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Determination of Occupational Disease in Worker with Liver Cirrhosis That Exposed by Vinyl Chloride Superimposed with Hepatitis B Infection

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Abstract

Background: Liver cirrhosis is the final pathological result of various chronic liver diseases that characterized by the formation of regenerative nodules and fibrotic tissue. The etiology of liver cirrhosis are hepatitis C, hepatitis B, alcohol, nonalcoholic fatty liver disease, and can also be caused by chemicals in the workplace. The occupational diagnosis of Liver Cirrhosis that exposed by vinyl chloride superimposed with hepatitis B infection with was performed by using The Seven Steps of Occupational Diagnosis, a method that issued by PERDOKI (Indonesian Occupational Medicine Association-IOMA). The aim of this case report is to determine whether liver cirrhosis in this patient is an occupational disease or not.
Case Presentation: Fifty years old man came to Emergency Room with complaints of vomiting black blood since 4 hours. Vomiting blood as much as 5 times with a volume of about 200 cc each time. One day before, patient admitted that his defecation is black, watery, and smell bloody. Volume of defecation was unknown. Three months before, patient complainted that the stomach often felt bloated, enlarged, and got full quickly. There was no icteric in eyes and body.
This complaints (vomiting black blood and black stools) were often occured since 2017. In 2017, 2018 and 2020, this patient was hospitalized once while in 2019, the patient was hospitalized twice for this complaint. In 2017, when the complaint first appeared, the patient was declared to have hepatitis B and in 2019, the patient underwent an endoscopy and was said to have enlarged blood vessels in the esophagus, and an abdominal ultrasound was performed and was said to be suspected of liver cirrhosis.This patient works as a family owned chemical industry. The chemical produced is called zamitex, a mixture for paints. These chemicals contain formaldehyde, Vinyl Chloride, and CMC (Carboxymethyl Cellulose). This patient had worked in this field for 21 years, and was exposed to these chemicals. In addition, there are also dangers of heat, awkward positions, and psychosocial.
Conclusion: Based on The Seven Steps of Occupational Diagnosis, Liver cirrhosis in this patient can be categorized as an occupational disease superimposed with hepatitis B infection. Liver cirrhosis in this patient can be caused by prolonged exposure to Vinyl Chloride. Vinyl Chloride is known to cause damage to the liver, especially to cause carcinoma of the liver. There is a synergistic effect between exposure to Vinyl Chloride and hepatitis B infection, exacerbating the condition of liver damage. However, because the exposure to Vinyl Chloride has been going on for a longer time, compared to hepatitis B infection, the condition of liver cirrhosis in this patient is still categorized as an occupational disease
Keyword: liver cirrhosis, vinyl chloride, hepatitis b infection, occupational diagnosis

Introduction

Liver cirrhosis is the final pathological result of various chronic liver diseases that characterized by the formation of regenerative nodules and fibrotic tissue[1,2]. The etiology of liver cirrhosis are hepatitis C, hepatitis B, alcohol, nonalcoholic fatty liver disease, and can also be caused by chemicals in the workplace[1,3]. Some chemicals can cause liver damage such as organic solvents and mixtures thereof, pesticides, and metals[3].

One of the chemicals present in the workplace is Vinyl Chloride. According to ACGIH, Vinyl Chloride is categorized as A1 which means it has been proven to cause Liver Malignancy in humans[4]. However, chronic exposure to vinyl chloride can also cause damage to liver cells and lead to liver cirrhosis.[5]

The presence of other etiological factors coupled with exposure to chemicals in the workplace can have a synergistic effect. These effects can aggravate and accelerate the damage to liver cells. One of the causes of liver cirrhosis is hepatitis B infection[1,3]. Therefore, further investigation is needed to determine the main cause of liver cirrhosis in this patient, whether caused by exposure to Vinyl Chloride at work or hepatitis B infection.

