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Zieve's syndrome presenting with coagulopathy, skin and subcutaneous haemorrhage

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Zieve syndrome is characterized by hepatic dysfunction, jaundice, hyperlipidaemia, and reversible hemolytic anaemia after alcohol abuse. We report a rare case of this syndrome presenting with coagulopathy and subcutaneous haemorrhage. Laboratory tests showed macrocytic anaemia, hyperbilirubinemia, increased activity of aminotransferases, hyperlipidemia, coagulopathy, signs of haemolysis: reduced concentration of haptoglobin, free hemoglobin. These abnormalities improved during 20 days. Ultrasonography revealed subcutaneous haemorrhagias, liver biopsy was consistent with steatohepatitis. There are a small number of reported cases of Zieve syndrome, and the reason could be the lack of pathognomonic symptoms, rapid decrease of hyperlipidaemic serum levels after alcohol withdrawal, patients denial of drinking. There is no specific treatment, therapy is similar to that for acute alcoholic hepatitis. The Zieve syndrome must be allways considered in the differential diagnosis of uncertain origin liver injury, hemolysis or coagulopathy.

Key words: Zieve syndrome, subcutaneous haemorrhage, hyperlipidaemia, hemolytic anaemia

INTRODUCTION

The Zieve syndrome is characterized by fatty liver or cirrhosis, and jaundice, hyperlipidemia, hemolytic anaemia after alcohol abuse (1). We report an unusual case of Zieve's syndrome presenting with subcutaneous haemorrhage. This article also aims to expand the awareness of this rare disorder.

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CASE PRESENTATION

A 45 year old Caucasian female was referred to our Gastroenterology Department because of weakness, anorexia, jaundice, spontaneous haemorrhage, bleeding from the gums, peripheral edemas, upper abdominal discomfort. These complaints lasted for five days. There was no history of abdominal pain. The patient denied chronic alcohol consumption, but later the binge drinking before 6 days came to light.

Physical examination revealed jaundice, an enlarged liver, palpable skin and subcutaneous

haemorrhagias, peripheral edemas, signs of minimal encephalopathy.

Laboratory tests showed hyperchromic and macrocytic anaemia: red blood cell count 3.21 × 10^9l (reference range, 3.7–5.3 × 10^9l), hemoglobin concentration (Hb) – 112 g/l (reference range, 123–153 g/l), hematocrit – 36% (reference range, 35–47%), mean corpuscular volume – 112.6 fl (reference range, 80–96 fl), mean corpuscular hemoglobin – 36.6 pg (reference range, 28–33 pg)), with acantocytes in peripheral blood smear, trombocytes 191–225 × 10^9/l (reference range, 130–400 × 10^9/l).

Increased activity of aminotransferases: aspartate aminotransferase (AST) – 141 IU/l (reference range, 9–36 IU/l), alanine aminotransferase (ALT) – 66 IU/l (reference range, 10.0–28.0 IU/l)), alkaline phosphatase (ALP) – 319.0 IU/1 (reference range, 40–141.1 IU/l), gamma-glutamyltranspeptidase (γ-GT) – 506 IU/1 (reference range, 7–64 IU/l), bilirubin – 337.20 μmol/l (reference range, 3.4–20.5 μmol/l), direct bilirubin – 207.60 μmol/l (reference range, 0–6.8 μmol/l), indirect bilirubin – 129.60 μmol/l.

Hyperlipidemia: triglyceride – 5.49 mmol/l (reference range, 0–1.45 mmol/l), low-density lipoprotein (LDL) – 7.36 mmol/l (reference range, 0–2.59 mmol/l), high-density lipoprotein (HDL) – 0.44 mmol/l (reference range, 1.55–10 mmol/l), cholesterol – 10.12 mmol/l (reference range, 0–5.2 mmol/l).

Impaired tests of the liver biosynthetic capacity: protrombin index (SPA) – 56% (reference range, 70–130%), activated partial thromboplastin time (APTT) – 69.8 s (reference range, 28–38 s), fibrinogen – 4.42 g/l (reference range, 2–4 g/l), albumin – 35 g/l (reference range, 35–48 g/l).

Signs of haemolysis: reduced concentration of haptoglobin – 22 mg/l (NR 360–2 000 mg/l), free hemoglobin – 0.7 g/l.

Coagulopathy, anaemia, hyperbilirubinemia improved rapidly during the treatment. Protrombin index (SPA), activated partial thromboplastin time (APTT) reached normal levels after two weeks. The dynamics of bilirubin levels are shown in Fig. 1, aminotransferase in Fig. 2, APTT in Fig. 3, SPA in Fig. 4, lipids in Fig. 5.

