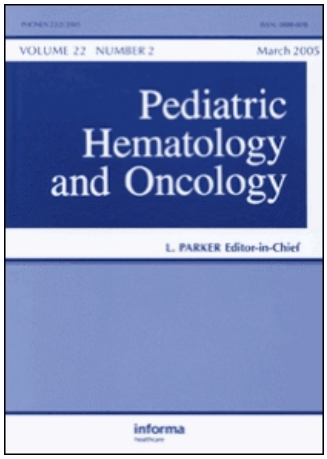

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HEMOPHAGOCYTIC SYNDROME AND ACUTE LIVER FAILURE ASSOCIATED WITH ETHYLENE GLYCOL INGESTION: A Case Report

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HEMOPHAGOCYTIC SYNDROME AND ACUTE LIVER FAILURE ASSOCIATED WITH ETHYLENE GLYCOL INGESTION: A Case Report

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□ *The authors describe a case of accidental ethylene glycol poisoning in an 18-month-old boy who developed hemophagocytic syndrome (HPS). Ethylene glycol is a common substance in various antifreeze preparations. Acute ethylene glycol intoxication is a medical emergency that, if not diagnosed correctly and treated aggressively, will lead to serious neurological, cardiopulmonary, and renal dysfunction, and may result in death. The taking of a detailed history, physical examination, and laboratory testing are essential for diagnosis. To the best of the authors' knowledge this is the first case in the literature of a subject who developed HPS after ethylene glycol intoxication.*

Keywords acute liver failure, ethylene glycol, hemophagocytic syndrome

Ethylene glycol, a common antifreeze, coolant, and industrial solvent, is responsible for many instances of accidental and intentional poisoning annually [1]. Ethylene glycol is not toxic itself, but its various metabolites, such as calcium oxalate, can cause permanent and life-threatening multiorgan damage and death [2]. Severe ethylene glycol toxicity can cause profound morbidity and is almost universally fatal if untreated [3]. The

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hemophagocytic syndrome (HPS) is characterized by a systemic activation of macrophages/histiocytes, which are induced to undergo phagocytosis of hematopoietic elements. Two forms of HPS, primary and secondary, have been reported. Secondary HPS has been reported in association with many different conditions [4, 5]. However, no report of an association between a toxic substance and HPS has been hitherto reported in the literature. Here we present an 18-month-old boy who developed HPS after ethylene glycol ingestion.

CASE REPORT

An 18-month-old boy who had ingested oil solvent 3 weeks prior to presentation suffered from fever, nausea, and bloody vomiting. He was admitted to a local health center with a diagnosis of hepatic encephalopathy and gastrointestinal bleeding, and referred to our intensive care unit. On admission, physical examination revealed hepatomegaly 3 cm below the costal margin and lethargy. Blood cultures (bacterial and fungal) were sterile. Serologic tests for EBV, CMV, HSV-I, HSV-II, HBV, HCV, HAV, and PCR for parvo virus B-19 were either negative or consistent with prior exposure. The laboratory findings of the patient are summarized in Table 1.

After initial evaluation, IV fluid, fresh frozen plasma, antibacterial treatment, lactulose, and rectal enema with gentamycin were started. The patient's clinical condition deteriorated during the following days. Gastrointestinal bleeding persisted and the patient developed clonus on day 2, and a focal convulsion on day 3. Mechanical ventilation was instituted due to respiratory depression, and chest X-ray showed the presence of pleural effusion. A toxicological study revealed that the oil solvent was ethylene glycol. The level of consciousness decreased during the following days and he developed a coma. Peritoneal dialysis was performed for anuria on day 4. The pleural and peritoneal fluid became hemorrhagic.