Case Presentation

Fifty years old man came to Emergency Room with complaints of vomiting black blood since 4 hours. Vomiting blood as much as 5 times with a volume of about 200 cc each time. Prior to this symptom, the patient admitted that he was not coughing or had been straining hard, but according to the patient, for the past few days he likes to drink ice water. The patient does not eat something spicy, sour, or coconut milk. After vomiting blood, the patient feels weak as if he is about to pass out.

One day before administrating hospital, patient admitted that his defecation is black, watery, and smell bloody. Volume of defecation was unknown. Prior to this symptom, the patient admitted that he was not coughing or had been straining hard, but according to the patient, for the past few days he likes to drink ice water. The patient does not eat something spicy, sour, or coconut milk.

Three months before administrating hospital, patient complainted that the stomach often felt bloated, enlarged, and got full quickly. There was no icteric in eyes and body.

This symptoms (vomiting black blood and black stools) were often occured since 2017. In 2017, this patient was hospitalized once. In 2018, he was hospitalized once. In 2019, he was hospitalized twice. In 2020, he was hospitalized once. The patient did not know the cause of vomiting blood or black stools. According to the patient, this happened suddenly, but the patient suspected it could be because he was too tired.

In 2017, when the complaint first appeared, the patient was declared to have hepatitis B and in 2019, the patient underwent an endoscopy and was said to have enlarged blood vessels in the oesophagus, and an abdominal ultrasound was performed and was said to be suspected of liver cirrhosis.

This patient had a tattoo on his left forearm at 14 years old and a tattoo on his left thigh at 16 years old. Tattoos are made by himself using new needle. Patient has history of smoking 3 cigarettes / day from the age of 14 to 28 years (14 years of smoking), then quit smoking. Patient has history of drinking alcohol from the age of 14 to 25 years (11 years of drinking alcohol). The alcohol consumed is Anker or TKW beer, 100cc per drink, but doesn't drink every day, only when hanging out with friends. The patient also admitted that he had had free sex with his hangout friend 4 times for 1 year (1994 – 1995). The patient admitted that he had vaginal intercourse and did not use a condom. No drugs, herbs or supplements were consumed.

This patient works as a family owned chemical industry. The chemical produced is called zamitex, a mixture for paints. These chemicals contain formaldehyde, Vinyl Chloride, and CMC (Carboxymethyl Cellulose). This patient had worked in this field for 21 years, and was exposed to these chemicals. In addition, there are also dangers of heat, awkward positions, and psychosocial.

This patient's job is in the packaging department. This patient has 5 workers who help him. This patient's duties are to receive ready-made chemicals (zamitex), supervise the packing process, assist in the packing process (from putting zamitex chemicals into plastics to sealing plastics), and checking goods for delivery. In a day, they can pack about 200 kg of zamitex which

is packaged in 1 kg and ½ kg. Patients exposed to chemicals, especially Vinyl Chloride is when receiving chemicals, supervising the packing process, and assisting the packing process.

When he was first admitted to the hospital, the patient's hemoglobin dropped to 5.4 g/dl so the patient was admitted to the Intermediate Care Unit and received a transfusion of 4 PRC bags. On June 4th, 2021, an ultrasound examination of the abdomen was performed, the picture of chronic parenchymal liver disease was obtained with splenomegaly and widening of the splenic vein, suggestive of liver cirrhosis, attentional portal hypertension and ascites.

So Based on Seven Steps of Occupational Diagnosis6, the diagnosis of this patient is Liver Cirrhosis et causa Occupational Disease superimposed with Hepatitis B infection. To make the investigation easier, a timeline of this patient's disease is made.

