An unusual presentation of Tangier disease with gallbladder involvement

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Abstract

Tangier disease is a rare, autosomally inherited disorder of lipoprotein metabolism characterized by absence or marked deficiency of normal high density lipoprotein (HDL) cholesterol in plasma resulting in the accumulation of cholesterol esters in various organs. A 57-year old male with a past medical history of hypertension, coronary artery disease and splenectomy admitted to our hospital for rectal bleeding. In routine laboratory tests thrombocytopenia, hypocholesterolemia and low HDL levels were detected. Colonoscopy revealed 1-3 mm sized, brownish, spotty lesions spread throughout the colonic mucosa. Histopathologically accumulation of foam cells which showed lipid vacuoles and myeline figures on electron microscopy were observed. Bone marrow biopsy was also suggestive of lipid storage disease. The laparoscopic operation performed for acute cholecystitis showed similar appearances in the gall bladder and liver. The case was diagnosed as rare presentation of Tangier disease with gallbladder involvement in view of the low HDL cholesterol level and systemic lipid deposition. (Acta gastroenterol. belg., **2008**, 71, **397-400**).

Key words : Tangier disease, gallbladder, colon.

Introduction

Tangier disease (TD) is characterized by absence or marked deficiency of normal high density lipoproteins (HDL) in plasma and results in the accumulation of cholesterol esters in the tonsils, spleen, lymph nodes, thymus, liver, intestinal mucosa, nerves, and cornea. Cholesterol levels are low and triglyceride levels are normal to elevated. Plasma apolipoprotein (apo) A-I, the primary protein in HDL, concentration is very low (~3% of normal). Chylomicron remnants and very low density lipoproteins are abnormal in structure (1).

The defect in TD appears to involve mutations in the ATP-binding cassette (ABCA1) gene on chromosome 9q31, which encodes for the cholesterol efflux regulatory protein (2-5). ABCA1 appears to play a central role in intracellular cholesterol transport and is associated with increased HDL catabolism (6). HDL-mediated cholesterol efflux from macrophages and intracellular lipid trafficking are impaired in this disorder, leading to formation of foamy appearance in macrophages and other cells of the reticuloendothelial system throughout the body (7).

There is no specific treatment of TD. Transmission is in an autosomal codominant mode. Heterozygotes have no clinical manifestations though they have half the normal concentrations of HDL, cholesterol, apo A-I, and apo A-II, however obligate heterozygotes are also at increased risk of premature coronary heart disease. Homozygotes develop cholesterol ester deposition in tonsils (orange tonsils), liver, spleen, gastrointestinal tract, lymph nodes, bone marrow, and schwann cells. The main clinical manifestations are hepatosplenomegaly and premature coronary disease ; a neuropathy occurs in at least 50 percent of patients and is the most debilitating feature of the disease (7).

Gastrointestinal system involvement is rare in TD. Endoscopically cases showing gastrointestinal involvement present with yellow to orange discoloration and show numerous 1-2 mm irregularities in mucosa (8-10). Histopathological finding of widespread tissue deposition of cholesterol esters in the cells of mononuclear phagocyte system is diagnostic

We hereby present a case of TD presenting with coronary artery disease and widespread accumulation of lipid in various organs including the gallbladder which has not been previously reported.

Case

A 57-year old male with a past medical history of hypertension, coronary artery disease and splenectomy admitted to our hospital for rectal bleeding. Previously, for coronary artery disease, a metallic stent was applicated to circumflex artery and splenectomy was performed for thrombocytopenia due to hypersplenism. There was no family history of coronary artery disease.

Physical examination revealed hepatomegaly but no tonsillary or neurological involvement. Laboratory studies were as follows : Hemoglobin 14,3 g/dl, hematocrit 45%, leukocyte count 7500×10^3/dl, platelet count 43.000×10^6/dl, fasting plasma glucose 87 mg /dl, serum creatinine 0.9 mg/dl, BUN 25 mg/dl, total protein 8 gr/dl, albumin 4 gr/dl, AST 23 IU/dl, ALT 28 IU/dl, GGT 43 IU/dl, calcium 9 mg/dl, potassium 4 mg/dl, sodium 142 mg/dl. The lipid profile revealed a total cholesterol level of 78 mg/dl (normal, 80 to 120), HDL

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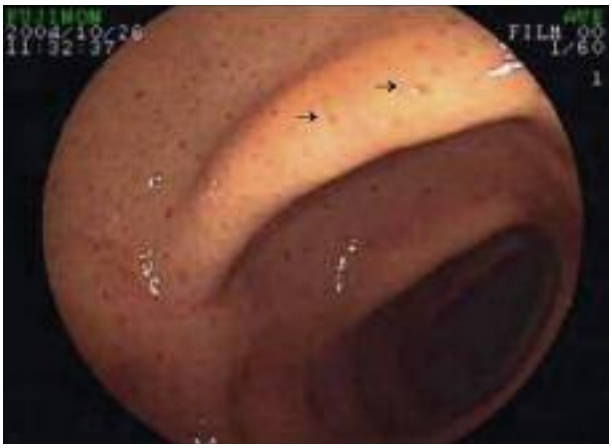

