Transient Dyslipidemia Mimicking the Plasma Lipid Profile of Tangier Disease in a Diabetic Patient with Gram Negative Sepsis

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Abstract. Tangier disease is a rare genetic disorder of lipid metabolism characterized by low concentrations of plasma high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol with normal or elevated levels of triglycerides. In this case report we describe a patient with diabetes who experienced an episode of urosepsis with a plasma lipid profile resembling Tangier disease. Experimental evidence in the literature suggests that similar lipid changes may occur due to cytokines released during sepsis. Clinicians should be aware of these changes to avoid misdiagnosis of lipid disorders.

Introduction

Tangier disease (familial alpha lipoprotein deficiency) is a rare genetic disorder of lipid metabolism characterized principally by a severe deficiency of high density lipoprotein (HDL), accompanied by low plasma levels of low density lipoprotein (LDL) cholesterol, normal or elevated plasma levels of triglycerides, and accumulation of cholesteryl ester in reticuloendothelial tissue [1, 2]. Phenotypically, patients with Tangier disease may have enlarged orange tonsils, hepatosplenomegaly, peripheral neuropathy, hemolytic anemia and bleeding diathesis. These patients often have premature cardiovascular disease. Tangier disease is caused by a homozygous mutation of the ATP – binding cassette transporter protein A1 (ABC-A1) [2]. It is noteworthy that cytokines, notably TNF-α, down-regulate the ABC-A1 [3, 4]. Thus it is possible that increased TNF-α production, such as in sepsis, may produce lipid abnormalities that resemble those seen in Tangier disease.

We describe a patient with diabetes who transiently had a plasma lipid profile resembling Tangier disease during an episode of urosepsis. Within two weeks post recovery the dyslipidemia resolved and the plasma lipid profile returned to baseline values.

Clinical History

The patient was a 58-year-old woman presenting with the chief complaint of generalized abdominal pain with nausea, vomiting, and fever for four days. Past medical and surgical history were significant for diabetes mellitus, an ovarian cyst, nephrolithiasis and oophorectomy. Family history was negative for coronary disease or diabetes mellitus. She denied smoking or alcohol use and she ate an exclusively vegetarian diet. The only prescribed medication was metformin 1,000 mg orally twice per day.

The physical examination was unremarkable and the patient was in no acute distress. Blood pressure was 112/75 mm Hg, heart rate was 103 beats/minute, respiratory rate was 16/minute, and her temperature was 98.4° F. Oxygen saturation was 100% on room air. The tonsils were not enlarged, there was no clouding or opacification of the cornea, no hepatosplenomegaly, and the neurological examination was unremarkable.
Laboratory evaluation revealed a normal blood count with the exception of elevated white blood cell count of 14,400/ml, normal serum electrolytes, creatinine, liver enzymes, amylase, lipase, albumin, bilirubin, prothrombin time and thyrotropin. Urinalysis showed pyuria with 1,514 white blood cells and 139 red cells per high power field. The urine and blood cultures grew *E. coli*. The blood glucose and lipid profile of the patient during hospitalization, 3 months prior, and 10 days after hospitalization are summarized in Table 1.

Lipids were measured on a Roche Modular automated chemistry analyzer using Cobas reagents (Roche Diagnostics, Indianapolis, IN). Triglycerides were measured with an enzymatic method involving hydrolysis of triacylglycerides to glycerol by lipoprotein lipase, conversion of glycerol to glycerol-3-phosphate (G-3-P) by glycerol kinase, oxidation of G-3-P to dihydroxyacetone phosphate by glycerol phosphate oxidase, and photometric quantification of the peroxide byproduct. Cholesterol esters were hydrolyzed with cholesterol esterase prior to oxidation with cholesterol oxidase and photometric measurement of the peroxide byproduct. HDL-cholesterol was measured with polyethylene glycol-modified cholesterol esterase and oxidase enzymes (HDL-C Plus 3rd Generation, Roche Diagnostics). LDL-cholesterol was measured as above after selective partitioning into a nonionic detergent (LDL-C Plus 2nd Generation, Roche Diagnostics). The laboratory does not estimate LDL concentration with the Friedewald equation if the triglyceride concentration exceeds 400 mg/dL.

Lipoprotein electrophoresis was performed at a referral laboratory (LabCorp, Burlington, NC) on a specimen collected during the patient’s hospitalization, and the result appears in Figure 1. No chylomicrons were detected, but the pre-beta (VLDL) band was significantly increased while the alpha and beta bands were reduced or absent.

