to time, but the average exposure for any 8-hour work shift should not exceed 25 ppm. There is also a Short Term Exposure Limit (STEL) of 100 ppm (1075 mg/m^3), which should not be exceeded during any 15-minute averaging period (4), and a Ceiling Limit of 300 ppm (1612 mg/m^3) that must never be exceeded for any period of time. TCE is acutely toxic, primarily because of its anesthetic effect on the central nervous system. Exposure by inhalation is followed by rapid absorption into the bloodstream. Concentrations of 3000 ppm can cause unconsciousness in less than 10 minutes and anesthetic effects can occur after 20-minute exposure to 400 ppm[4]. Several systemic adverse events, including encephalopathy, carpal spasm, headache, dizziness, nausea with vomiting, fatigue, vertigo, tremors, anorexia, polyneuropathy, rash, uveitis, and even death, have been reported in workers secondary to acute or chronic exposure to TCE (5-11). Interestingly, renal impairment was reported in some patients implying a hypersensitivity reaction mechanism either to TCE or one of its metabolites. However, hepatitis in industrial workers exposed to TCE is extremely rare (8,12-21). Acute hepatic injury, sometimes fatal, has been reported (18). Instances of chirrhosis have also been ascribed to repeated acute hepatic injury due to exposure to TCE (22). Schattner (15) *et al.* reported a patient with uveitis and anicteric hepatitis associated with TCE exposure, with recurrence of symptoms after re-exposure to the agent. In a case series from Singapore (8), 5 patients were described with hepatitis and Stevens-Johnson syndrome

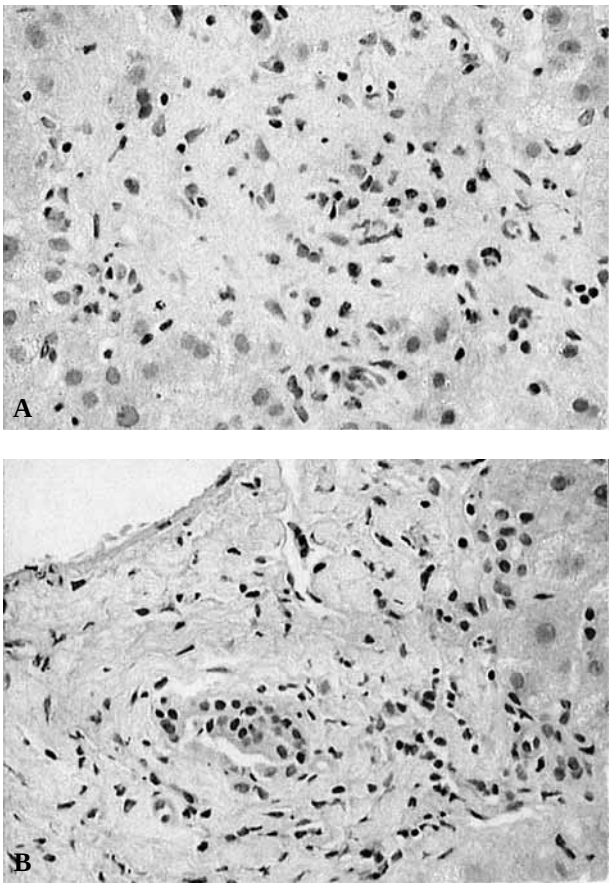

Fig. 1A,B. — Histology revealed centrilobular necrosis and portal fibrosis, compatible with a toxic origin of the hepatitis. (Hematoxylin & eosin).

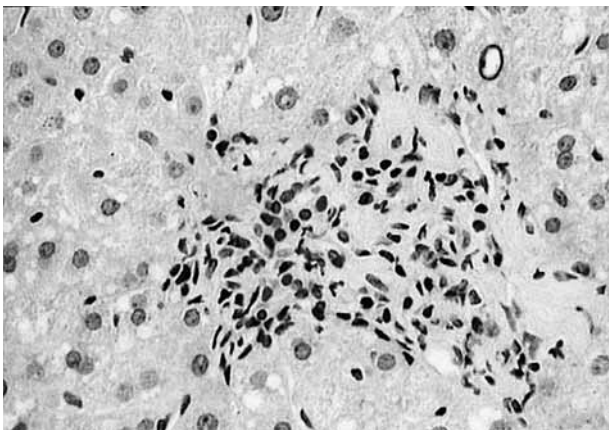

Fig. 2. — Improvement on histologic findings is evident on follow-up biopsy after 6 months. There is no centrilobular necrosis anymore ; portal fibrosis is markedly reduced (Hematoxylin & eosin).

2-5 weeks after TCE exposure. Bauer (12) *et al.* described three patients exposed to TCE, with various symptoms including fever, exfoliative dermatitis, macular papular rash and liver enzyme elevation. Intense exposure to TCE was the cause of hepatic flare in a

hepatitis C virus asymptomatic chronic carrier (17). Cotrim (23) studied 1500 symptomless Brazilian workers chronically exposed to TCE and found that 112 had elevated serum transaminases levels that returned to normal after TCE withdrawal. The causative role of organic solvents in fatty liver disease has been also shown in a study by Lundqvist (24), in which moderate or intense exposure to organic solvents carried a risk for fatty liver disease of 4,3% and 7.7% respectively. However, McCarthy (25) reviewed 288 cases of industrial poisoning by TCE, and found that only five persons showed clinical evidence (i.e., symptoms and signs) of hepatic disease.