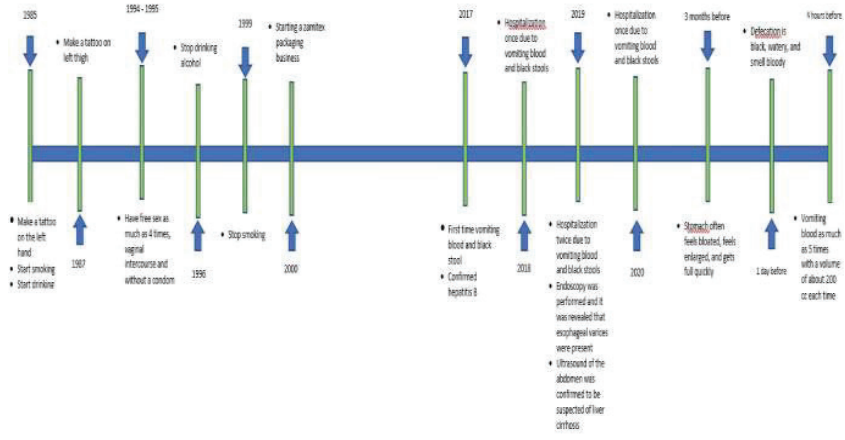
Discussion

Liver cirrhosis is the final pathological result of various chronic liver diseases that characterized by the formation of regenerative nodules and fibrotic tissue[1,2]. The etiology of liver cirrhosis are infections, alcohol, non-alcoholic such as fatty liver, diabetes, and can be caused by chemicals in the workplace. A rare but possible cause of liver cirrhosis is a genetic disease, such as hemochromatosis or Wilson's disease. Some chemicals that are known to cause liver damage are organic solvents and their mixtures, pesticides, and metals[1,3]. In this case, exposure to the chemical Vinyl Chloride which is known to cause liver problems.

Vinyl Chloride is a chlorinated hydrocarbon that occurs as a colorless and highly flammable gas with a mild, sweet odor. Because it is a gas, the inhalation route is the main route for this exposure to be absorbed in the body. Vinyl Chloride that enters the body will be rapidly metabolized and excreted by the body. Vinyl Chloride will be metabolized in the liver and the metabolites will be excreted through urine[7].

Toxicity of Vinyl Chloride is related to the highly reactive metabolite, 2-chloroethylene oxide. These metabolites can bind to DNA and RNA, as well as proteins to form DNA adducts or protein adducts, causing mutations in DNA. Vinyl Chloride is known to be a carcinogenic agent especially in the liver and lungs[7,8].

Liver is the main target organ for Vinyl Chloride toxicity. Liver sensitivity to vinyl chloride exposure is consistent with the mechanism of action in which vinyl chloride metabolizes via mixed function oxidase (MFO), particularly Cytochrome P450 2E1 (CYP2E1) which produces a highly reactive metabolite, namely 2-chloroethylene oxide. These metabolites have been shown to bind to DNA and hepatocellular proteins.

