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Splenomegaly with sea-blue histiocytosis, dyslipidemia, and nephropathy in a patient with lecithin-cholesterol acyltransferase deficiency: a clinicopathologic correlation

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Abstract

A 31-year–old man with no significant medical history presented with a 5-day history of progressive left upper quadrant abdominal pain. Physical examination revealed a tender guarded abdomen, no icterus, and bilateral corneal "arcus senilis"–like changes. Laboratory workup showed a mild normocytic, normochromic anemia; and target cells were seen in the peripheral blood smear. Serum was turbid; and the lipid profile showed elevated total cholesterol, low high-density lipoprotein cholesterol, and elevated triglycerides. Urinalysis revealed nephrotic range proteinuria with microhematuria. An abdominal computed tomographic scan demonstrated a homogeneously enlarged spleen. The patient was discharged after symptomatic treatment to be followed as an ambulatory patient. Several days later, he returned with severe left upper quadrant pain and was admitted to the surgical service for further evaluation. A splenectomy was performed for a suspected splenic lymphoma. Upon gross examination, spleen was moderately enlarged, weighing 780 g. Sectioning revealed a beefy red cut surface without gross lesions. Wright-Giemsa–stained touch imprints showed many sea-blue histiocytes. A renal biopsy was also performed, demonstrating focal segmental glomerular sclerosis and mesangial expansion with extramembranous and intramembranous deposition of lipids. In the absence of hematologic malignancy and in light of the abnormal lipid profile, a disorder of lipid metabolism was suspected. Histologic and ultrastructural findings in the kidney and spleen raised the likelihood of lecithin-cholesterol acyltransferase (LCAT) deficiency, which was confirmed by the markedly decreased serum LCAT activity and serum LCAT mass. We describe a case with the triad of splenomegaly with sea-blue histiocytes, nephropathy, and dyslipidemia in a patient with LCAT deficiency.

1. Introduction

Lecithin-cholesterol acyltransferase (LCAT) is a plasma enzyme that converts cholesterol and phosphatidylcholines (lecithins) into cholesteryl esters and lysophosphatidylcholines by a transesterification reaction [1]. Lecithin-cholesterol acyltransferase is active on both low-density lipoproteins (apolipoprotein [apo] B–containing lipoproteins, eg, low-density lipoprotein, very low-density lipoprotein) and high-density lipoproteins (HDLs), corresponding to the β- and α-activity of LCAT, respectively [2]. However, LCAT preferentially binds to HDL particles that contain apo A-I, the most potent activator of the enzyme, and is responsible for the formation of most of the cholesteryl esters found in human plasma [2,3]. High-density lipoprotein plays a key role in the process of reverse cholesterol transport, in which it promotes the efflux of excess cholesterol from peripheral tissues and returns it to the liver for biliary excretion [4]. Nascent HDL is secreted by liver and intestine as lipid-poor apo A-I and undergoes lipidation and dynamic intravascular maturation and remodeling. Lecithin-cholesterol acyltransferase plays an important role in this maturation process. Lecithin-cholesterol acyltransferase is thus essential for maintaining cholesterol homeostasis and regulating its transport in circulation.

The deficiency of LCAT may be either acquired, usually secondary to liver disease, or congenital with an autosomal recessive mode of inheritance. Mutations in the LCAT gene result in either familial LCAT deficiency (FLD) or the milder

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phenotype known as *fish-eye disease* (FED) [5]. Inheritance of a mutated LCAT genotype causes a gene-dose–dependent alteration in plasma lipid/lipoprotein profile, renal disease, and hematologic abnormalities, with or without premature cardiovascular disease [6-8]. Patients with FLD have complete loss of LCAT activity with an increased proportion of unesterified cholesterol in plasma with markedly reduced HLD. Clinical manifestations include corneal opacification, anemia, and renal disease with proteinuria, with progression to end-stage renal disease (ESRD) [5]. In FED, there is a partial loss of LCAT activity, that is, a selective loss of HDL-associated α-LCAT activity (but preserved activity toward apo B–containing lipoproteins), with normal to slightly elevated free cholesterol in plasma with marked reduction in HDL cholesterol and corneal opacification without renal disease [9,10]. Premature coronary artery disease is absent in most FLD cases but may be present in some patients with FED [8].

