Original article

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A case of uncommon cause of hypercholesterolemia

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Abstract

Cholestasis is a rare cause of secondary hypercholesterolemia which may be attributed to increased production of an abnormal lipoprotein (apo), known as Lp-X. We present the case of a patient admitted due to cholestatic jaundice and pruritus and showed excess hypercholesterolemia due to increased production of Lp-X. The patient was diagnosed with an adenocarcinoma of the pancreas. Surgical restoration of the bile flow resulted in normalization of lipids.

Key words: Secondary hypercholesterolemia; lipoprotein X; cholestasis; jaundice

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Introduction

Hypercholesterolemia is a metabolic disorder affecting millions of individuals around the globe and can be mainly attributed to either increased concentration of low density lipoprotein cholesterol (LDL-C),) or very low density lipoprotein cholesterol (VLDL-C). Increased levels of cholesterol can be due to either primary or secondary

Citation

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causes; the latter must be always ruled out before a diagnosis of a primary hypercholesterolemia is established. Common causes of secondary hypercholesterolemia include nephrotic syndrome, chronic kidney disease, hypothyroidism, metabolic syndrome and type 2 diabetes mellitus, multiple drugs and cholestasis; these should be ruled out by using simple tests (such as thyroid stimulating hormone levels, glucose levels, kidney function, liver function tests assessments) before the diagnosis of primary hypercholesterolemia syndrome is established [1, 2].

Cholestasis, intra-hepatic and extra-hepatic, is a rather uncommon cause of secondary hypercholesterolemia characterized by an increased LDL-C concentration and total cholesterol (T-CHOL) levels. The observed increased of LDL-C is due to the production of an abnormal lipoprotein particle, known as Lipoprotein-X (Lp-X) [3]. Lp-X is consisted mostly of phospholipids (approximately 60% w/w) and free cholesterol (FC-25% w/w) as well as by small amounts of protein, triglycerides and cholesterol esters [4]. The outer membrane constitutes of a mixture of an abnormal apolipoprotein, apolipoprotein X (60%), and albumin (40%) [5]. Herein, we describe the case of a patient who presented with excess hypercholesterolemia, jaundice and pruritus.