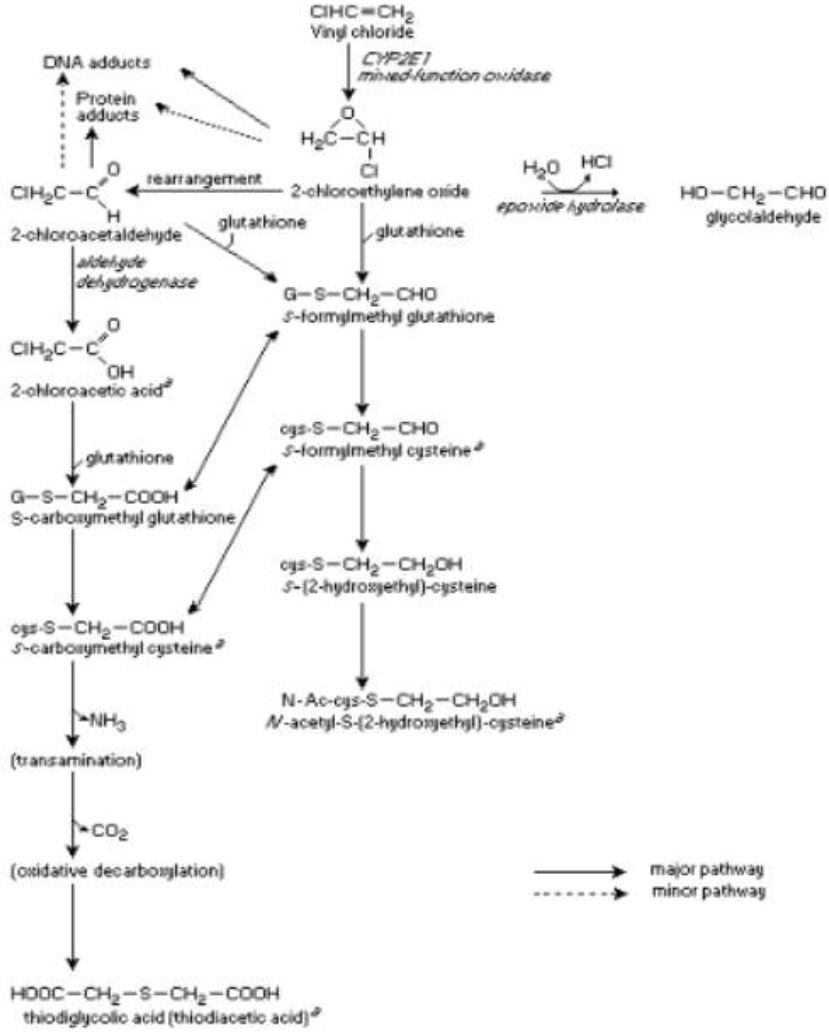


Picture 1. Timeline of patient's disease

Thus, the prevalence of MFO activity in the liver and the resulting reactive metabolite production resulted in the observed liver sensitivity to both cancerous and noncancerous effects. Vinyl chloride may induce genetic polymorphisms in Cytochrome P450 2E1 (CYP2E1), which can lead to liver fibrosis[7,9].

The incidence of portal hypertension and liver fibrosis has been reported in workers exposed to Vinyl Chloride since 1970. Research on 757 workers in Italy exposed to high doses of Vinyl Chloride showed an increased prevalence of periportal liver fibrosis. In Taiwan, 347 male workers who had a history of high exposure to Vinyl Chloride also showed an increased risk of developing liver fibrosis. In this study, we also looked at other risk factors such as overweight/obesity and Hepatitis B/Hepatitis C infection. Workers with hepatitis B or hepatitis C infection and high exposure to Vinyl Chloride were at the highest risk of liver fibrosis[9].

Chronic hepatitis B infection can cause serious health problems. This infection is known to develop into liver cirrhosis or liver malignancy. Studies have shown that most patients with cirrhosis have active HBV DNA replication. In a prospective study in Taiwan, patients with chronic hepatitis B showed 30% of the 93 patients



Picture 2. Vinyl Chloride Metabolism and Mechanisms of Toxicity[8]

were seropositive for HBeAg and 73% had a serum HBV DNA level >10,000 copies/ml(2000 IU/ml) at the time of cirrhosis detection with a mean age of 43.6 (24–69) years. Two earlier studies from Europe showed that 35%-55% of patients with compensated cirrhosis were HBeAg positive and 48% of patients in one study were HBV DNA positive at presentation. These studies suggest that at least 30–70% of the patients still have active viral replication at pre-sentation of compensated cirrhosis, and that active viral replication is associated with continued liver disease progression and decreased survival over time[10,11].

Based on The seven Steps method of Occupational Diagnosis, liver cirrhosis in this patient can be categorized as an occupational disease superimposed with hepatitis B infection. This determination is based on the patient's disease history. The patient has been exposed to Vinyl Chloride for a period of 21 years, while hepatitis B infection has only been known for 4 years. However, the data on the dose of Vinyl Chloride exposure in this case is not known. However, based on the sources obtained, exposure to Vinyl Chloride is cumulative, so even though the exposure dose is small, if exposed every day, there is still a risk of liver cirrhosis[9].