Patients with LCAT deficiency show heterogeneous tissue and plasma lipoprotein abnormalities [11]. Lesions are found in such tissues as kidney, spleen, cornea, and erythrocytes, presumably secondary to lipid abnormalities [12,13]. Cytologic specimens from the spleen and the bone marrow from these patients reveal the presence of "sea-blue histiocytes," which are also seen in a variety of other conditions including hematologic neoplastic proliferations (ie, chronic myelogenous leukemia), lysosomal storage diseases (ie, Niemann-Pick, Gaucher disease, Tay-Sachs disease), severe hypertriglyceridemia, and apolipoprotein abnormalities, all sharing the common denominator of disordered lipid metabolism [6,14]. Kidney disease is a major cause of morbidity and mortality, where progressive renal failure ultimately leads to ESRD [15]. Ultrastructural analysis of kidney shows expansion of mesangium and peripheral basement membranes with irregular vacuoles containing highly osmiophilic "lamellar bodies" [16]. Formation of these excess lamellar bodies containing unesterified cholesterol and phosphatidylcholine has also been described in spleen and bone marrow histiocytes [17].

We report on a patient who presented with symptoms related to splenomegaly and was found to have an abnormal lipid profile, nephropathy, and splenomegaly with sea-blue histiocytosis; he was ultimately diagnosed with LCAT deficiency. This case describes the spectrum of biochemical and multiorgan system manifestations of LCAT deficiency with associated histologic and ultrastructural findings.

2. Case

A 31-year–old man was admitted to the surgical service for evaluation of progressive left upper quadrant (LUQ) abdominal pain of several days' duration accompanied by nausea and nonbloody vomiting. He reported no fever, chills, or constitutional symptoms, but a 20-lb weight gain during the last year. His family history and surgical history were noncontributory. He used no prescription drugs.

2.1. Physical examination

The patient appeared generally healthy, but acutely uncomfortable. The initial blood pressure (BP) was 185/117. The following morning, it was 170/110; but all subsequent BP recordings were within reference range. He was afebrile and had a heart rate of 103 per minute and a respiratory rate of 23 per minute; both the heart rate and the respiratory rate returned to normal the following morning. Neither pallor nor jaundice was clinically evident. The abdomen was somewhat distended. Guarding was evident, and considerable muscular spasm prevented an adequate abdominal examination. The remainder of the physical examination was unremarkable.

2.2. Laboratory data on admission

The initial peripheral blood counts were essentially within normal limits (white blood cells, [WBC] 6200; hemoglobin, 13.3 g/dL; platelet count, 168 000). The following morning, the values were as follows: hemoglobin, 10.8 g/dL, mean corpuscular volume, 82.9 μm^3; WBC, 5200; and platelet count, 123 000. Peripheral blood smear showed anisopoikilocytosis with target cells. Other than hydration parenterally and pain relief, no other interventions had occurred. Admission urinalysis on a voided urine specimen showed 300 mg protein with 15 to 20 red blood cells (RBCs). A 24-hour urine collection revealed 4 g of protein, blood urea nitrogen was 22 mg/dL, and creatinine was 1.3 mg/dL. Serum protein electrophoresis showed an albumin of 2.8 g/dL with all forms of globulins at the lower limits of normal. Serum bilirubin was 1.8 mg/dL. Liver function tests and lactate dehydrogenase levels, prothrombin time, and partial thromboplastin time were within normal limits.

2.3. Imaging and additional tests

An abdominal computed tomographic scan demonstrated a homogeneously enlarged spleen. No lymph node enlargement was seen. Bone marrow biopsy showed a hypercellular maturing trilineage hematopoiesis with increased megakaryocytes and erythroid hyperplasia.

2.4. Clinical course

Several additional laboratory studies were requested. A definitive diagnosis was not established; it was felt that the symptoms were due to perisplenitis, and the possibility of an isolated splenic lymphoma was considered. The urinary abnormalities were not explained. He was discharged to be followed as an ambulatory patient in the hope that other findings might appear that would permit a definitive diagnosis and possible treatment.