Case presentation

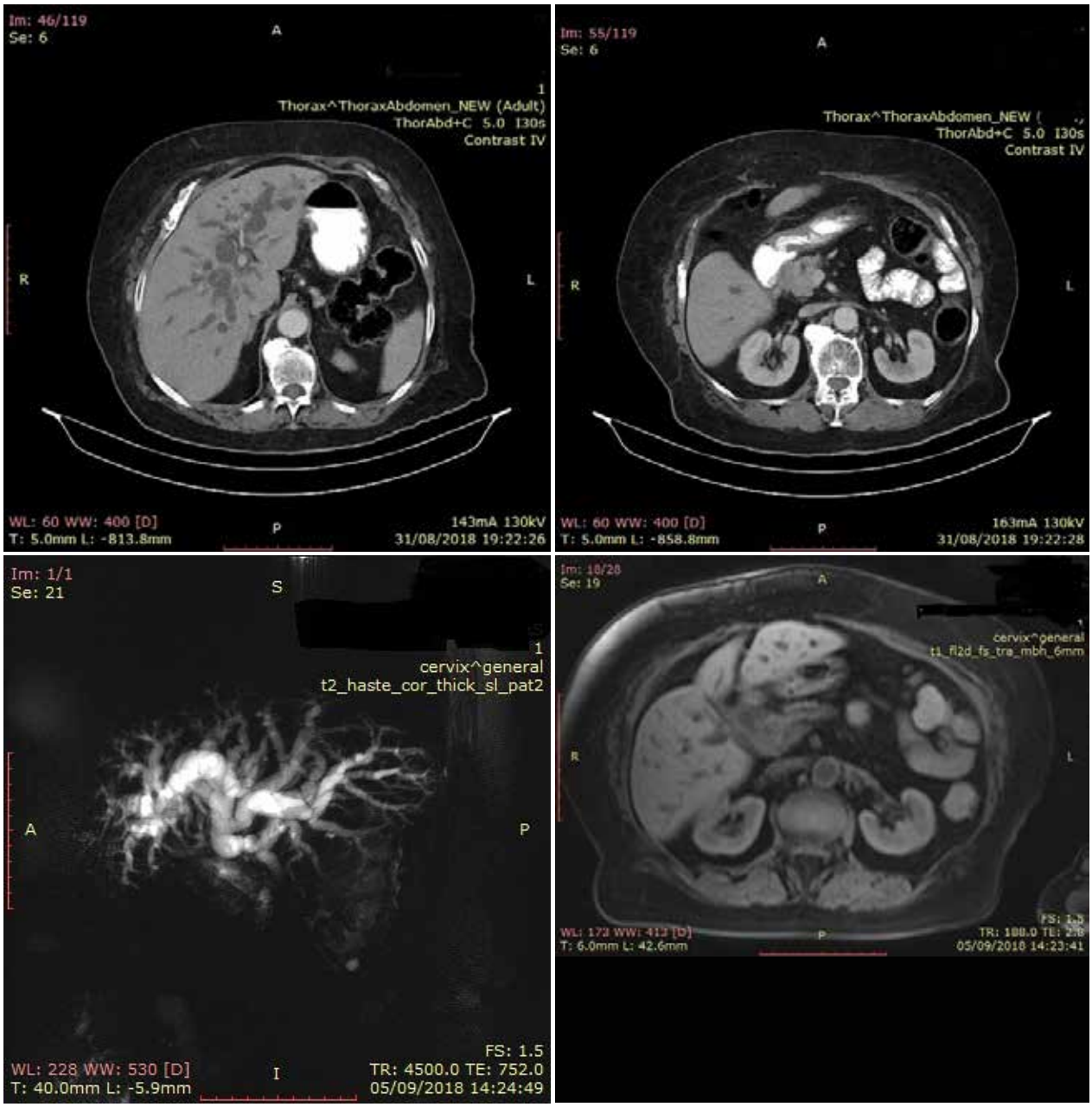
A 78-year old woman was referred to our hospital for the evaluation of a new onset pruritus and 'painless' jaundice. Two weeks before, the patient complained of severe itching on her feet and hands, while her family noticed a yellow discoloration of her eyes and skin. Anorexia starting a month prior to admission was also reported by the patient. Her medical history involved type 2 diabetes mellitus treated with insulin glargine s.c. (glycated hemoglobulin 6%), cholecystectomy and a right inguinal hernia repair. The family history was unremarkable and she did not report any allergies, smoking or alcohol drinking. Jaundice (sclerae and skin) was evident on physical examination.

Laboratory work-up (**Table 1**) revealed in-

Table 1: Baseline laboratory work up

Hematocrit	31.7 %
Hemoglobulin	10.3 g/dl
WBC	5950/μl
Platelets	252000/μl
Glucose	133 mg/dl
Urea	15 mg/dl
Creatinine	0.71 mg/dl
AST	135 IU/l
ALT	194 IU/l
ALP	604 IU/l
γGT	655 IU/l
Tbil	21.7 mg/dl
Dbil	12.6 mg/dl
Uric acid	2.6 mg/dl
Total protein	5.6 g/dl
Albumin	3 g/dl
CK	15 IU/l
LDH	291 U/l
T-CHOL	636 mg/dl
Triglycerides	275 mg/dl
HDL-C	38 mg/dl
LDL-C	544 mg/dl
Apolipoprotein-A1	27.8 mg/dl
Apolipoprotein-B	200 mg/dl
Apolipoprotein-E	355 mg/l
Lipoprotein (a)	2 mg/dl
TSH	0.76 μIU/ml

Abbreviations: WBC: White blood cells; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; γGT: γ-glutamyl-transferase; Tbil: Total bilirubin; Dbil: Direct bilirubin; CK: Creatine kinase; LDH: Lactate dehydrogenase; T-CHOL: Total cholesterol; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; TSH: Thyroid stimulating hormone.



