Familial hypercholesterolaemia: 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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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 periostea. 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

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

| Parameter (unit)                     | Index patient | Sister | Normal range |
|-------------------------------------|---------------|--------|--------------|
| Total cholesterol (mg/dl)           | 458           | 561    | <160         |
| Serum triacylglyceride (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

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

| Parameter (unit)                     | Value   | Normal range |
|-------------------------------------|---------|--------------|
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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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Conflicts of interest
There are no conflicts of interest.

References
1. Roy AK, Das S, Chowdhury J, Bhanja D. Tendinous xanthoma with familial hypercholesterolemia. Indian Dermatol Online J 2014;5:559-60.
2. Soutar AK, Naoumova RP. Mechanisms of disease: Genetic causes of familial hypercholesterolemia. Nat Clin Pract Cardiovasc Med 2007;4:214-25.
3. Mangili LC, Miname MH, Silva PRS, Bittencourt MS, Rocha VZ, Mangili OC, et al. Achilles tendon xanthomas are associated with the presence and burden of subclinical coronary atherosclerosis in heterozygous familial hypercholesterolemia: A pilot study. Atherosclerosis 2017;263:393-7.
4. Tsouli SG, Kiortsis DN, Argyropoulou MI, Mikhailidis DP, Elisaf MS. Pathogenesis, detection and treatment of Achilles tendon xanthomas. Eur J Clin Invest 2005;35:236-44.
5. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: Guidance for clinicians to prevent coronary heart disease Consensus Statement of the European Atherosclerosis Society. Eur Heart J 2013;34:3478-90.
6. Oosterveer DM, Versmissen J, Yazdanpanah M, Defesche JC, Kastelein JJP, Sijbrands EJG. The risk of tendon xanthomas in familial hypercholesterolaemia is influenced by variation in genes of the reverse cholesterol transport pathway and the low-density lipoprotein oxidation pathway. Eur Heart J 2010;31:1007-12.
7. Gagné C, Gaudet D, Bruckert E, Ezetimibe Study Group. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolaemia. Circulation 2002;105:2469-75.
8. Yamashita S, Arai H, Bujo H, Masuda D, Ohama T, Ishibashi T, et al. Probucol trial for secondary prevention of atherosclerotic events in patients with coronary heart disease (PROSPECTIVE). J Atheroscler Thromb 2020. doi: 10.5551/jat.55327.
9. Thompson GR. LDL apheresis. Atherosclerosis 2003;167:1-13.
10. Ahn JH, Chun TJ, Lee S. Nodular excision for painful localized Achilles tendon xanthomas in type II hyperlipoproteinemia: A case report. J Foot Ankle Surg 2011;50:603-6.