The patient returned several days later with severe LUQ abdominal pain. An elevated BP (180/120) was noted upon admission, which returned to within normal limits on all

subsequent recordings. The physical examination was largely unchanged. Less guarding was evident; a nontender enlarged spleen was palpable. On this admission, blood work showed WBC of 7800, hemoglobin of 14.7 g/dL, and platelet count of 184 000. A few target cells were noted on the peripheral smear. Urinalysis showed 200 mg of protein and more than 8 RBCs per high-power field. Serum lipid profile of a blood sample taken 5 days earlier (during the previous admission), using routine enzymatic methods (University of Cincinnati Hospital Laboratory), showed total cholesterol (TC) of 210 mg/dL, HDL of 12 mg/dL (normal, >35%), serum cholesterol esters of 16% (reference range, 60%-70%; based on 95% confidence interval), and triglycerides (TG) of 766 mg/dL. The serum appeared milky and turbid.

He was provided with symptomatic relief and steadily improved. He was discharged and was scheduled for a splenectomy. One week later, he was admitted to the surgical service for a splenectomy, a left kidney biopsy, and a liver biopsy.

2.5. Pathologic findings

2.5.1. Spleen

Gross examination of the splenectomy specimen showed a moderately enlarged spleen, weighing 780 g (normal, 150 g), with a beefy red cut surface without any gross lesions. Histologic examination showed an expanded splenic red pulp with sea-blue histiocytosis (Fig. 1). Numerous periodic acid-Schiff–positive foamy macrophages were apparent (Fig. 1, inset). Flow cytometry was performed on the splenic tissue showing polyclonal B-cells and reactive T-cells, with no immunophenotypic evidence of lymphoma. Electron microscopic examination of splenic tissue revealed characteristic large histiocytes (30 μm) containing numerous granules of various sizes and shapes. Some granules were electron dense with a homogeneous appearance (not shown). Other structures composed of lamellar membrane-like material resembling “rose petals” were also seen in abundance (Fig. 2).

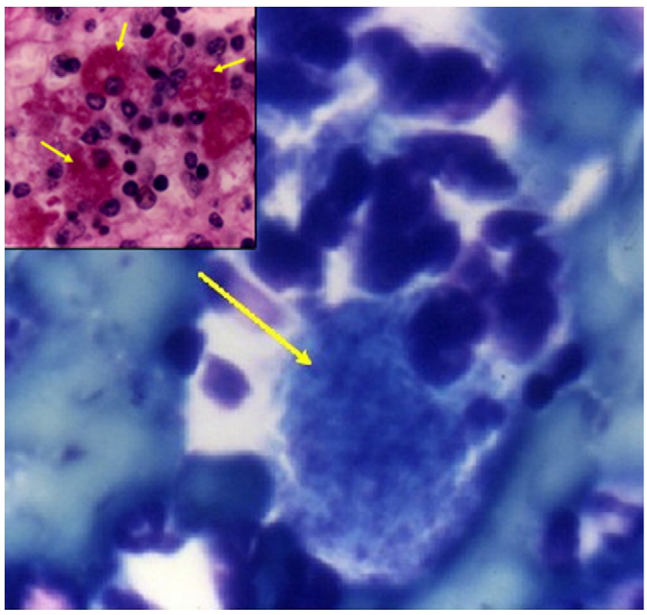

Fig. 1. Sea-blue histiocyte in the spleen from patient with LCAT deficiency (Wright-Giemsa stain, original magnification ×1000). The inset shows periodic acid-Schiff–stained splenic tissue.