Upper images: *Abdominal computed tomography (CT) showing dilation of intra and extrahepatic bile ducts and a mass of the head of the pancreas*
Lower left image: *Magnetic retrograde cholangiopancreatography (MRCP) showing diffuse dilation of bile ducts*
Lower right image: *Abdominal magnetic resonance imaging (MRI) showing the mass of the head of the pancreas*

creased levels of cholestatic enzymes (i.e. alkaline phosphatase and γ-glutamyltransferase) as well as of total bilirubin with a direct component predominance and transaminases. T-CHOL and LDL-C were remarkably elevated, whilst triglycerides and HDL-C levels were normal. The patient did not report a family history of hypercholesterolemia or a personal history of increased cholesterol levels.

An abdominal ultrasound revealed extrahepatic bile ducts as well as main pancreatic duct dilatations. Subsequently, the patient underwent

Table 2: **Lipid levels on admission and after surgical intervention**

	Levels on admission	Levels after choledochojejunostomy
T-CHOL	636 mg/dl	209 mg/dl
Triglycerides	275 mg/dl	213 mg/dl
HDL-C	38 mg/dl	29 mg/dl
LDL-C	544 mg/dl	138 mg/dl
Apolipoprotein-A1	27.8 mg/dl	87.4 mg/dl
Apolipoprotein-B	200 mg/dl	117 mg/dl
Lipoprotein (a)	2 mg/dl	5.7 mg/dl

Abbreviations: T-CHOL: Total cholesterol; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol

an abdominal computed tomography (CT) and a magnetic retrograde cholangiopancreatography (MRCP) which revealed a mass at the area of the head of pancreas, dilatation of the common bile duct and main pancreatic duct and regional lymphadenopathy, extending to the porta hepatis, with no secondary focal lesions in the liver parenchyma (**Image 1**). With the suspicion of secondary hypercholesterolemia possibly mediated by increased Lp-X levels due to cholestasis, a lipoprotein electrophoresis was also ordered. A Lipoprint LDL system electrophoresis (a gel electrophoresis lipoprotein subfractionation method, allowing the assessment of the cholesterol concetration of different lipoprotein subfracions [6]) was performed showing increased levels of VLDL cholesterol (**Figure 1**). As studies have shown that increased levels of lipoprotein x are not associated with atherosclerosis and increased frequency of cardiovascular events, the patient did not receive statin treatment [7].

The patient underwent a choledochojujenostomy, while biopsies of the pancreatic mass were taken perioperatively. Biopsy examination was compatible with a diagnosis of pancreatic adenocarcinoma. The patient was deemed unfit for further oncological treatment and a strategy of best supportive/palliative care was undertaken. Following surgery and relief of bile obstruction, her cholesterol levels returned to normal (**Table 2**). VLDL-C levels also returned to normal (**Figure 2**).

Discussion

This is a case of secondary hypercholesterolemia owing to cholestasis as a result of an adenocarcinoma of the head of pancreas. Restoring 'bile flow' via surgery normalized lipid abnormalities consistent with increased production of Lp-X. Indeed, the electrophoresis findings were consistent with the reported properties of Lp-X particles. Lp-X is similar in size with VLDL particles, while its density is similar with that of the LDL particles.

A distinguishing feature of Lp-X particles is that these particles own a characteristic cathodal mobility on 'agar gel' electrophoresis, compared to other lipoproteins which have an anodal mobility [8]. Since the Lipoprint LDL system electrophoresis distinguishes lipoprotein subclasses by their size, the increased VLDL levels observed on presentation and the normalization of VLDL levels following surgery is consistent with the presence of Lp-X.

