Acute steatohepatitis, due to extreme metabolic dysregulation, as the first presentation of non-alcoholic fatty liver disease

Georgios Kranidiotis, Angeliki Angelidi, Emmanouel Sevdalis, Thomas-Nikolaos Telios, Alexandra Gougoutsi, Andreas Melidonis

1st Department of Internal Medicine, "Tzaneion" General Hospital, Piraeus, Greece

Abstract

Non-alcoholic fatty liver disease (NAFLD) is a slowly progressive chronic disease, with a high prevalence among obese, dyslipidemic or diabetic people, commonly presented as an asymptomatic mild elevation of serum aminotransferases. We report a patient who experienced an acute form of non-alcoholic steatohepatitis, as the first manifestation of NAFLD, due to exacerbation of pre-existing metabolic disorders by an extremely unhealthy lifestyle. A 50-year old, obese, diabetic man presented with a one-week history of jaundice and malaise. Analysis revealed elevated liver enzymes, bilirubin, lipids, and glucose. Based on patient's history, physical examination, laboratory results, and imaging findings, acute non-alcoholic steatohepatitis was established as a diagnosis of exclusion. The patient was started on a low-calorie diet free of carbohydrates and fats, in combination with insulin. A dramatic improvement of clinical and laboratory parameters was observed. In the context of extreme metabolic dysregulation, induced by unhealthy diet, NAFLD may present as an acute steatohepatitis.

Introduction

Non-alcoholic fatty liver disease (NAFLD) has been increasingly recognized as the most common liver disease. Its prevalence in the general population is estimated to be 20-40%,[1] while higher prevalence rates (80-90%) are observed in individuals with obesity, diabetes or dyslipidemia.[2,3]

The diagnosis of NAFLD requires evidence of hepatic steatosis, either by imaging or by histology, in the absence of causes for secondary hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medication, or hereditary disorders. NAFLD encompasses a wide spectrum of fat-induced liver injury, ranging from simple steatosis to steatohepatitis and cirrhosis, with subsequent evolution to liver failure, or rarely hepatocellular carcinoma. Depending on the presence or not of inflammation with hepatocyte ballooning, it is categorized into non-alcoholic steatohepatitis (NASH) and NAFL, respectively.[4]

NAFLD is pathophysiologically related to insulin resistance and hyperinsulinemia.[5]

It is associated with metabolic risk factors such as obesity, diabetes mellitus, or dyslipidemia, and is therefore considered the hepatic expression of metabolic syndrome.[6]

As a rule, NAFLD is a slowly progressive chronic disease, commonly presented as an asymptomatic mild elevation of serum aminotransferases.[7] We herein report the case of a patient who experienced an acute, aggressive form of NASH, as the first manifestation of NAFLD, due to exacerbation of pre-existing metabolic disorders by an extremely unhealthy lifestyle.

Case Report

A 50-year old man was admitted to our hospital because of a 1-week history of jaundice, fatigue and malaise. On physical examination, the patient was obese, with a body mass index of 37 kg/m^2, and a waist circumference of 136 cm. His temperature was 36.6°C, blood pressure 160/90 mmHg, and heart rate 107 bpm. Hepatomegaly was detected. The liver was soft, and nontender, with a smooth edge palpable 5 cm below the right costal margin. No xanthomas were found.

The patient's medical history included type II diabetes mellitus, diagnosed 7 years ago, dyslipidemia (elevated triglycerides, mildly increased cholesterol, and reduced high density lipoprotein - cholesterol), two-vessel coronary artery disease, treated with percutaneous transluminal coronary angioplasty plus stenting 7 months before this admission, and an episode of acute pancreatitis 4 years ago. His family history was notable for gastric cancer in his father.

The patient was an unmarried chandler, who lived with his parents and brother in a working-class suburb of Athens. He had been a heavy smoker (approximately 115 pack-years), but consumed only small quantities of alcohol during social events (<100 g per week). He reported no use of illicit drugs or anabolic steroids, no ingestion of mushrooms, herbal preparations or nutritional supplements, and no exposure to environmental toxins. He was following an extremely unhealthy dietary pattern, characterized by exorbitant calorie intake (estimated amount of 8000 kcal per day), and excessive consumption of saturated animal fats and simple carbohydrates, combined with a sedentary lifestyle and lack of physical activity. His daily medication regimen included aspirin, nebivolol, enalapril, metformin, vildagliptin, and omega-3 fatty acids [eicosapentaenoic (EPA), and docosahexaenoic acid (DHA)].

