Skin manifestations in familial heterozygous hypercholesterolemia

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Familial hypercholesterolemia, a form of primary hyperlipoproteinemia, is an autosomal dominant disorder characterized by an increase in serum LDL cholesterol concentrations. Multiple types of xanthomas occur, such as tendinous, tuberous, subperiosteal, and xanthelasma. Intertriginous xanthomas are rare, but if present are pathognomonic in this disorder. We report a patient with multiple xanthomas including the very rare intertriginous variety.

Case report

A 65-year-old male developed multiple skin lesions appearing over several years. The lesions involved his fingers, hands, elbows, knee, and feet. They were initially soft but later they became firm nodes. Additional yellow lesions appeared around his eyes. He complained of chest pain and shortness of breath. Physical examination revealed the presence of subcutaneous nodules at the knuckles of his fingers (Fig. 1a), elbows, knees, and Achilles tendons (Fig. 1b). They were up to 5 cm in size and partly mobile. In the creases of his palms, especially over the tendons, yellowish plaques with a slightly corrugated surface (Fig. 1c) were found. On his abdomen and trunk, reddish-yellow papules (Fig. 1d) 2 mm in diameter were observed. In the periorbital area bright yellow plaques with irregular edges were present (Fig. 1e). The ocular exam showed a circular white-grey deposit corresponding to arcus senilis between 4 and 12 o'clock (Fig. 1g).

The serum lipid profile was abnormal: triglyceride was low at 71 mg/dl (0.8 mmol/l), total cholesterol was increased at 398 mg/dl (10.28 mmol/l), HDL 54 mg/dl (1.4 mmol/l), LDL 328 mg/dl (8.48 mmol/l), VLDL was normal at 16 mg/dl (0.41 mmol/l), and
Lp(a) was 103 mg/dl (2.66 mmol/l) (normal below 30 mg/dl, 0.78 mmol/l).

Cardiological and angiological examination showed severe generalized atherosclerosis. No other relevant pathologic finding was obtained. The noncompliant patient refused skin biopsy and any cardiological intervention. Erbium-YAG-Laser treatment was performed for his xanthelasma with an excellent cosmetic result (Fig. 1f).

Discussion

The term hyperlipidemia or hyperlipoproteinemia is used when there is an elevation of serum lipid levels in the blood. The plasma lipids are transported in lipoproteins. Electrophoresis and ultracentrifugation of blood are used to differentiate four principle fractions of plasma lipoproteins: chylomicrons, VLDLs, LDLs, and HDLs. On the basis of the electrophoretic lipoprotein phenotype, Frederickson et al. (Table 1) classified primary hyperlipoproteinemias into five major types (types I–V) (1). Familial hypercholesterolemia (FH) is a hereditary autosomal dominant disorder of lipoprotein metabolism characterized by a defect in the low-density lipoprotein (LDL) receptor gene (2), which leads to progressive increase of LDL cholesterol levels in the blood.

Familial hypercholesterolemia is expressed at birth or in early childhood (3). Heterozygous and homozygous variants have been described. The heterozygous form has a prevalence of approximately 1 in 500 individuals in most parts of the world, whereas the homozygous form is very rare (1 in 1,000,000) (4, 5). In the homozygous form, high levels of LDL 600–1000 mg/dl (15.5–25.84 mmol/l) can be found between birth and 5 years of age (6); clinically, this is characterized by severe xanthomatosis developing in the first few years of life, multiple types of xanthomas can occur (7), and coronary atherosclerosis usually develops earlier, before the teenage years (8). In the heterozygous form, the cholesterol levels are approximately twice normal, with values usually in the 270–550 mg/dl (6.98–14.21 mmol/l) range (9); in this form the xanthomatous lesions develop during the third to sixth decades. Familial homozygous hypercholesterolemia is a type II hyperlipoproteinemia; it is sub-classified into types IIa and IIb on the basis of defects found: type IIa is characterized by LDL-receptor protein deficiency with increased LDL, whereas type IIb, called combined hyperlipidemia, is characterized by...
decreased LDL-receptor and increased ApoB with additional tendency for elevated LDL and VLDL.

In our patient, the lipid profile was suggestive of heterozygous type IIa hyperlipoproteinemia, with markedly elevated LDL cholesterol levels and normal VLDL and triglyceride levels. Intertriginous, tendinous, tuberous xanthomas and xanthelasma palpebrarum are typical manifestations.

Xanthoma (from Greek ξανθός ‘yellow’) is a deposition of yellowish material formed by lipids in foam cells (10) (macrophages with phagocytosed lipid material) and collagen. There are different xanthomas based on their clinical and morphological aspects.

Various experiments have been conducted to define the mechanism of lipid deposition in tendon xanthomas. LDL derived from plasma is trapped in the collagen and glycosaminoglycans of the tendon matrix and can be oxidized at these sites. The reaction of LDL with macrophages or other cells of the tendon can explain the modification of LDL into oxLDL, which is taken up mainly by macrophages, thereby promoting the formation of foam cells (11, 12), which extravasate through the vascular walls and deposit in perivascular connective tissue.