Fig. 1. — 1-3 mm sized, brownish, macular lesions were seen in colonic mucosa.

cholesterol 5 mg/dl (normal, 40 to 80), LDL cholesterol 37 mg/dl (normal, 70 to 130) and serum triglyceride 178 mg/dl (normal, < 150 mg/dl). In abdominal ultrasound, hepatomegaly and hepatic steatosis were identified by increased echogenity. In upper gastrointestinal system endoscopy, eosofagitis and antral gastritis were found. In colonoscopic examination 1-3 mm in diameter, brownish, macular lesions were seen throughout the colonic mucosa (Fig. 1). Histologic examination of the biopsies taken from rectum and colonic mucosa, revealed the infiltration of foamy cells with vacuolated pale eosinophilic cytoplasm in the lamina propria. Involvements of different organs with foamy histiocyetes were shown in figure 2. PAS stains before and after diastase treatments were negative. Cytoplasmic lipid vacuoles and myelin figure were seen in electron microscopic examination of the specimens (Fig. 3). According to these findings, the patient was reported to have a lipid storage disease.

Six months after the first admission of the patient to our clinic, he was hospitalized for acute cholecystitis. Laparoscopic cholesystectomy was performed and during the operation a spotted appearance on the liver was observed. Liver wedge biopsy and cholecystectomy specimen revealed similar infiltration of foamy cells with pale eosinophilic cytoplasm. Similar findings were reported in the re-examination of the bone marrow and liver biopsies taken from the patient three years ago, along with splenectomy specimens. No neuropathy was detected in the electromyographic examination of extremities. On follow up the patient is stable.

Discussion

Since its original description in 1961 (11), TD has been considered as a fascinating lipoprotein disorder. Mutations at the ABCA1 transporter gene have been shown to be associated with TD. Although the role of ABCA1 is not completely understood, it is postulated to act as a transporter of cholesterol and phospholipids to the plasma membrane, probably from the trans-Golgi network (12).

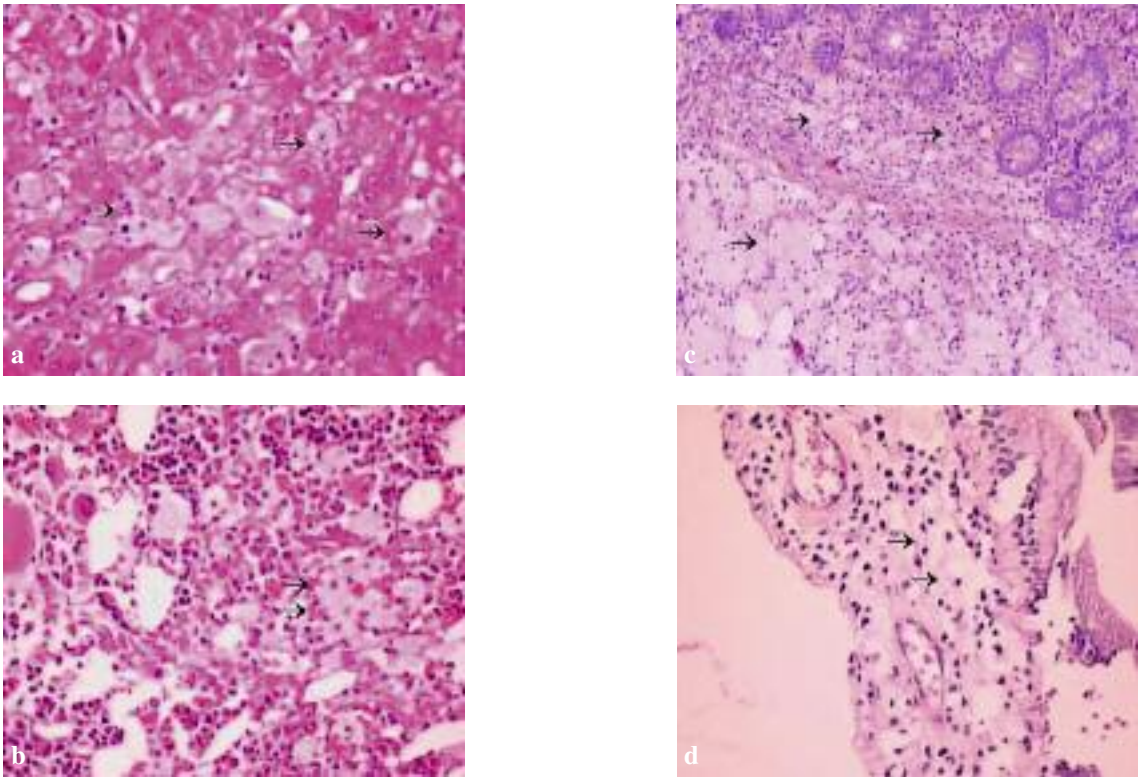

Fig. 2. — Foamy histyocytic cells (arrowed) in liver, bone marrow, colon and gall bladder, a-d, respectively (H&E, ×400)