The Hb level decreased to 4.9 mg/dL, the white blood cell (WBC) count increased to 19,200/μL, blood pH and bicarbonate levels decreased to 6.99 and 8.6 mmol/L, respectively (sodium was 137 mEq/L, chloride 91 mEq/L, yielding an anion gap of 37.4), and his creatinine level increased to 1.33 mg/dL. Liver enzymes remained elevated (AST 19753U/L, ALT 2850 U/L), and total bilirubin increased to 4.73 mg/dL, with the fraction of conjugated bilirubin 2.06 mg/dL. INR increased to 4.67, and aPTT increased to 119.3 s. The patient met the diagnostic criteria of HLH described by the Histiocyte Society [6].

The patient died on day 5. Bone marrow aspiration performed on day 3, and postmortem examination of bone marrow showed an increased number of histiocytes with hemophagocytosis (Figure 1).

TABLE 1 Initial Laboratory Findings of the Patient

	Results	Normal values
Hemoglobin, g/dL	11.7[a]	10.5–14
WBC, μL^{-1}	2300	6000–17,000
Platelet, μL^{-1}	65,000	15,0000–45,0000
ALT, U/L	1736	5–40
AST, U/L	14,729	8–33
Total bilirubin, mg/dL	1.27	0.1–1.2
Conjugated bilirubin, mg/dL	0.5	0–0.3
Blood urea nitrogen, mg/dL	8.7	5–18
Creatinine, mg/dL	0.15	0.6–1.2
Sodium, mEg/L	128	138–145
Potassium, mEq/L	2.86	3.4–4.7
Chloride, mEq/L	97	95–110
Calcium, mg/dL	7.88	8.6–10.2
Triglycerides, mg/dL	140	<200
Total cholesterol, mg/dL	120	<200
Blood pH	7.49	7.35–7.45
Bicarbonate, mmol/L	22.5	21–28
Fibrinogen, mg/dL	125	170–405
Ferritin, μg/L	10,000	23–70
PT, s	21.7	10.6–11.4
INR	2.0	0.96–1.04
aPTT, s	51	26–36
TT, s	71.1	15–22
AT III activity, %	111	80–120
D-Dimer, μg/mL	>20	0–0.5

[a]Transfusion at another hospital.

Note. ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalization ratio; aPTT, activated partial thromboplastin time; PTA, prothrombin time activity; PT, prothrombin time; TT, thrombin time; AT III, antithrombin III activity.

DISCUSSION

Ethylene glycol poisoning represents one of the most dramatic and potentially lethal toxic substance ingestions [3]. In the United States, the incidence of ethylene glycol ingestion is approximately 5000/year [3]. This odorless, nonvolatile, colorless alcohol is found in a large number of household products [3, 7]. Its accessibility and sweet taste have made it a frequent culprit in both accidental and intentional poisoning [1]. Diagnosis of ethylene glycol intoxication is based on history, clinical presentation, and 3 key laboratory findings, including high anion gap metabolic acidosis, high osmolality with osmolal gap, and oxalate crystalluria [8]. The last 2 tests were not available in the present case. Hematemesis, hepatic damage, anuric renal failure, large anion gap metabolic acidosis, hypocalcemia, persistent coma, and seizures, all of which occurred in our patient, are well-known manifestations of ethylene glycol intoxication [3]. The previously reported hematologic effects of ethylene glycol toxicity include hemolytic anemia, nonhemolytic anemia, thrombocytopenia, leukemoid reaction, bone marrow suppression