Table 2 Studies investigating the association between occupational exposure and liver fibrosis/liver cirrhosis in vinyl chloride workers

Ref. location	Study description	Disease assessment	Exposure assessment	Exposure categories	Number of cases	Relative risk (95%CI)	Notes
Maroni *et al*[23] (2003), Italy, four VC plants	Survey of 757 active workers	Liver ultrasonography: Periportal fibrosis	Job exposure matrix: Max Exposure (ppm)	0	Overall prevalence 16.0%	1.0	Adjusted for age, alcohol, body mass index, viral hepatitis
				1-10		1.55 (P = 0.276)	
				50		1.54 (P = 0.405)	
				200		4.12 (P = 0.005)	
				500		2.47 (P = 0.064)	
Hsiao *et al*[25] (2003), Taiwan, five VC plants	Survey of 347 active workers	Liver ultrasonography: Liver fibrosis including pre-cirrhosis and cirrhosis	Job exposure matrix: Cumulative exposure (ppm-years)	Low	3	1.0	Adjusted for age, alcohol, body mass index
				Moderate	5	4.6 (1.0–25.5)	
				High (> 2400)	12	5.9 (1.7–28.2)	
Mastrangelo *et al*[5] (2004), Italian plant	Nested case-control study: 40 Cases and 139 controls	Cirrhosis at histology and/or clinical records	Job exposure matrix: Cumulative exposure (ppm-years)	Each 1000 ppm-years increase	40	1.37 (1.13-1.69) alcohol/virus adjusted	Additional analyses on joint effects
Ward *et al*[3] (2001), European cohort	Cohort study, 12700 workers	Cause of death from death certificates	Job exposure matrix: Cumulative exposure (ppm-years)	< 524	8	1.0	
				524-998	8	9.38 (3.52-25.0)	
				999-3428	9	4.01 (1.55-10.4)	
				3430-5148	8	9.77 (3.66-26.1)	
				5149+	9	8.28 (3.15-21.8)	
Mundt *et al*[9] (2017), United States cohort	Cohort study, 9951 workers	Cause of death from death certificates	Job exposure matrix: Cumulative exposure (ppm-years)	< 63	11	1.0	
				63-286	19	1.8 (0.9-3.8)	
				287-864	22	2.0 (1.0-4.1)	
				865-2270	24	2.1 (1.0-4.3)	
				2271+	21	1.7 (0.9-3.7)	
Fedeli *et al*[11] (2019), Italian plant	Cohort study, 1685 workers	Deaths from cirrhosis + deaths from liver cancer with histological/clinical evidence of cirrhosis	Job exposure matrix: Cumulative exposure (ppm-years)	< 734	35	1.0	
				734-2378	8	1.18 (0.55-2.55)	
				2379-5187	12	2.43 (1.26-4.70)	
				≥ 5188	8	2.60 (1.19-5.67)	

VC: Vinyl chloride; CI: Confidence interval.

Picture 3. Vinyl Chloride Cumulative Exposure and Risk[9]

Hepatitis B infection in this patient, cannot be used as the main cause of liver cirrhosis. This is because not all patients with chronic hepatitis B infection will develop liver cirrhosis.

Conclusion

Based on information about patient's disease history, hazardous exposures, the description of the work in this worker and enforcement of the seven steps of occupational diagnosis, it can be concluded that liver cirrhosis in this patient can be categorized as an occupational disease superimposed with hepatitis B infection. Vinyl Chloride is the main cause of liver cirrhosis in this patient. Vinyl Chloride exposure is acquired in the workplace. The presence of hepatitis B infection worsens the patient's condition. Occupational management is needed, especially when he returning to work. For workers, it is important to avoid excessive coughing and forceful straining, as they can cause esophageal varices to rupture. In addition, it is necessary to do engineering control by modifying the wind direction, so that Vinyl Chloride is not inhaled. The use of chemical respirator masks should be considered. Because the patient is the owner of this business, the patient can delegate the process to his subordinates, to carry out the direct supervision process. Patients simply monitor via CCTV and do not go directly into the field.

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