Autopsy of a young alcohol abuser with severe fatty cirrhosis revealed potential interactions among alcohol-related disorders

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Abstract: We performed the autopsy of a man in his late twenties who was found dead in his house. The man had abused alcohol for the last few years, and the autopsy revealed a yellowish and clearly enlarged liver. Histological examination revealed severe fatty cirrhosis with few normal hepatocytes. However, postmortem biochemical and serological examinations revealed elevated levels of hemoglobin A1c and ketone bodies, which indicated the previously unknown existence of diabetes mellitus (DM) and ketoacidosis. Liver cirrhosis, DM, and ketoacidosis influence each other and are all aggravated by alcohol abuse. As the ketoacidosis was thought to be caused by the DM (diabetic ketoacidosis), we suspected that these factors were involved in his death, despite the apparent fatty cirrhosis. However, the blood levels of ketone bodies were not high enough to cause his death, which is likely because the damaged liver became unable to produce ketone bodies (liver failure mitigated the ketoacidosis). Therefore, we concluded that the cause of death was liver failure due to alcoholic fatty cirrhosis. Given the complicated interactions among alcohol-related disorders, postmortem histological, biochemical, and serological examinations are indispensable for clarifying the cause of death in similar cases.

Key Words: alcohol abuse, fatty cirrhosis, diabetes mellitus, ketoacidosis.

INTRODUCTION

Alcohol-related death is an important social problem for persons of all ages [1, 2], and the etiologies of alcohol-related death are classified as acute events or chronic disorders. The acute events mainly consist of accidental death, including ethanol intoxication, drowning, falling, and traffic accidents. In contrast, chronic disorders are frequently associated with pre-existing diseases. For example, hepatic disorders are a common complication of chronic alcohol abuse, and one of the final stages is fatty cirrhosis [3]. Diabetes mellitus (DM) can also be triggered and aggravated by heavy alcohol consumption [4]. Moreover, the coexistence of cirrhosis and DM can lead to mutual aggravation, regardless of which condition developed first [5]. This report describes our findings from an autopsy that was performed for a young man with the most severe fatty cirrhosis that we had ever encountered. The postmortem examinations revealed the coexistence of type 1 DM (T1DM), ketoacidosis, and liver cirrhosis, which can all influence each other and are aggravated by alcohol abuse. Therefore, we discuss the potential interactions among these alcohol-related disorders in the present case.

CASE REPORT

A man in his late twenties was found dead in an electric blanket on a winter morning by his brother. The man had abused alcohol for the last few years and quit his job 1 week before his death. Although he lived with his father and brothers, they seldom talked to each other and the family could not provide detailed information regarding his condition on the day before his death or
his medical history. However, the brothers testified that he had drunk beer the day before his death and that they had no family history of DM.

**Autopsy findings**

A medico-legal autopsy was performed approximately 60 h after his death, which revealed moderate putrefactive discoloration on the abdomen. The man was 156 cm tall and weighed 50.5 kg (body mass index: 20.75 kg/m²). No obvious injuries or jaundice were observed during an external examination, and we did not detect intracranial hemorrhage. The heart weighed 268 g with the smooth coronary arteries. The lungs weighed 572 g (left) and 535 g (right), and exhibited remarkable congestion with bilateral pleural effusion (left: 230 mL, right: 250 mL). The intraperitoneal fluid volume was 210 mL. The liver was yellowish and remarkably enlarged (weight: 3,382 g) (Figs 1A and B). The hen's egg-sized gall bladder contained 20 mL of highly viscous bile. The small and large intestines contained white muddy stool (Fig. 1C). No other macroscopic lesions were detected in the other main organs.

Histological examinations revealed severe congestion and edema in both lungs (Fig. 2A). Severe fatty degeneration and cholestasis were apparent in the liver and few normal hepatocytes were detected (Figs 2B and C). Fibrous proliferation and pseudolobule formation were revealed using azan staining (Fig. 2D). Detailed pathohistological findings and results from immunostaining for CD3 and CD68 were difficult to obtain, which was likely because of autolytic changes that were evident in the pancreas (data not shown). Formalin pigment deposition was observed in the vacuolated epithelial cells of the proximal kidney tubules (Fig. 2E). Proliferation of the glomerular mesangial cells was not identified during periodic acid-Schiff staining (Fig. 2F). Excluding decomposition, none of the other organs exhibited pathological changes.

Table 1 shows the data from the postmortem biochemical and serological examinations. The levels of hemoglobin A1c (HbA1c) and 3-hydroxybutyric acid (3HB) were elevated, and antibodies to insulin were detected in the man's serum. These findings indicated the existence of DM, which was not known before his death.

![Figure 1. Macroscopic findings regarding the liver and intestine contents. A) The enlarged liver had a yellowish exterior color. B) The divided face of the liver. C) The white muddy stool in the large intestine.](image-url)
The total protein level was within the normal range, although the albumin level was decreased. The blood and urine alcohol concentrations were 1.6 mg/mL and 1.2 mg/mL, respectively. A toxicological examination using liquid chromatography-mass spectrometry revealed negative findings.