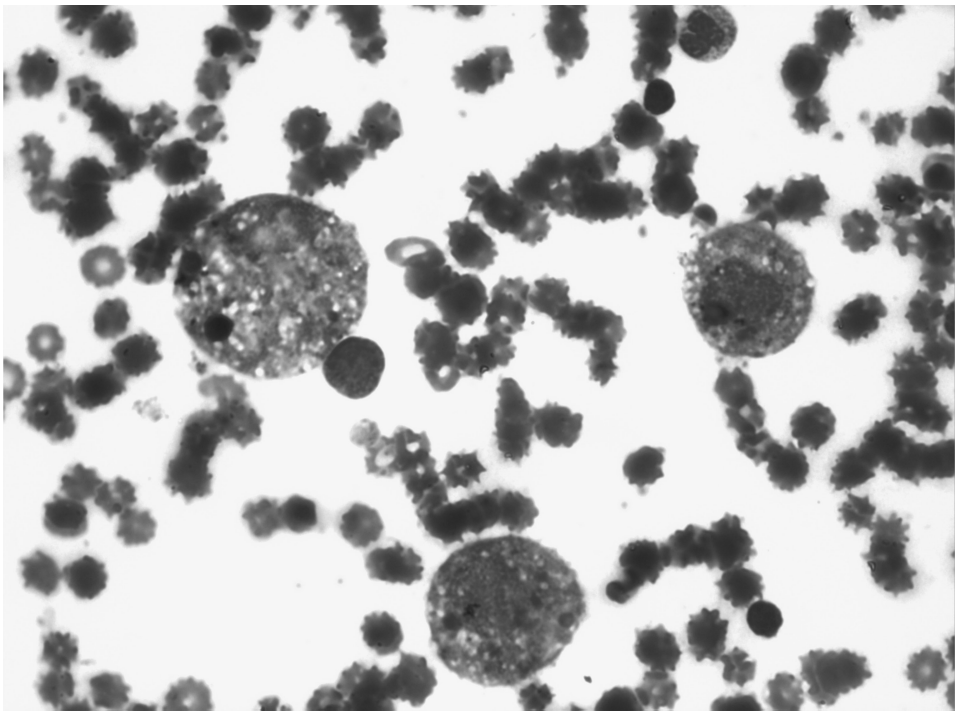

FIGURE 1 Hemophagocytosis in bone marrow.

with pancytopenia, and disseminated intravascular coagulation syndrome [1, 9–11].

There are rare reports of fulminate hepatic failure together with HPS. Two adults, one with Still disease and the other with malignant lymphoma, have been reported as presenting with hepatic failure and HPS [12, 13]. Also, 2 infants with HPS presenting with signs of acute hepatic failure were misdiagnosed as neonatal hemochromatosis [14]. In this case pancytopenia, liver insufficiency, neurological changes, hypofibrinogenemia, hyperferritinemia, and hemophagocytosis in the bone marrow were the findings of HPS. Although splenomegaly and hypertriglyceridemia are the diagnostic criteria of HLH, they have not been observed in all patients like our patient. For instance, splenomegaly and hypertrigyceridemia have been reported to be 35–100 and 59–100%, respectively [15, 16]. The frequency of lymphoadenopathy has also been reported as 17–52% in patients with secondary HLH [15, 16]. However, the data of our patient, including pancytopenia, liver insufficiency, and neurological changes, may be secondary to ethylene glycol intoxication and HPS. Disseminated intravascular coagulopathy was also observed (Table 1). This condition may have been associated with HPS or it may have been secondary to acute hepatic failure.

Secondary HPS has been documented in association with many different infections, malignant neoplasms, rheumatoid disorders, metabolic disorders, prolonged intravenous nutrition, and possibly drugs [7]. The detailed history and physical examination revealed that none of the known causes of HPS were present in this patient.

HPS has been reported to be a result of a defect of immune regulation. Markedly reduced or absent cytotoxic T cells and defective natural killer (NK) cell function, as well as excessive cytokine production, have been reported in HPS [17]. On the other hand, it was previously shown in mice that the activity of natural killer cells was reduced by acute poisoning with ethylene glycol, methanol, and ethanol [18]. Similarly, Zabrodskii et al. showed that ethylene glycol, methanol, and ethanol have inhibitory effects on the functional activity of natural killer cells in vitro [19]. These findings might explain the association of HPS in a case of EG poisoning.

It seems that following ethylene glycol intoxication, although NK cell activity was not studied, reduced NK cells activity may be responsible for the development of HPS. Therefore, we suggest that patients with ethylene glycol intoxication who develop bicytopenia or pancytopenia and other criteria for HPS should be examined with bone marrow aspiration for demonstration of hemophagocytosis.

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