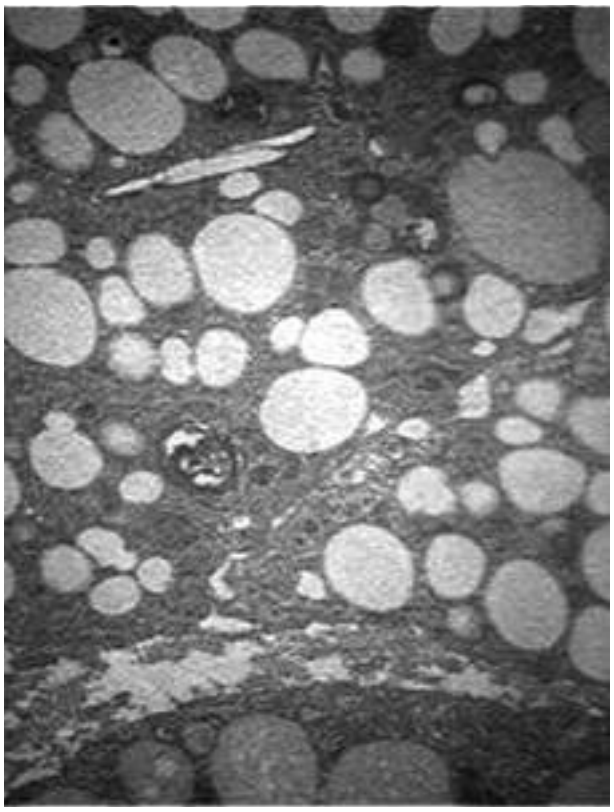

Fig. 3. — Cytoplasmic vacuoles and concentric myelin-like lamellar bodies (Electron microscopy, ×3597).

The major clinical signs of TD are : hyperplastic orange tonsils, splenomegaly and relapsing neuropathy. The disease is characterized by absence or marked deficiency of normal HDL in plasma (13-15). The findings of low HDL cholesterol, marked hypocholesterolemia and the past history of splenomegaly and atherosclerosis confirm the diagnosis of TD in the present case. However the tonsils were normal in appearance and no neurological involvement confirmed with a normal electromyographic examination of the extremities was revealed in our patient.

Gastrointestinal involvement in TD is very rare with unexplained diarrhea as the most common symptom which has a reported frequency of 8% (1). The site most likely to give a positive biopsy result would appear to be rectal mucosa, as lipid deposits or yellow patches here have been reported in previous cases who underwent proctoscopy, all of whom were adults. The endoscopic appearance of rectal mucosa has been abnormal in up to 30% of patients presented in previous publications (1,8, 9) as our case which showed typical endoscopic findings of TD in rectal and colonic mucosa. Similarly liver surface had typical spotted appearance observe during cholecystectomy.

Pathological examination of rectal, colonic mucosa, liver, and gallbladder revealed the infiltration of foamy histyocytes with pale eosinophilic vacuolated cytoplasm. Gallbladder involvement seems to be a very rare presentation since we failed to find a similar case with gallbladder involvement in the English literature. This patient had a past history of thrombocytopenia due to hypersplenism and was investigated in hematology department and after the evaluation splenectomy had been performed. Infiltrations of foamy histyocytes were found in the re-examination of both splenectomy specimen and bone marrow biopsy. Transmission electron microscopy, revealed cytoplasmic vacuoles and numerous membranous myelin-like lamellar bodies known as myelin figures consistent with lipid accumulation. Some other conditions may bear a superficial resemblance to TD, but can usually be excluded by critical microsco py and special stains. Thus, in Gaucher's disease the cells are more opaque and wrinkled, and their cytoplasm stain strongly with PAS. Generalized gangliosidosis unlike TD, shows cells which stain positively with PAS and Alcian blue as well as with Sudan stains.

In conclusion, Tangier disease is a rare inherited disorder of lipid metabolism that results in cholesterol ester accumulation in many tissues throughout the body. Gastrointestinal involvement is very rare. However, endoscopic findings in the form of typical orange-yellow colored lesions in the gastrointestinal mucosa would suggest the diagnosis of TD. Therefore endoscopists must be aware of this disease in a patient with hypocholesterolemia and very low serum HDL. Our case is unique as it is the first report of gallbladder involvement in an otherwise typical case of TD.

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