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Case Report

Case report—Rapid regression of xanthomas under lipoprotein apheresis in a boy with homozygous familial hypercholesterolemia

Julius Katzmann, MD*, Carsten Schürfeld, MD, Winfried März, MD, Ulrich Laufs, MD

Klinik und Poliklinik für Kardiologie, Universitätsklinikum Leipzig, Leipzig, Germany Drs Katzmann and Laufs.; GZ–Vauban, Gemeinschaftspraxis, Saarlouis, Germany Dr Schürfeld; and Medical Clinic V (Nephrology, Rheumatology, Hypertensiology, Endocrinolgy, Diabetology), Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany; Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria; Synlab Academy, Synlab Holding Deutschland GmbH, P5, 7, Mannheim, Germany Dr März

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Abstract: Xanthomas are visibly deforming cholesterol deposits that develop after long-term exposure to high serum low-density lipoprotein cholesterol concentrations. We present the case of a 10-year-old boy suffering from homozygous familial hypercholesterolemia with generalized atherosclerosis and large xanthomas. The case impressively demonstrates the potential of low-density lipoprotein cholesterol lowering to rapidly regress pathologic cutaneous manifestations of hypercholesterolemia.

Introduction

Long-term exposure to high serum low-density lipoprotein cholesterol (LDL-C) concentrations leads to atherosclerosis and in patients with very high LDL-C levels, to cutaneous deposits of cholesterol. Here we present the case of a 10-year-old boy with homozygous familial hypercholesterolemia (HoFH) with large xanthomas, which showed marked and rapid regression under treatment with statin and lipoprotein apheresis (LA).

Familial hypercholesterolemia (FH) is an autosomal dominant disease characterized by markedly elevated levels of LDL-C. In most cases, FH is caused by a mutation of the LDL receptor. The prevalence of heterozygous FH is 1 of 500 to 1 of 200.[1] The homozygous form of FH is a rare and severe condition; affected patients develop atherosclerotic lesions at a young age and untreated carriers usually die before the age of 30 years.[2] Xanthomas develop after long-term exposure to high blood concentrations of cholesterol and are associated with coronary atherosclerosis.[3]

Case report

In 2016, a 10-year-old boy of Syrian descent was referred to our lipid clinic. For 3 months, he had lived in Germany in a refugee accommodation together with one of his brothers. At physical examination, the boy showed large xanthomas of the skin between the fingers and at the left hallux, tuberous xanthomas over both elbows, and tendinous xanthomas over the extensor tendons of the knees and feet and over the Achilles tendons (Fig. 1, left side). An arcus cornea was present. He had no xanthelasma.

Laboratory examination showed markedly elevated serum concentrations of total cholesterol (727 mg/dL [18.9 mmol/L]), LDL-C (679 mg/dL [17.7 mmol/L])

