Case Report

Familial hypercholesterolemia: The skin speaks

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Abstract

Familial hypercholesterolaemia (FH) is an autosomal dominant inherited disorder of lipoprotein metabolism caused by defects in the low-density lipoprotein receptor (LDLR) gene. It is characterized by high low-density lipoprotein (LDL) cholesterol levels, premature cardiovascular disease (CVD), and tendon xanthomas. We present the case of a 26-year-old gentleman who presented with multiple nodular eruptions over the extensor aspects of upper and lower limbs and was diagnosed as FH on the basis of positive family history, typical lipid profile abnormalities, and biopsy of the nodule consistent with tendon xanthomas. The diagnosis and management of this case is deftly feasible at the primary care level.

Keywords: Familial hypercholesterolemia, lipid disorder, tendon xanthoma

Introduction

Tendon xanthomas (TX) are cholesterol deposits in tendons and are commonly caused by a disturbance of lipoprotein metabolism. This case highlights the typical presentation of tendon xanthoma in a person which led to the diagnosis of Familial Hypercholesterolemia (FH) which can be easily diagnosed and managed at the primary care level.

Case Report

A 26-year-old non-obese gentleman presented to a primary care physician with a painless nodular eruptions over bilateral elbows, dorsum of the wrist, and both ankles for the last 10 years. He gave history of similar swellings over the anterior aspect of both knees which were surgically removed 1 year ago. On examination smooth, skin colored painful nodules were noted over the lower part of both tendo-achilles, bilateral elbows, and dorsum of bilateral wrist. [Figure 1] The skin overlying the nodules was freely mobile. He was accompanied by her younger sister and on examination she was also found to have similar nodules with same pattern of distribution [Figure 2]. He had two more siblings with similar nodules (but not accompanying him). There was history of coronary artery disease in mother at the age of 58 years. He denied history of smoking and alcohol intake. A clinical diagnosis of tendinous xanthoma was considered, and the patient was evaluated for the etiology.

Investigations revealed elevated low-density lipoprotein levels. He was also evaluated for secondary causes of dyslipidemia and were found to be normal. The results are tabulated in Table 1. Electrocardiogram and ultrasonography of the abdomen were normal. Biopsy from the nodule showed aggregates of foamy macrophages admixed with mild to moderate infiltrates of lymphocytes and histiocytes in the mid and deep dermis suggestive of xanthoma. Sister's biochemical evaluation also revealed high LDL levels and is tabulated in Table 1.

The diagnosis of FH was made based on the elevated LDL levels, tendon xanthomas, and significant family

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Table 1: Biochemical parameters of the index patient and his sister

Parameter (unit)	Value		Normal range
	Index patient	Sister	
Total cholesterol (mg/dl)	458	561	<160
Serum triglyceride (mg/dl)	158	81	<150
Serum HDL (high density lipoprotein) (mg/dl)	31	43	40-60
Serum LDL (low density lipoprotein) (mg/dl)	390	490	<100
Fasting blood glucose (mg/dl)	103	99	70-110
HbA1c (%)	5.3	5.3	<5.7
TSH (Thyroid stimulating hormone) (mU/L)	3.71	4.734	0.3-4.5

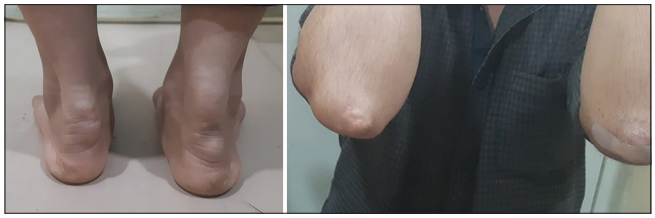

Figure 1: Tendinous xanthoma in the patient at tendo-achilles and elbows

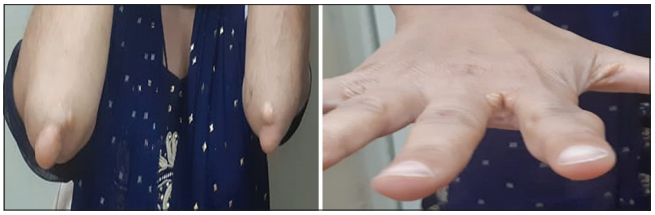

Figure 2: Tendinous xanthoma in patient's sister at elbow and extensor tendons

history (xanthoma/premature coronary artery disease/elevated LDL levels).

Discussion

TX are cholesterol deposits in tendons. They appear as slowly enlarging papules or subcutaneous nodules usually attached to tendons, but can also be attached to ligaments, fascia, and periosteum. These xanthomas typically occur over the Achilles tendon, while the other common sites are subpatellar, and hand extensor tendons. Histopathologically, xanthomas are characterized by the presence of vacuolated macrophages in dermis. These macrophages are filled with lipid droplets that are dissolved and removed during tissue processing.[1]

The presence of TX is a clinical sign of FH, an autosomal dominant inherited disorder of lipoprotein metabolism. FH is caused by defects in the low-density lipoprotein receptor (LDLR) gene (85–90%), pathogenic variants of the apolipoprotein B (ApoB) gene resulting in decreased binding of LDL to the LDL receptor (5–15%), or gain of function mutations in the gene for proprotein convertase subtilisin/kexin 9 (PCSK9) (1%), resulting in increased destruction of LDL receptor.[2] TX appear in homozygous FH patients from their childhood, while heterozygous FH patients develop TX by the age of 20 years.[3] The proportion of patients with TX increases with age. It can be observed in 75% of patients with FH as they grow older.

TX are also present rarely in other hyperlipidemic states (drug-induced hyperlipidaemia [antiretroviral therapy] or familial recessive hypercholesterolaemia) and normolipidemic states (Apolipoprotein E3 deficiency, Overproduction of apolipoprotein B, cerebrotendinous xanthomatosis.[4]

According to European Atherosclerosis society guidelines, any adult with a high serum cholesterol (>310 mg/dl), premature coronary artery disease, TX should be screened for FH.[5] Thus TX forms an important skin manifestation of FH. The presence of xanthomas is associated with a three-fold higher risk of CVD in patients with FH.[6]

Dietary and lifestyle modifications (avoid smoking, regular exercise, and maintaining a healthy body weight) are the starting points for LDL lowering in patients with FH. Treatment of atherosclerotic cardiovascular disease (ASCVD) risk factors, such as hypertension and diabetes mellitus, should be optimized.[5] Statins with or without ezetimibe is the first line drug therapy for FH.[7] In patients with FH and an LDL level ≥100 mg/dL on maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor or other newer agents may be considered.[8] If very high LDL persists following maximally tolerated lipid lowering therapy, lipid or lipoprotein apheresis (formerly known as LDL apheresis) may be attempted.[9] TX may require surgical excision if they are disfiguring or hamper functioning.[10]

Conclusion

The key summary points from this case for a physician in primary practice are that TX serves as an important skin manifestation of FH cases. Its awareness could also lead to the diagnosis of FH in related patients of the index case. Moreover, it can promptly be managed in the primary care setting as early lipid lowering therapy is essential to decrease the risk of coronary heart disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients

understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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