In our case, the diagnosis of TCE-induced hepatitis was based upon clinical history, abnormal liver tests, features of the initial liver biopsy, lack of other possible causes of hepatitis, and – finally – resolution of the disease after TCE-exposure withdrawal. *The second liver biopsy (six months after the first one) could have been avoided, since repeat liver biopsy is unnecessary to confirm the diagnosis and given the potential complications of this invasive diagnostic procedure ; however, patient's course was uneventful.*

In conclusion, good work practices and medical follow-up are necessary when using potentially toxic substances. Toxic hepatitis must be considered in patients whose initial diagnostic workout is negative for common causes of acute or chronic hepatitis, and a good history should be taken with emphasis on patient's job and working conditions.

References

1. MESSITE J. Trichloroethylene. *J. Occup. Med.*, 1974, **16** : 194-197.
2. National Institute of Occupational Safety and Health. US Department of Health, Education and Welfare. Special occupational hazard review of trichloroethylene. Washington DC : 1978, pp. 78-130.
3. American Conference of Governmental Industrial Hygienists. Documentation of the threshold limit values. Cincinnati, Ohio, 1982, pp. 407-409.
4. Agency for Toxic Substances and Disease Registry. (ATSDR). Trichloroethylene. Atlanta USA. September 1997.
5. KILBURN K.H. Is neurotoxicity associated with environmental trichloroethylene ? *Arch. Environ. Health*, 2002, **57** : 113-120.
6. BAUER M., RABENS S.F. Cutaneous manifestations of trichloroethylene toxicity. *Arch. Dermatol.*, 1974, **110** : 886-890.
7. PRIEST R., HORN R. Trichloroethylene intoxication. *Arch. Environ Health*, 1965, **11** : 361-365.
8. PHOON P.H., CHAN M.O., RAYAN V.S., TAN K.J., TRIRUMOORTHY T., GOH C.L. Stevens-Johnson syndrome associated with occupational exposure to trichloroethylene. *Contact Dermatitis*, 1984, **10** : 270-276.
9. GOON A.T., LEE L.T., TAY Y.K., YOSIPOVITCH G., NQ S.K., GIAM Y.C. A case of trichloroethylene hypersensitivity syndrome. *Arch. Dermatol.*, 2001 Mar, **137** (3) : 274-276.
10. SCOTT C.S., COGLIANO V.J. Trichloroethylene health risks-state of the science. *Environ Health Perspect.*, 2000, **108** Suppl 2 : 159-160.
11. BAELUM J. Acute symptoms during non-inhalation exposure to combinations of toluene, trichloroethylene, and n-hexane. *Int. Arch. Occup. Environ Health*, 1999, **72** : 408-410.
12. BAUER M., RABENS S.F. Cutaneous manifestations of trichloroethylene toxicity. *Arch. Dermatol.*, 1974, **110** : 886-890.
13. CHITTASOBHAKTRA T., WANNANUKUL W., WATTANAKRAI P., PRAMOOLSINSAP C., SOHONSLITDSUK A., NITIYANANT P. Fever, skin rash, jaundice and lymphadenopathy after trichloroethylene exposure : a case report. *J. Med. Assoc. Thai*, 1997, **80** Suppl. 1 : 144-148.
14. HISHANAGA N., JONAI H., YU X., OGAWA Y., MORI Y., KAMIGIMA M. *et al.* Stevens-Johnson syndrome accompanied by acute hepatitis in workers exposed to trichloroethylene or tetrachloroethylene. *Sangyo Eiseigaku Zasshi*, 2002, **44** : 33-49.
15. SCHATTNER A., MALNICK S.D. Anicteric hepatitis and uveitis in a worker exposed to trichloroethylene. *Postgrad. Med. J.*, 1990, **66** : 730-731.
16. NAKAYAMA H., KOBAYASHI M., TAKAYASHI M., AGEISHI Y., TAKANO T. Generalized eruption with severe liver dysfunction associated with occupational exposure to trichloroethylene. *Contact Dermatitis*, 1988, **19** : 48-51.
17. CAPRIOLI F., POMETTA R., VISENTIN S., MASSIRONI S., CONTE D. "Hepatic flare", asthenia, peripheral polyneuropathy and diffuse liver steatosis in a hepatitis C virus asymptomatic chronic carrier. *Digest. Liver Dis.*, 2001, **33** : 359-362.
18. MC CUNNEY R.J. Diverse manifestations of trichloroethylene. *Br. J. Ind. Med.*, 1988, **45** : 122-126.
19. BOND G.R. Hepatitis , rash and eosinophilia following trichloroethylene exposure : a case report and speculation on mechanistic similarity to halothane induced hepatitis. *J. Toxicol. Clin. Toxicol.*, 1996, **34** : 461-466.
20. BAERG R., KIMBERG D. Centrilobular hepatic necrosis and acute renal failure in "solvent sniffers". *Ann. Intern. Med.*, 1970, **73** : 713-720.
21. JORON G.E., CAMERON D.G., HALPENNY G.W. Massive necrosis of the liver due to trichloroethylene. *Can. Med. Assoc. J.*, 1955, **73** : 890-891.
22. THIELE D.L., EIGENBRODT Y., WARE D.J. Cirrhosis after repeated TCE and 1,1,1-trichloroethylene exposure. *Gastroenterology*, 1982, **83** : 926.
23. COTRIM H.P., ANDRADE Z.A., PARANA R., PORTUGAL M., LYRA L.G., FREITAS L.A. Nonalcoholic steatohepatitis : a toxic liver disease in industrial workers. *Liver*, 1999, **19** : 299-304.
24. LUNDQVIST G., FLODIN U., AXELSON O. A case control study of fatty liver disease and organic solvent exposure. *Am. J. Ind. Med.*, 1999, **35** : 132-136.
25. MC CARTHY T.B., JONES R.D. Industrial gassing poisonings due to trichloroethylene, perchloroethylene and 1,1,1 trichloroethanio 1961-1980. *Br. J. Ind. Med.*, 1983, **40** : 450-455.