Lp-X is an abnormal lipoprotein which may be found in patients with either intrahepatic or extrahepatic cholestasis (for example in patients with primary biliary cholangitis (formerly known

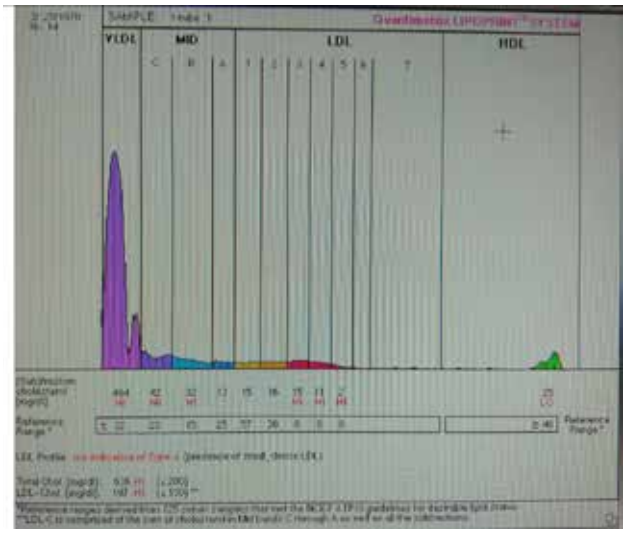


Figure 1. *LDL Lipoprint results on presentation showing increased levels of VLDL cholesterol but not of LDL cholesterol.*

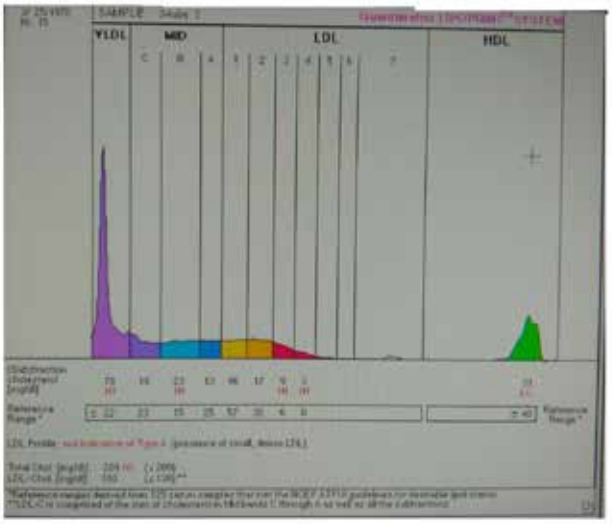


Figure 2. *LDL Lipoprint results following surgical intervention showing that VLDL cholesterol levels decreased substantially*

as primary biliary cirrhosis), drug induced cholestasis and extra hepatic bile flow obstruction). Furthermore, Lp-X can be found in patients with lecithin-cholesterol acyl transferase (LCAT) deficiency, either inherited or acquired, and in patients receiving lipid infusions [9, 10]. The presence of Lp-X should be excluded in every patient presenting with new onset hypercholesterolemia with extremely elevated LDL-C levels. A useful distinguishing feature might be the presence of a relatively 'low' apolipoprotein-B concentration as compared with the remarkably high LDL-C levels.

Conflict of interest

There is no conflict of interest.

Περίληψη

Ασυνήθιστη περίπτωση υπερχοληστερολαιμίας

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Η χολόσταση αποτελεί σπάνιο αίτιο δευτεροπαθούς υπερχοληστερολαιμίας, η οποία μπορεί να αποδοθεί στην παραγωγή μιας παθολογικής λιποπρωτεΐνης, γνωστής ως Lp-X. Περιγράφεται η περίπτωση ασθενούς που εισήχθη με χολοστατικό ίκτερο και γενικευμένο κνησμό, ο οποίος εμφάνιζε σοβαρή υπερχοληστερολαιμία εξαιτίας της αυξημένης παραγωγής Lp-X. Ο ασθενής διεγνώσθη με αδενοκαρκίνωμα του παγκρέατος. Υπεβλήθη σε χειρουργική επέμβαση για την αποκατάσταση της ροής στα χοληφόρα με αποτέλεσμα την επιστροφή των λιπιδαιμικών παραμέτρων εντός φυσιολογικών ορίων.

Λέξεις ευρετηρίου: δευτεροπαθής υπερχοληστερολαιμία, λιποπρωτεΐνη Χ, χολόσταση, ίκτερος

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