**DISCUSSION**

Acute alcohol intoxication was excluded in the present case based on the man’s blood alcohol concentration. However, the macroscopic and microscopic findings confirmed the existence of fatty cirrhosis. Thus, as hepatitis viruses were not detected, the fatty cirrhosis was attributed to alcohol abuse. Decreased albumin production caused by liver dysfunction likely reduced the colloid osmotic pressure and resulted in the pulmonary edema. Cholestasis was observed during the histological examination and was supported by the elevated level of γ-glutamyl transpeptidase. Decreased oral intake must have impaired the secretion of cholecystokinin (a gastrointestinal hormone), which plays an important role in the stimulation of gallbladder contraction and bile excretion [6]. Thus, the malfunctioning gallbladder could have increased the bile’s viscosity and decreased its flow [7]. The impaired bile production and excretion likely led to the white stool in the intestines without signs of jaundice. Taken together, these findings suggested that the man’s death was related to liver failure caused by the fatty cirrhosis. However, postmortem examinations revealed two unexpected pathological conditions (DM and ketoacidosis), which can both be influenced by alcohol abuse. Thus, we considered the possibility that these alcohol-related disorders were all involved in the man’s death (Fig. 3).

The increased level of ketone bodies (3-HB plus acetoacetate) indicated the existence of ketoacidosis. In addition, vacuolization and deposition of formalin pigmentation in the proximal kidney tubules are characteristic histological findings of ketoacidosis [8-10]. Thus, alcoholic ketoacidosis (AKA) and diabetic ketoacidosis (DKA) should both be considered as...
likely causes of the ketoacidosis. For example, AKA is a significant cause of mortality among alcohol abusers with severely depleted hepatic glycogen stores (caused by their liver dysfunction), as ketoacidosis can easily be induced by cessation of alcohol consumption (which is a major source of alcoholics’ energy supply). Thus, the development of AKA almost always occurs after the person experiences alcohol consumption-related nausea or abdominal pain, and a low/absence blood alcohol concentration is a diagnostic criterion for AKA [11, 12]. Therefore, we excluded the possibility of AKA, based on the man’s relatively high blood alcohol concentration.

Nevertheless, malnutrition related to alcohol abuse must have contributed to the development of ketoacidosis. Alcohol abuse can aggravate DM, and elevated HbA1c levels are a clear sign of DM (Fig. 3). In the present case, DM was the most likely cause of ketoacidosis, although the DM might have been relatively new, given the absence of diabetic glomerulopathy during periodic acid-Schiff staining. Interestingly, the presence of antibodies to insulin in this case indicated the existence of T1DM (insulin-dependent DM), rather than type 2 DM, and DKA generally occurs in patients with T1DM [13]. Thus, fulminant T1DM (FT1DM) is a possible cause of death, as this condition rapidly progresses to hyperglycemia and ketoacidosis [14]. The diagnosis of FT1DM is based on three findings: (1) elevated levels of ketone bodies in the serum or urine, (2) a high plasma glucose level (>288 mg/dL) plus an HbA1c level of <8.5%, and (3) decreased C-peptide levels in the plasma or urine [15]. The test results from the present case fulfilled some of these criteria (high plasma glucose, relatively low HbA1c, decreased plasma C-peptide), although we are not aware of any cases involving FT1DM with antibodies to insulin. Nevertheless, there are reports of FT1DM cases that were positive for antibodies to glutamic acid decarboxylase [16, 17]. Because FT1DM can occur in association with insulinitis that is caused by viral infection [18], immunostaining for inflammatory cells is useful for the postmortem diagnosis of FT1DM [19]. Unfortunately, we were unable to obtain clear results from immunostaining for CD3 (T cells) and CD68 (macrophages), which was likely related to autolytic changes in the pancreas. Thus, we cannot confirm or exclude the existence of FT1DM. However, previous reports have indicated that ketoacidosis can be considered the cause of death in cases with blood ketone body levels of >2,500–3,000 μmol/L [20, 21], and other reports have indicated that DKA-related mortality can involve extremely high levels of ketone bodies (>10,000 μmol/L) [19, 22]. Therefore, the blood level of ketone bodies in the present case does not seem sufficient to have caused the man’s death. As the liver is the primary site of ketone body production [23], the man must have lacked the ability to produce large amounts of ketone bodies. Hence, the DKA likely would not have progressed to a fatal level even if FT1DM was present.

Chronic alcohol abuse exerts harmful effects throughout the body, although the effects of alcohol abuse on the man’s T1DM and ketoacidosis does not appear to have made these conditions direct causes of his death. Thus, we conclude that the man died because of liver failure caused by severe fatty cirrhosis, which would have led to a reduced colloid osmotic pressure and subsequent pulmonary edema. Given the potentially complicated interactions among alcohol-related disorders, unexpected conditions may be obscured by the most obvious disease in these cases. Therefore, comprehensive postmortem histological, biochemical, and serological examinations are indispensable for clarifying the cause of death in similar cases.

Conflict of interest. The authors declare that there is no conflict of interest.

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