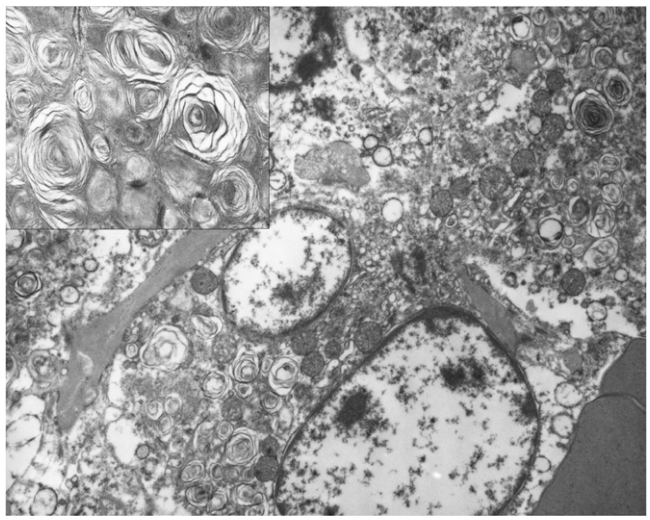

Fig. 2. Transmission electron micrograph of the spleen showing rose petal arrangement of lamellar membrane-like bodies in the cytoplasm of a sea-blue histiocyte (original magnification ×9960). The inset shows higher magnification of rose petal arrangements (original magnification ×49 800).

2.5.2. Kidney

Renal biopsy light microscopy showed focal segmental glomerular sclerosis along with mesangial expansion, a mild increase in mesangial cellularity, and irregular thickening of the glomerular capillary walls, with vacuolization of the glomerular basement membrane due to intramembranous lipid deposits, resulting in a “foamy” appearance (Fig. 3). Electron microscopy showed expansion of the mesangium and glomerular basement membranes by numerous variably sized vacuoles with or without osmiophilic particles and lamellar serpiginous linear arrays forming “fingerprint-like” arrangements (Fig. 4).

2.5.3. Liver

Liver biopsy revealed no significant pathologic findings.

2.6. Biochemical investigation

2.6.1. Methods

Blood samples were obtained intravenously. Total cholesterol, free cholesterol, and TG were measured by standard enzymatic methods [18,19]. High-density lipoprotein cholesterol was measured by heparin-calcium precipitation method [20]. Assays for plasma esterified cholesterol, plasma LCAT mass, and plasma LCAT activity as determined by plasma cholesterol esterification rate were

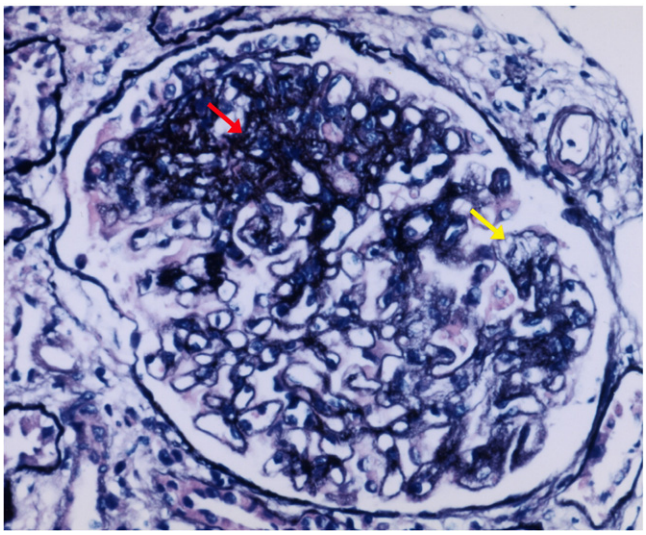

Fig. 3. Glomerular lesions in patient with LCAT deficiency. Light microscopy of a glomerulus showing expanded mesangium and thickened capillary loops (red arrow); some capillary loops are distended with foamy lipid-like vacuoles (yellow arrows) (periodic acid methenamine-silver stain, original magnification ×200).

performed at Mayo Clinic Laboratories (Rochester, MN). Briefly, plasma esterified cholesterol was determined as described elsewhere [21]; cholesterol esters were reported as a percentage of free cholesterol. Determination of plasma LCAT activity involved the use of radiolabeled cholesterol dispersed in Tween 20 as a tracer and endogenous lipoproteins as a substrate for measuring the rate of serum cholesterol esterification in vitro [22]. The LCAT mass was determined by a radioimmunoassay using a polyclonal antibody and ^{125}I-labeled LCAT [23]. To establish a reference range (Mayo Clinic), data were obtained on the serum of 65 healthy subjects without manifestations of atherosclerosis, lipidosis, diabetes mellitus, nephrosis, or other disease known to be associated with abnormal serum lipid profiles. All the samples were obtained after an overnight fast [22].