Tendon xanthomas are firm subcutaneous nodules, which may be hard due to fibrosis. They are usually skin colored and do not appear yellow because the cholesterol ester is deposited deep within the tendons. They are localized over the proximal finger joints, the insertions of the patellar tendons, and the Achilles tendons (13). This disfiguring pathological state may interfere with function and cause achillodynia and, rarely, spontaneous tendon rupture (14). Tendonitis, peritendinitis or bursitis, trauma, nodules from rheumatic arthritis, or gout tophi are other frequent conditions that may lead to Achilles tendon (AT) thickening, and in such cases differential diagnosis from ATX (Achille tendon xanthoma) may be difficult. Detailed family and medical history, serum lipid analysis, and ultrasound of the affected tendon may help in the differential diagnosis (15, 16). Ultrasound is the most important imaging method used for evaluating ATX (16–18).

The sonographic aspect, with 7.5 MHz linear array transducer, of our patient’s Achilles tendon was characterized by a focal hypoechoic lesion (Fig. 2). The deposition of cholesterol in xanthomas is similar to that in atherosclerotic lesions (19). Clinical and imaging studies have suggested that a positive correlation exists between tendon xanthoma regression and improvement in atherosclerotic disease (20), which is the main cause of death in dyslipidemic patients.

Xanthelasma palpebrarum is the most important clinical manifestation visible around the eyes. According to many epidemiologic studies, xanthelasma is thought to be a determinant of an increased risk of atherosclerosis (21). Very rare are intertriginous xanthomas, consisting of a yellow dermal plaque with corrugated surface localized in the finger webs, palmar creases, axillae, buttocks, and antecubital and popliteal fossae (22, 23). Other type of xanthomas are the eruptive form localized in the gluteal region, trunk, and extensor surface of the extremities; these lesions are small, light yellow, and usually surrounded by an inflammatory halo. An important sign is the corneal arcus or arcus senilis, which appears as a single grayish ring parallel to the limbus and is separated from it by a 1 mm lucid interval of Vogt. It is typically localized between 6 and 12 o’clock. It develops as a result of lipid deposition in the deep corneal stroma and the limbal sclera, and its prevalence increases with age. Various techniques and methods have been described in the literature to treat this condition, including application of trichloroacetic acid (TCA), electric cautery, surgical excision, carbon dioxide laser removal.
vaporization, and cryosurgery with varying degree of success. In fact, surgery can be a good choice for xanthelasma, but it is difficult when lesions are very close to the eye, multiple, and, above all, the patient does not opt for it. TCA is a simple and effective method, and achieves a satisfactory cosmetic result after 10 days and high patient satisfaction, but dietary modification and drug therapy with statins form the initial treatment strategy. Statins (HMG-CoA reductase inhibitors) act by reducing the liver cholesterol stores, which upregulate LDL-receptor expression and produce a subsequent fall in the plasma LDL levels. Pharmacotherapy combined with dietary modification is generally helpful in patients with the heterozygous form, but it may not be adequate for the homozygous form, in which LDL-apheresis and liver transplantation are recommended. Our patient is receiving therapy with ASA, β-blockers, and simvastatin to control his hypercholesterolemia and atherosclerosis.

**Table 1: Fredrickson et al. classification of hyperlipoproteinemia.**

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<th>Type</th>
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| I (rare) | Synonyms: Buerger-Gruetz syndrome, primary hyperlipoproteinaemia, familial hyperchylomicronemia  
Problems: Decreased lipoprotein lipase (LPL) or altered ApoC2  
Increased lipoprotein: Chylomicrons  
Treatment: Diet control  
Serum appearance: Creamy top layer |
| IIa | Synonyms: Polygenic hypercholesterolaemia or familial hypercholesterolemia  
Problems: LDL receptor deficiency  
Increased lipoprotein: LDL  
Treatment: Bile acid sequestrants, statins, niacin  
Serum appearance: Clear |
| IIb | Synonyms: Combined hyperlipidemia  
Problems: Decreased LDL receptor and increased ApoB  
Increased lipoprotein: LDL and VLDL  
Treatment: Statins, niacin/fibrates  
Serum appearance: Clear |
| III (rare) | Synonyms: Familial dysbetalipoproteinemia  
Problems: Defect in Apo E 2 synthesis  
Increased lipoprotein: IDL  
Treatment: Fibrate  
Serum appearance: Turbid |
| IV | Synonyms: Familial hyperlipemia  
Problems: Increased VLDL production and decreased elimination  
Increased lipoprotein: VLDL  
Treatment: Fibrates and niacin  
Serum appearance: Turbid |
| V (rare) | Synonyms: Endogenous hypertriglyceridemia  
Problems: Increased VLDL production and decreased LPL  
Increased lipoprotein: VLDL and chylomicrons  
Treatment: Niacin/fibrates  
Serum appearance: Creamy top layer and turbid bottom |

**References**


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The document contains references to various studies and articles related to skin manifestations in familial heterozygous hypercholesterolemia, discussing topics such as metabolic and nutritional disorders, lipoprotein metabolism, and the pathophysiology of familial hypercholesterolemia. It also highlights the diagnostic and clinical significance of Achilles tendon changes in patients with hypercholesterolemia.