The ultrasonography revealed subcutaneous haemorrhagias (Fig. 6). Abdominal ultrasound showed hyperechogenic liver, hepatomegaly, mini-

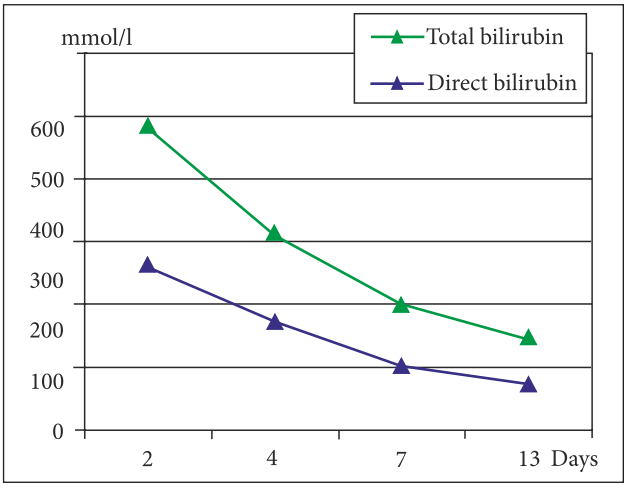

Fig. 1. The dynamics of total and direct bilirubin levels during the treatment

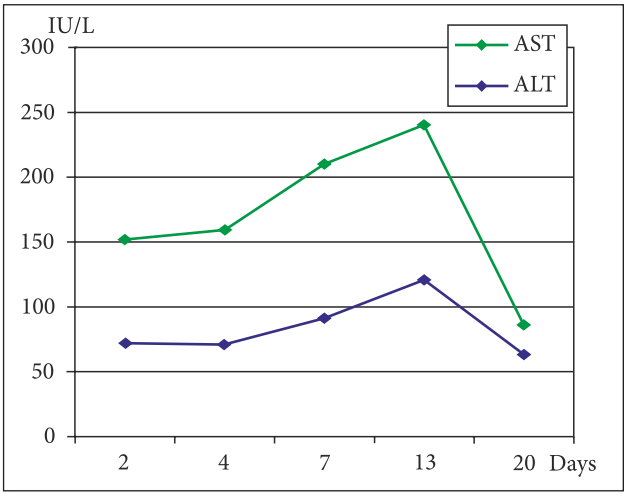

Fig. 2. The dynamics of aspartate (AST) and alanine aminotransferase (ALT) levels during the treatment

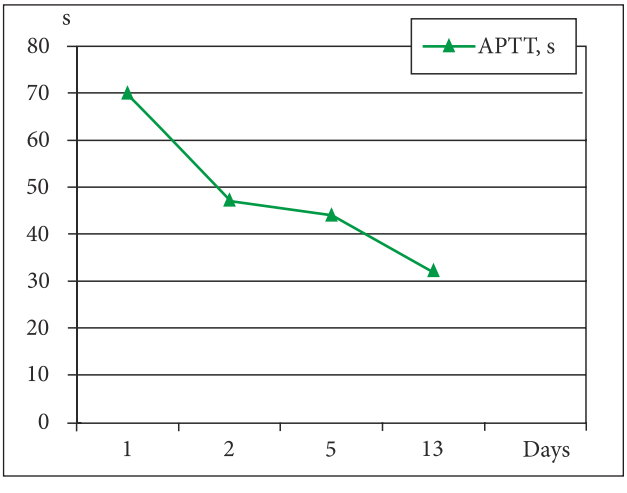

Fig. 3. Changes of activated partial thromboplastin time (APTT)

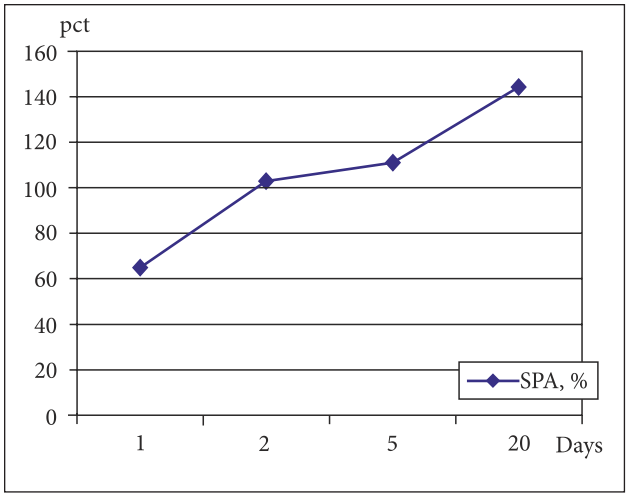

Fig. 4. Changes of protrombin index (SPA)