2.6.2. Findings

In vitro plasma LCAT activity was 12.1 nmol/mL/h, which was markedly reduced as compared with normal (80.9 ± 11.2 nmol/mL/h). The LCAT mass was 0.1 μg/mL, which was also markedly reduced as compared with normal (reference range, 3.1-6.7 μg/mL). Lipid profile, 1 month postsplenectomy, showed TG of 3590 mg/dL, TC of 610 mg/dL, and HDL of 16 mg/dL; plasma appearance was milky and turbid.

3. Discussion

Familial LCAT deficiency was initially described in people of northern European origin and subsequently in patients from a wide geographic distribution, including other parts of Europe, Japan, and North America [7,8,24,25]. Clinical and biochemical manifestations of LCAT deficiency are variable and include corneal opacities, an abnormal lipid profile (characterized by hypercholesterolemia with markedly decreased HDL and hypertriglyceridemia), hematologic abnormalities (normochromic anemia of varying intensity), nephropathy (initially characterized by proteinuria with progressive deterioration of renal function), splenomegaly, and variable early coronary artery disease [8,17,26]. In the current case, the presence of an abnormal lipid profile (characterized by hypercholesterolemia with decreased HDL and hypertriglyceridemia), mild hemolytic anemia, and nephropathy raised the likelihood of a disorder of lipid metabolism. In light of the histologic finding of characteristic sea-blue histiocytes in the moderately enlarged spleen, LCAT deficiency was considered. The diagnosis was further supported by the renal biopsy findings of focal segmental glomerular sclerosis and renal lipidosis by light microscopy, as well as the ultrastructural findings of mesangial and glomerular basement membrane expansion by vacuoles and lamellar membrane-like structures. Finally, the evaluation of the plasma LCAT enzymatic activity and LCAT mass, revealing markedly decreased LCAT activity (12.1 nmol/mL/h; reference range, 80.9 ± 11.2 nmol/mL/h) and LCAT mass (0.1 μg/mL; reference range, 3.1-6.7 μg/mL), in conjunction with a decreased proportion of esterified cholesterol in plasma (16% of TC; reference range, 60%-70%), confirmed the diagnosis.

In our review of the literature, in addition to biochemical, hematologic, and renal findings, associated splenic enlargement has been clinically described in patients with LCAT deficiency [17,26,27]. Description of the accompanying histologic and ultrastructural findings in the spleen is

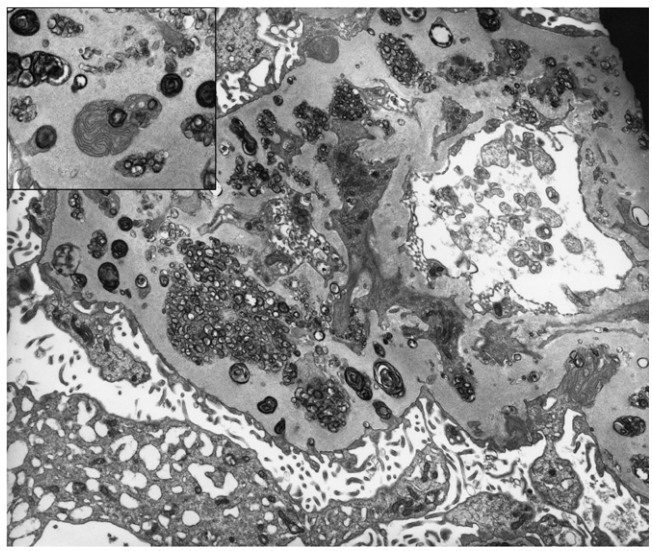

Fig. 4. Transmission electron micrograph of the kidney depicting glomerular lesions in LCAT deficiency. Glomerular basement membrane is expanded by numerous variably sized vacuoles and lamellar membranous-like bodies forming fingerprint-like arrangements (original magnification ×11 800).

