Zieve's Syndrome and Hemochromatosis, are they Related?

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Case Report

A 42 years old man with alcoholic liver cirrhosis was admitted to our hospital for the persistence of a few days of gingival bleeding, jaundice and abdominal pain. The patient reported a recent alcohol abuse. At physical examination was revealed the presence of scleral jaundice, hepatosplenomegaly, gengiva bleeding and bronzed skin. At laboratory tests was showed an increase in total bilirubin (10.20 mg/dL) mainly of direct fraction (7.60 mg/dL), amylase (152 U/L), lipase (936 U/L), transaminases (GOT 400 U/L and GPT 165 U/L), GGT (326 U/L), alkaline phosphatase (333 U/L), PCR 6.2 mg/dL, macrocytic anaemia (Hb 7.7 g/dL, MCV 109.5 fl), INR 2.

Moreover, further exams were performed:

- Study of iron status that showed a significant increase in serum ferritin (4144 mcg/L, so it was performed the genetic study that affirmed the alcoholic etiology of the hemochromatosis)
- Peripheral smear showed the presence of schistocytosis
- Haptoglobin assay (undetectable)
- Direct Coombs test (negative) and indirect Coombs (positive)
- Reticulocytes with physiological increase after anaemia
- TORCH, HBV and HCV negative
- ANA, ENA, anti-LKM, anti-SMA anti SLA, anti-AMA negative

Sonography with ecocolor excluded the presence of biliary obstruction but showed signs of chronic cirrhosis complicated from portal hypertension.

At the EGDS was showed oesophageal varices (grade I) in the context of a congestive gastropathy and antral gastritis. So the patient was treated with fasting, abstaining from alcohol and fluids therapy, branched amino acids and gastric protection with progressive improvement in clinical exams and laboratory tests. Furthermore, it was referred to a center for alcohol detoxification and start iron chelation therapy. At the end the patient was discharged with a diagnosis of alcoholic cirrhosis in Zieve syndrome and secondary hemochromatosis from alcohol abuse (Figures 1-3).

Discussion

Zieve’s syndrome, described for the first time by Leslie Zieve in 1958, it is characterized by the presence of jaundice, haemolytic anaemia, increased transaminases and transient hyperlipidemia associated with alcohol abuse [1]. Zieve saw that after interruption of alcohol consuming, jaundice and hypercholesterolemia improved
quickly. There aren’t pathognomonic symptoms or clinical signs of the syndrome, so it is difficult to recognize this disease. A further cause for underdiagnosing of this illness may be that hyperlipidemic status rapidly decreases after stop alcohol intake.

Some authors showed that hyperlipidemia stopped before the appearance of haemolysis that is caused by an acquired deficiency of pyruvate kinase blood red cells’s. This finding is absent in patient with alcoholic cirrhosis uncomplicated from haemolysis [2,3]. We have shown a case of Zieve syndrome without hyperlipidemia because the patient was being treated with simvastatina 40 mg. This therapy was set few years before in another hospital admission where he showed, after an alcohol abuse, the same clinical and laboratory findings but this time associated with hyperlipemia (total cholesterol 210 mg/dL).

Zieve’s syndrome can occur, also, in patients with or without pre-existent alcohol liver damage. The diagnosis requires exclusion of viral, autoimmune hepatitis and biliary obstruction; negativity of serologic and autoimmune markers. Hemochromatosis is an abnormal accumulation of iron in parenchymal organs of the body that leads, if not treated to organ dysfunction [4,5]. Iron overload syndromes are divided into two main groups (Tables 1 and 2).

### Table 1: Iron overload syndromes – Primary.

| HFE related hemochromatosis (Type 1) | Primary            |
|--------------------------------------|-------------------|
|                                      | C282Y/C282Y       |
|                                      | C282Y/H63D        |
| Other HFE mutations Non-HFE related hemochromatosis (Type 2) |                |
|                                      | Type 2A – Hemojuvelin mutations |
|                                      | Type 2B – Hepcidin mutations |
| Transferrin receptor 2 hemochromatosis (Type 3) |                |
| Ferroportin diseases (Type 4)        |                |
|                                      | Classical         |
|                                      | Nonclassical      |

### Table 2: Iron overload syndromes – Secondary.

|                                |
|--------------------------------|
| Alcoholic liver disease        |
| NAFLD iatrogenic               |
| Red Blood cell transfusion     |
| Long-term haemodialysis        |
| Miscellaneous                  |
| Aceruloplasminaemia            |
| African iron overload          |
| Neonatal iron overload         |

Hemochromatosis is still underdiagnosed by clinicians because it is considered a rare disorder. The majority of patients with hemochromatosis appear asymptomatic but when they become symptomatic may present with: fatigue, right upper quadrant abdominal pain, arthralgias, (typically of the second and third metacarpophalangeal joints), chondrocalcinosis, impotence, decreased libido, and symptoms of heart failure or diabetes. Physical findings depends of organ damage: an enlarged liver, signs of cirrhosis, testicular atrophy, diabetes, congestive heart failure, skin pigmentation, changes of porphyria cutanea tarda, and arthritis [6].

At physical examination, our patient showed with bronzed skin and clinical signs of liver cirrhosis (hepatosplenomegaly, elevation of the umbilicus, ascites, thrombocytopenia), which added to the results of laboratory tests, induced us to suspect the diagnosis of alcoholic hemochromatosis, later confirmed by genetic testing. In fact, the diagnosis of hemochromatosis is based on evidence of increased iron stores, demonstrated by elevated serum ferritin levels, which reflects an increase in hepatic iron content.

The hereditary hemochromatosis can be defined genotypically by the familial occurrence of iron overload associated with some genetic mutation (C282Y homozygosity or C282Y/H63D compound heterozygosity). Liver biopsy should be considered only for demonstrate the presence or absence of advanced fibrosis or cirrhosis, which does have prognostic value.

The treatment of hemochromatosis is based on the removal of iron excess that can be made with phlebotomy or with the use of chelating drugs.

### Conclusions

Zieve’s syndrome is a rare condition characterized by haemolytic anaemia, jaundice and hyperlipidemia after alcohol abuse in patients with chronic liver disease [3]. So, in these patients, it must be considered in the differential diagnosis of certain unknown liver injury, haemolysis or hemorrhagias.

The relation between liver iron stores and alcoholic liver disease is well demonstrated since the 1964, and hemochromatosis is believed to be a particular manifestation of alcoholic cirrhosis [7,8]. The liver iron surplus is an independent risk factor for fibrosis, while in alcoholic cirrhosis the accumulated liver iron concentrations correlate inversely with patient survival. It is known that serum iron and ferritin increase linearly with daily alcohol consumption [9].
In our case we have showed that alcohol is the string that joins two rare illnesses, because: after an acute alcohol abuse our patient have manifested a Zieve’s syndrome, but is exactly the chronic alcohol consumption that has caused a secondary hemochromatosis and cirrhosis. So we can concluded that even in the face of a common disease as alcoholic cirrhosis we should ask ourselves if it hides a rare diseases, because the treatment requires not only the stop of alcohol consumption but also additional measures, such as the use of chelating agents to avoid further organ damage.

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