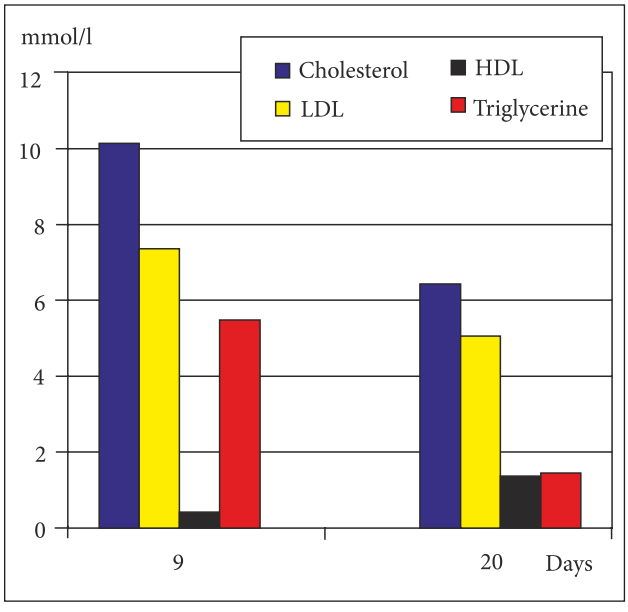

Fig. 5. Dynamics of the serum lipids

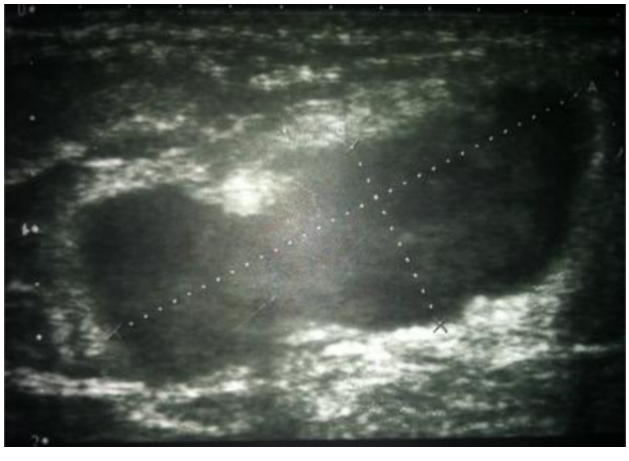

Fig. 6. Ultrasonography showing subcutaneous haemorrhagia

mal ascitis, no evidence of dilated extrahepatic biliary ducts or obstruction, enlarged spleen.

Transjugular liver biopsy findings were consistent with steatohepatitis: infiltration by neutrophils, macrovesicular steatosis in 90%, fibrosis in the pericentral zone.

Criteria of metabolic liver diseases, serology tests for hepatitis B and C, autoantibodies were negative.

The patient was given a fat-free diet, vitamin K and folic acid substitution, parenteral fluids, diuretics, acidum ursodeoxycholicum, omega-3 fatty acids.

Clinical condition improved and at the end of the hospitalization period was satisfactory.

DISCUSSION

This syndrome was described by Leslie Zieve in 1958 at the 38th Annual Session of the American College of Physicians in Boston. It is characterized by jaundice, hepatic dysfunction, transient hyperlipidemia and haemolytic anemia associated with alcohol abuse. When excess alcohol ingestion is the proximate cause, the condition improves rapidly when alcohol consumption is stopped (1, 2). Zieve syndrome was reported mostly in the 1970s and only rarely in the English literature after the mid-1990s (1–3).

In the original case series, L. Zieve described 20 male, aged 26 to 65 years, with history of alcoholism. Of the 16 patients who underwent liver biopsy, fatty infiltration was present in 88%. Most patients complained of upper abdominal pain (simulating an acute abdomen), had macrocytic anaemia and about half of them had hyperlipemia. L. Zieve observed that once the patients stopped consuming alcohol, their jaundice improved relatively quickly. In most of the patients, the hypercholesterolemia and jaundice resolved by the third week of hospitalisation (1–4). Zieve's syndrome may rarely occur with intracranial haemorrhage. Although it remains unclear whether there is a causal relationship between these two conditions, it seems that hyperlipidemia may be a major cause of intracranial bleeding (5). There is a pathogenetic relationship among the clinical and biological parameters in this syndrome. In Zieve's syndrome hemolytic anaemia and jaundice are short in duration, and the serum lipids decrease in a few days

(6–8). The clinical manifestations of the syndrome contain no pathognomonic symptoms. This is possibly the cause of rare recognition of the syndrome, it may be more common than previously thought. Another reason for a small number of reported cases may be that hyperlipidemic serum levels rapidly decrease after alcohol withdrawal. Its frequency in a general medical ward has been estimated at one in 1 600 admissions (9).