however limited to a few case reports [17,28]. Splenomegaly and the associated RUQ pain were the initial clinical presentation in our patient. He was subsequently found to have an abnormal lipid profile characterized by high TC, high TG, low HDL, and low esterified cholesterol. The low HDL cholesterol level is thought to be responsible for the less efficient reverse cholesterol transport and therefore the accumulation of cholesterol in tissue [29]. Splenomegaly could have resulted from the increased uptake of unesterified cholesterol (and other circulating lipids) by splenic macrophages. This hypothesis is supported by the exacerbation of the abnormal lipid profile (ie, dramatic increase in TG and TC) that was observed in our patient after splenectomy, allowing lipoproteins and their remnants to further accumulate and circulate in the plasma. In addition to removal of cholesterol from peripheral tissue, HDL has been shown to remove oxidized lipids from peripheral tissue [30]. Thus, decreased LCAT activity that results in markedly decreased mature HDL particles may ultimately lead to severe impairment of the removal of oxidized lipids from the peripheral tissue. Consequently, oxidized lipids and lipid aggregates cause the activation of scavenger receptors on macrophages and subsequent accumulation of lipids, promoting foamy histiocytes formation [31]. Ongoing accumulation of lipids in splenic macrophages thus leads to foamy histiocytosis and to gradually increasing size of the spleen and the observed splenomegaly. Our patient's splenic tissue contained numerous characteristic sea-blue histiocytes. Ultrastructurally, these histiocytes contained cytoplasmic vacuoles and membrane-like lamellar structures resembling rose petals, indicating that they are composed of phospholipid-containing membranes. Although some of these may represent breakdown products of phagocytosed cells (ie, RBCs, platelets), the uptake of excess and abnormal plasma lipids could be the major contributing factor to the pathogenesis of the sea-blue histiocytosis in LCAT deficiency. Indeed, as previously mentioned, abnormal plasma lipoprotein particles with unusual shape and an ultrastructural lamellar or "serpiginous" pattern have been described in the plasma of patients with LCAT deficiency [11,28].

Mild anemia with anisopoikilocytosis and target cells was seen in our patient. Anemia is presumably caused by slight hemolysis in conjunction with insufficient erythropoiesis [24]. The erythrocytes of patients with LCAT deficiency have structural, compositional, and functional abnormalities, including decreased osmotic fragility and alterations in phospholipid composition (increased contents of cholesterol and lecithin) [32]. These abnormalities in lipid composition might possibly lead to phagocytosis and the observed mild hemolytic anemia phenotype [17].

Although our patient initially presented with symptoms related to splenomegaly, he was found to have asymptomatic proteinuria. Renal disease is reported to be a major cause of morbidity and mortality in patients with LCAT deficiency. Progressive renal failure leads to ESRD, which frequently necessitates dialysis and kidney transplantation [14,15]. Our patient was found to have the typical early renal manifestations and corresponding pathologic findings that are related to the abnormal lipid metabolism in patients with LCAT deficiency. Abnormal storage of lipids in kidney occurs in a number of diseases either because of an inborn error of metabolism (eg, lack of a specific enzyme) or as a consequence of a complex metabolic alteration (eg, as in nephrotic syndrome) [33]. The characteristic light microscopic findings (ie, mesangial expansion, capillary wall thickening, and vacuolation) and the ultrastructural appearance (lipid deposit in many areas including subendothelium and mesangium, and serpiginous structures) of the kidney specimen from our patient are typical findings in LCAT deficiency [33].

In conclusion, the clinical manifestations of patients with LCAT deficiency may vary even among the members of the same family carrying identical mutations [34]. To our knowledge, the present case is the first reported case of LCAT deficiency presenting with symptoms related to splenomegaly in a patient with no obvious family history. This case describes a spectrum of biochemical and multiorgan system manifestations of LCAT deficiency with histologic and ultrastructural correlates. We underline the importance of a complete physical examination and biochemical and histologic assessment of patients presenting with symptoms related to splenomegaly and multiorgan system lipidosis in the absence of an obvious family history of a disorder of lipid metabolism. Lecithin-cholesterol acyltransferase deficiency may result in a triad of splenomegaly with characteristic sea-blue histiocytes, dyslipidemia, and nephropathy. Patients may present with renal disease or with symptoms related to splenomegaly only. Lecithin-cholesterol acyltransferase deficiency should therefore be considered in the differential diagnosis of lipid storage disorders in a patient with splenomegaly and sea-blue histiocytes, and an abnormal lipid profile.

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