A chest radiograph was normal with no cardiomegaly, and CT imaging of the abdomen revealed no organomegaly. There was mild right hydronephrosis with a 2.1 cm calculus noted in the right renal pelvis, and a 2.6 cm right adnexal cyst for which follow-up was recommended. The patient was treated with intravenous ceftriaxone.

**Discussion**

The baseline lipid profile prior to this patient’s hospitalization was notable for hypertriglyceridemia with modestly low HDL.
cholesterol, typical of metabolic syndrome and type 2 diabetes [5-7]. Both HDL and LDL cholesterol concentrations decreased dramatically during her hospitalization and subsequently returned towards the baseline values two weeks after recovery from the acute illness. The lipid profile during hospitalization resembles Tangier disease. However, the patient did not have physical stigmata of Tangier disease, and the lipid abnormalities quickly resolved within two weeks of treatment.

Acute inflammation has been shown to produce lipid abnormalities [8, 9]. Injection of TNF-α in cynomolgus monkeys caused a 38% increase in plasma triacylglycerol, a 30% decrease in plasma cholesterol, along with significant decreases in apolipoproteins A-I and B. These changes were qualitatively similar to those seen after lipopolysaccharide injection [8]. However, the plasma total cholesterol levels did not change in the animals fed saturated fat and cholesterol because the decrease in cholesterol ester content of LDL and HDL was offset by an increase in very low density lipoprotein (VLDL) [9]. Thus, it is possible that the lipopolysaccharide produced during the gram negative E. coli sepsis raised TNF-α levels, which subsequently lowered HDL and LDL cholesterol levels. This biochemical scenario is highlighted in Figure 2.

Similar lipid abnormalities have been described in patients with severe sepsis, although the reductions in HDL and LDL cholesterol were not as extreme as seen in our patient [10]. It is noteworthy that these changes may have prognostic implications. In a study by Barlage, et al., changes in HDL-associated apolipoproteins were associated with mortality, and correlated with monocyte and platelet activation [11].

Multiple biochemical changes are potentially responsible for lipid abnormalities. The very low HDL cholesterol in this patient during an episode of acute septicemia is probably the result of down regulation of ABC-A1 transporter, decreased scavenger-class B type I (SR-BI) receptor that promotes cholesterol efflux from peripheral cells and mediates selective uptake of cholesteryl ester into hepatocytes [13], and the direct inhibitory effects of cytokines on apolipoprotein A1 synthesis, the principal protein of the HDL [14, 15].

The mechanism responsible for low LDL cholesterol in Tangier disease is not well understood, but may be due to enhanced catabolism of LDL [16]. Total cholesterol is often low in Tangier disease, but cases of normal total serum cholesterol can occur in patients that are heterozygous with familial combined hyperlipidemia [17]. Another explanation for the low LDL cholesterol in this patient may be that conversion of VLDL to LDL is reduced in septicemic conditions, since lipopolysaccharide and TNF-α cause a fall in lipoprotein lipase activity and in plasma concentration of lecithin:cholesterol acyltransferase [9].

Hypertriglyceridemia in Tangier disease is attributed to reduced levels of lipoprotein lipase activity, and a lower reactivity of VLDL with lipoprotein lipase, which may be the result of abnormal apolipoprotein composition [18]. Additionally, hepatocyte ABC-A1 may regulate VLDL triglyceride secretion through nascent HDL production [19]. Large nascent HDL particles, assembled by hepatic ABC-A1, generate a phosphoinositol-3 (PI 3) kinase-mediated autocrine signal that attenuates VLDL maturation and triglyceride secretion. This pathway may explain the elevated plasma triglyceride and the

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**Figure 2**: Changes in lipoprotein metabolism and their relation to cytokines. TNF-α: tumor necrosis factor-alpha; IL-1β: interleukin-1beta; IL-10: interleukin 10; ABC-A1: ATP – binding cassette transporter protein A1; SR-B1: scavenger class B type I receptor; apoA1: apolipoprotein A1; LDL: low density lipoprotein cholesterol; LPL: lipoprotein lipase; LCAT: lecithin:cholesterol acyltransferase; TG: triglyceride; HDL: high density lipoprotein cholesterol; VLDL: very low density lipoprotein cholesterol.

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inverse relationship between plasma HDL and triglyceride concentrations in individuals with compromised ABC-A1 function [19]. Increased exposure to lipopolysaccharides and TNF-α in gram negative septicemia may reduce ABCA1 function, increase insulin resistance, and aggravate hypertriglyceridemia.

Conclusion

This case report highlights an extreme case of dyslipidemia resembling Tangier disease possibly attributable to gram negative sepsis. Recent literature has described similar but transient changes in lipids associated with clinical sepsis, and clinicians should be aware of the transient nature of these lipid disorders.

References