We describe a rare case of this condition associated with spontaneous skin and subcutaneous haemorrhage. So far no analogous changes have been reported due to the Zieve syndrome. Hemolytic anaemia, jaundice, hyperlipidemia, palpable subcutaneous haemorrhage in hands, abdomen, spin and legs of our patient resolved after 20 days.

Zieve's syndrome can occur in a patient with or without pre-existent alcohol liver damage (10). To indentificate an alcoholic liver damage usually takes problems because of patient's denial of drinking. If the diagnosis is suspected, liver function and hematologic tests have to be done to detect signs of liver injury and anaemia. A complete medical history of the patient has to be taken. History should be confirmed by family members. Patients can be screened for alcoholism using the CAGE questionnaire (11, 12). The diagnosis requires exclusion of viral, autoimmune hepatitis and cholelithiasis. Serologic, autoimmune markers were negative in our patient. Although the findings in the present case were consistent with a diagnosis of the Zieve syndrome, the possibility of other causes of coagulopathy were excluded.

Most of the proteins involved in the coagulation process are produced in the liver. Worsening coagulopathy correlates with the severity of hepatic dysfunction. Various factors contribute to the abnormalities of coagulation seen in patients with liver disease:

- **Increased bleeding risk** – decreased production of non-endothelial cell-derived coagulation factors (II, V, VII, IX, X, XI, XIII), thrombocytopenia, abnormalities of fibrinogen.
- **Increased thrombotic risk** – decreased levels of proteins C and S, antithrombin, plasminogen, and elevated levels of endothelial cell-derived factor VIII and von Willebrand factor.

The following tests are helpful in determining the coagulation status of the patient with liver disease: platelet count, prothrombin time, APTT, thrombin time, fibrinogen level, fibrin D-dimer. Measurement of individual coagulation factors (e. g., factors V, VII, VIII) may be helpful in determining vitamin K status as well as the presence or absence of disseminated intravascular coagulation (13, 14).

There is no specific treatment, therapy is similar to that for acute alcoholic hepatitis. Abstinence leads to complete clinical remission and prevents recurrence.

CONCLUSIONS

Zieve syndrome is a rare condition characterized by hemolytic anemia in conjunction with secondary hyperlipidemia in patients suffering from alcohol related toxic liver damage. It must be considered in the differential diagnosis of uncertain origin liver injury, hemolysis or hemorrhgias as well as in our case. Further research is required to establish the pathogenesis of this syndrome.

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ZIEVE SINDROMAS IR SUTRIKĘS KREŠĖJIMAS, ODOS IR POODINĖS KRAUJOSRŪVOS

Santrauka

Zieve sindromui būdingas kepenų funkcijos sutrikimas, pasireiškiantis gelta, sutrikusiu krešėjimu, hiperlipidemija ir grįžtamąja hemolizine anemija pavartojus alkoholio. Straipsnyje aprašytas retas klinikinis atvejis, kai dėl sutrikusio krešėjimo atsirado didelės poodinės kraujosrūvos. Tyrimais buvo nustatyta makrocitinė anemija, hiperbilirubinemija, padidėjęs aminotransferazių aktyvumas, hiperlipidemija, koaguliopatija, hemolizės požymiai: sumažėjęs haptoglobinas, atsiradęs laisvasis hemoglobinas. Šie pokyčiai normalizavosi per 20 dienų. Atliekant ultrasonografiją buvo matyti poodinės kraujosrūvos, kepenų biopsijos duomenys buvo būdingi steatohepatitui. Tai, kad šio sindromo atvejų aprašyta nedaug, galėjo nulemti būdingų požymių stoka, greitas hiperlipidemijos, sutrikusio krešėjimo normalizavimasis nutraukus alkoholio vartojimą, kurį dauguma pacientų neigia ar slepia. Nėra specifinio šios patologijos gydymo. Apie *Zieve* sindromą reikėtų pagalvoti esant neaiškios kilmės kepenų pažeidimui, hemolizei ar koaguliopatijai.

Raktažodžiai: *Zieve* sindromas, poodinės kraujosrūvos, hiperlipidemija, hemolizinė anemija