The most prominent laboratory abnormalities were conjugated hyperbilirubinemia (total bilirubin 10 mg/dL, direct bilirubin 6.6 mg/dL), elevation of liver enzymes, with a disproportionate rise of aminotransferases in comparison to alkaline phosphatase (aspartate transaminase 474 U/L, alanine transaminase 647 U/L, gamma-glutamyltransferase >1453 U/L, alkaline phosphatase 409 U/L), and striking hypertriglyceridemia (triglycerides >1420 mg/dL). The glycosylated hemoglobin value of 11.1% indicated poor diabetic control. Additional abnormal test results were as follows: hematocrit 39%, hemoglobin 13g/dL, mean corpuscular volume 84 fl, lactate dehydrogenase 512 U/L, serum sodium 112 meq/L, glucose 431 mg/dL, total cholesterol >705 mg/dL, high density lipoprotein - cholesterol (HDL-C) 26 mg/dL, erythrocyte sedimentation rate 103 mm/h, C-reactive protein 43 mg/L. The

Correspondence: Georgios Kranidiotis, Kanari 39, 18537, Piraeus, Greece.
Tel.: +306974071547.
E-mail: gekranid@hotmail.com

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patient's plasma had a turbid appearance. Urinalysis showed marked glycosuria and bilirubinuria.

Hepatitis A immunoglobulin M (IgM) antibody, hepatitis B surface antigen and core IgM antibody, a polymerase chain reaction assay for hepatitis C viral RNA, and serologic tests for Epstein-Barr virus, human immunodeficiency virus, and cytomegalovirus were negative. Tests for anti-nuclear, anti-smooth-muscle, anti-liver-kidney microsomal type 1, anti-mitochondrial, and anti-neutrophil cytoplasmic antibodies were also negative. Levels of α1-antitrypsine and ceruloplasmin were normal, and transferrin saturation was less than 40%.

Abdominal ultrasound examination revealed hepatic enlargement and a diffuse increase in echogenicity of the liver as compared with that of the kidneys (*bright liver*). No other organ abnormality was observed. An abdominal computed tomography scan (Figure 1), obtained after oral and intravenous administration of contrast material, demonstrated a low-density hepatic parenchyma, which appeared darker than the spleen. Both imaging studies were consistent with fatty infiltration of the liver.

Given the patient's history, physical examination, laboratory results and imaging findings, we concluded the following clinical diagnoses: first, type IV hyperlipoproteinemia, according to Fredrickson's classification[8] (familial hypertriglyceridemia), exacerbated by excessive intake of simple carbohydrates, obesity, and insulin resistance, all of which increase very-low-density lipoprotein synthesis; second, acute form of NASH. Moreover, the patient met Adult Treatment Panel III criteria for metabolic syndrome.[9]

The patient was then started on a low calorie diet, with complete exclusion of carbohydrates and fats, and pure intake of high quality protein (chicken breast). He was also treated with isophane insulin (40-30 IU), and omega-3 fatty acids (EPA/DHA 920/760 mg bid). During the next 10 days, the patient showed dramatic improvement of his clinical and laboratory status (Table 1), and was discharged from the hospital. He was advised to keep on the medication received during his hospitalization, reduce calorie intake, eat plenty of vegetables and fruits, rich in fiber and complex carbohydrates with a low glycemic index, avoid saturated fats and simple carbohydrates, walk 30 min every day, quit smoking, and abstain completely from alcohol.

Eight weeks later, the patient was invited for a follow-up appointment. Having strictly implemented medical recommendations, he had lost 20 kg of body weight. His signs and symptoms were entirely resolved. Further, impressive amelioration of laboratory values was noted (Table 1). Continuation of lifestyle modification was emphasized, and isophane insulin dose was reduced by 20% (32-24 IU). Aspirin 100 mg qd, metformin 850 mg bid, pioglitazone 30 mg qd, atorvastatin 20 mg qd, and EPA/DHA 920/760 mg bid were prescribed.