* Corresponding author. Klinik und Poliklinik für Kardiologie, Universitätsklinikum Leipzig, Liebigstraße 20, Leipzig 04103, Germany.
E-mail address: julius.katzmann@medizin.uni-leipzig.de
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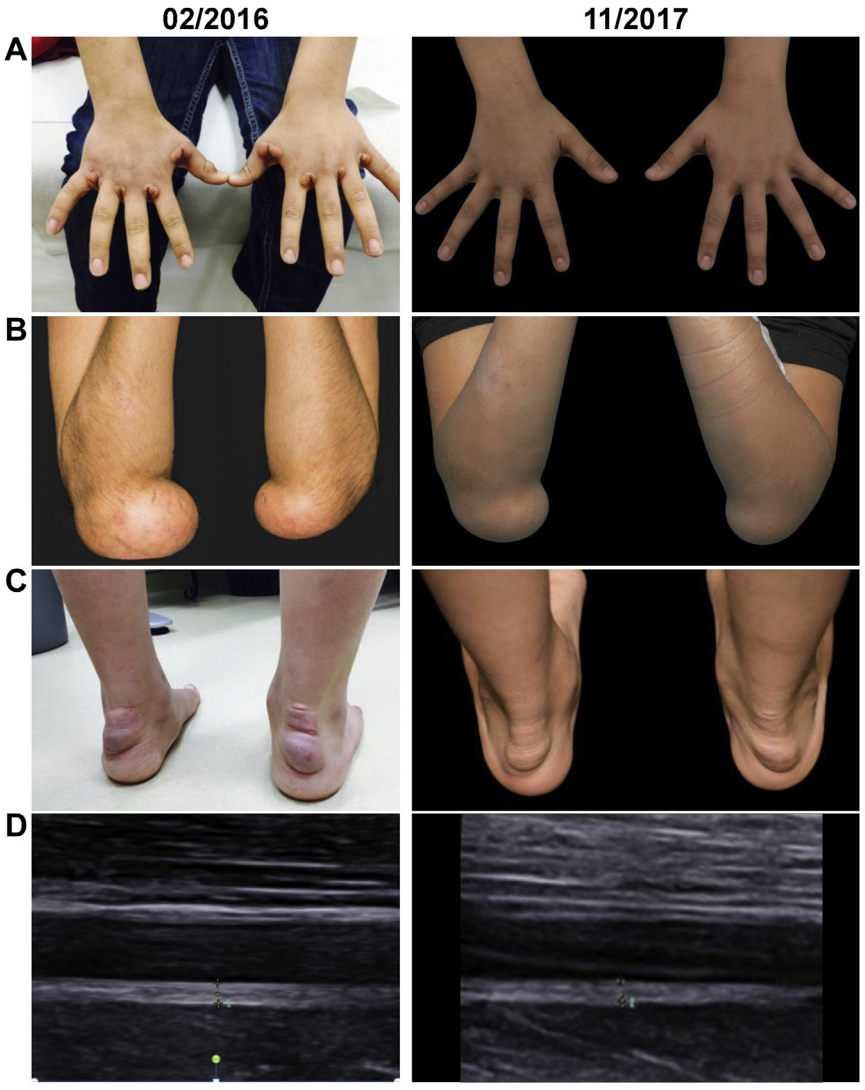

Figure 1 Photographs of the xanthomas (A–C) and ultrasound of the right superficial femoral artery (D) of a 10-year-old boy with homozygous familial hypercholesterolemia at presentation in 02/2016 and after 18 months of lipid-lowering treatment in 11/2017.

and apolipoprotein B (446 mg/dL [8.12 μmol/L]). Triglycerides were within the normal range (149 mg/dL [1.7 mmol/L]); high-density lipoprotein cholesterol (25 mg/dL [0.65 mmol/L]) and apolipoprotein A1 (78 mg/dL [27.85 μmol/L]) were low.

Genetic investigation revealed a homozygous mutation of the LDL receptor gene (c.1478_1479de/CT). This variant has been described in 1994 by Cavanaugh et al. as "FH-Sydney 2", a 2-bp deletion at position 1478 (codon 472) that leads to a premature truncation of the LDL receptor most likely resulting in no detectable protein.[4]

The boy had the APOE2/E3 genotype, which is commonly associated with low LDL-C. In addition, he showed increased lipoprotein(a) (245.1 nmol/L, approximately 98 mg/dL). The boy is negative for the lipoprotein(a) SNPs rs10455872 and rs3798220.

Further diagnostics revealed generalized atherosclerosis. Ultrasonographically measured intima-media thickness of the common carotid artery was 0.6 mm on the right and 1.6 mm on the left side. Femoral arteries showed advanced atherosclerosis (intima-media thickness of the left superficial femoral artery 1.6 mm). Echocardiography was normal.

We began a therapy with simvastatin 40 mg and aspirin 100 mg. Owing to legal restrictions, use of more potent statins such as atorvastatin or of ezetimibe was not possible. LA, requiring a shunt, was initiated and maintained weekly. With apheresis, LDL-C levels were around 250 mg/dL (6.5 mmol/L) before and 70 mg/dL (1.8 mmol/L) immediately after treatment. Apheresis was well tolerated. As soon as the boy turned 12 years old, we were able to obtain the permission of the state guardian for treatment with the PCSK9-inhibitor evolocumab that is approved in Germany for HoFH at the age of 12 years. He received 420 mg every 4 weeks based on the TESLA study.[5] However, careful measurements showed an LDL-C response below 10% after 12 weeks. This is in agreement with the mechanism of