Discussion

The initial step in the evaluation of a jaundiced patient with conjugated hyperbilirubinemia accompanied by other liver test abnormalities is to differentiate between a hepatocellular and a cholestatic process. In our patient, the pattern of liver enzyme elevations suggested a hepatocellular condition. Hepatocellular diseases that may produce jaundice include viral, alcoholic or autoimmune hepatitis, drug or environmental toxicity, hemochromatosis, α1-antitrypsine deficiency, Wilson's disease, and end-stage cirrhosis from any cause. On the basis of history, physical examination, and appropriate laboratory investigations, all possible causes of hepatocellular injury were excluded. Radiologic findings pointed towards hepatic steatosis. Thus, by exclusion, we assumed that we were faced with an acute, aggressive form of NASH, due to severe metabolic dysregulation, induced by an extremely unhealthy diet. The fact that the patient manifested an excellent response to diet and insulin alone supported our hypothesis, and made liver biopsy redundant, in regards to his management, and unethical, given the risks it carries. Besides, according to current guidelines,[4] though biopsy remains the gold standard for characterizing liver histology in patients with NAFLD, it should be performed only in those patients who are expected to benefit the most from diagnostic, therapeutic, and prognostic perspectives, on account of its economic cost and morbidity risk.

Several novel biomarkers for the presence of steatohepatitis in patients with NAFLD have been investigated, such as tumor necrosis factor-α (TNF-α),[10] adiponectin alone or in combination with homeostatic model assessment of insulin resistance (HOMA-IR) and type IV collagen 7S,[11] interleukin-6 (IL-6),[12] and cytokeratin-18 (CK-18).[13] CK-18, an intracellular protein released into blood by necrosis and apoptosis of hepatocytes, is the most promising, and the only one that has been independently validated.[14] However, it is not yet routinely disposable, and guidelines do not recommend it in daily clinical practice.[4] In regards to newer imaging techniques, ultrasound transient elastography (FibroScan®, Echosense, Paris, France) and its magnetic resonance (MR) equivalent represent rapid, non-invasive methods for assessment of liver fibrosis and determining need for biopsy.[7] MR spectroscopy has been used to measure changes in hepatic fat in response to lifestyle modification.[15]None of the aforementioned diagnostic modalities was available in our hospital.

Sporadic cases of acute NASH related to prednisolone therapy,[16-18] and a small number of patients with acute exacerbation of previously unrecognized NASH have been described. The latter were all obese and middle-aged women with no history of liver disease, but already established cirrhosis, as demonstrated histologically, who developed

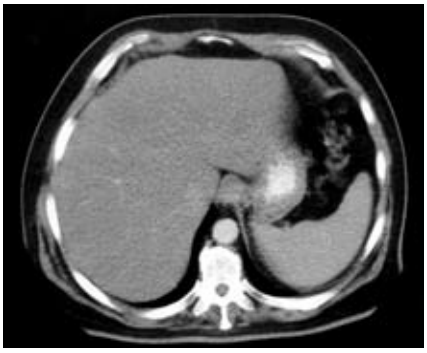

Figure 1. Abdominal computed tomography scan, obtained after oral and intravenous administration of contrast material, shows a low-density hepatic parenchyma, which appears darker than the spleen. This finding is consistent with fatty infiltration of the liver.

Table 1. Laboratory data.

Variable	On admission	After 10 days	After 8 weeks
Triglycerides (mg/dL)	>1420	478	275
Total cholesterol (mg/dL)	>705	669	213
Total bilirubin (mg/dL)	10	2.5	0.6
Aspartate transaminase (u/L)	474	89	22
Alanine transaminase (u/L)	647	165	27
C-reactive protein (mg/L)	43	8	2.7
Glycosylated hemoglobin (%)	11.1	-	6.7

subacute liver failure (over a period of 4-16 weeks).[19]

In the acute phase of steatohepatitis and subsequent elevation of aminotransferase levels >3 times the upper limit of normal, administration of oral antihyperglycemic agents, or lipid-lowering drugs, such as fibrates or statins, was contraindicated. After normalization of transaminases, our patient was started on a triple antidiabetic treatment, with insulin, metformin, and pioglitazone. Metformin and pioglitazone reduce insulin resistance, which is the pathogenetic basis of metabolic syndrome. Pioglitazone, additionally, has a beneficial effect on NAFLD, improving not only simple steatosis, but also inflammation and fibrosis. Atorvastatin was chosen to reduce low-density lipoprotein-cholesterol (LDL), and omega-3 fatty acids to treat remaining mild hypertriglyceridemia. Both atorvastatin and omega-3 fatty acids have been found to improve simple steatosis. While lifestyle intervention constitutes the cornerstone of NAFLD therapy, the utility of weight loss medications remains controversial. Orlistat confers no additional histological benefit, whereas rimonabant reverses steatosis, but has been withdrawn due to concern about psychiatric adverse effects.[20]

Conclusions

Unhealthy diet, by exacerbating preexisting metabolic disorders, can lead to immediate life-threatening situations. In the context of extreme metabolic dysregulation, NAFLD may present as an acute steatohepatitis.

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