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CASE REPORT

Early-onset familial hypercholesterolemia: A case of extensive xanthomas and premature coronary artery disease

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Key Clinical Message

Early recognition and management of familial hypercholesterolemia (FH) are crucial, especially in patients with extensive xanthomas and premature coronary artery disease. Prompt diagnosis and aggressive lipid-lowering therapy can significantly reduce morbidity and mortality rates. Careful clinical assessment in resource-limited settings is essential for optimal outcomes.

Abstract

Familial hypercholesterolemia (FH) is an autosomal dominant inherited disorder that causes chronically elevated levels of low-density lipoprotein (LDL) cholesterol. Based on LDL levels, FH can be heterozygous or homozygous, further established through clinical features, laboratory findings, and genetic analysis. Elevated cholesterol levels cause atherosclerosis, coronary artery disease, myocardial infarction, and sudden death. Xanthomas are a clinical manifestation of FH that reveal the underlying systemic genetic disease. We present the case of a 47-year-old male with triple vessel coronary artery disease and widespread xanthomas, diagnosed with homozygous FH based on "The Dutch Lipid Clinic Network Diagnostic Criteria for Familial Hypercholesterolemia." Lifelong therapy with lipid-lowering medications and lifestyle changes is necessary in such cases.

KEYWORDS

CABG, Dutch lipid clinic network diagnostic criteria, general medicine, lipid-lowering drugs, xanthomas

Guarantor: Sukhjot Kaur and Amogh Verma.

1 | INTRODUCTION

Familial hypercholesterolemia (FH) is an inherited disorder of lipoprotein metabolism caused by mutations in genes involved in the LDL receptor-mediated pathway for cellular uptake of LDL.[1] Most FH cases follow an autosomal dominant inheritance pattern, leading to persistently elevated LDL cholesterol levels and premature coronary artery disease (CAD) if left untreated.[2,3] Homozygous familial hypercholesterolemia (HoFH) presents with LDL-C levels twice as high as those in heterozygous FH (HeFH) and has a much poorer prognosis.[4] Emerging evidence suggest that HoFH prevalence may be higher than previously estimated, ranging from 1 in 170,000 to 1 in 300,000.[5]

Patients with HoFH often exhibit severe cardiovascular complications early in life, with LDL-C levels typically exceeding 500 mg/dL.[6,7] These individuals are frequently refractory to conventional lipid-lowering therapies, including statins, due to the near-complete loss of LDL receptor activity.[8,9] Therefore, early diagnosis and aggressive treatment, including lipoprotein apheresis and the use of novel therapeutic agents, are essential for preventing premature death.[10]

We present a particularly unique case of an adult patient with HoFH who exhibited extensive xanthomas leading to premature coronary artery disease. Such widespread cutaneous manifestations are rare and highlight the severity of lipid metabolism disorders when left untreated. Additionally, this case underscores the challenges of diagnosing and managing HoFH in resource-limited settings, emphasizing the critical importance of early recognition and intervention to prevent life-threatening cardiovascular events.

2 | CASE HISTORY/ EXAMINATION

A 47-year-old unmarried male from rural Punjab, North India, presented to the emergency department at a tertiary care center in Ludhiana with sudden onset dyspnea for 3 h and acute chest pain radiating to the left arm, associated with sweating and a sense of impending doom. His medical history included hypertension, diabetes mellitus, and hyperlipidemia. His family history was significant for the death of his elder sister at the age of 45 due to myocardial infarction. On arrival, his vital signs showed a temperature of 37.3°C, blood pressure of 100/62 mmHg, heart rate of 120 beats per min, respiratory rate of 24 breaths per minute, and oxygen saturation of 86% on room air. Physical examination revealed yellowish, elevated, painless masses on the bilateral elbow joints, and knee, consistent with xanthomas (Figure 1). Chest auscultation revealed bibasilar crepitus, and there was no focal neurological deficit, jugular venous distension, or abnormal heart sounds.

3 | METHODS (DIFFERENTIAL DIAGNOSIS, INVESTIGATION, AND TREATMENT)

Upon admission, laboratory results revealed a white blood cell count of 15.4 K/UL (normal range: 4.5–11 K/UL), hemoglobin of 12.6 g/dL (normal range: 13.5–17.5 g/dL), and a platelet count of 251 K/UL (normal range: 150–450 K/UL). Electrolyte levels showed sodium at 133 mEq/L (normal range: 135–145 mEq/L), potassium at 4.9 mmol/L (normal range: 3.5–5.0 mmol/L), chloride at 93 mEq/L (normal range: 98–107 mEq/L), and bicarbonate at 21 mEq/L (normal range: 22–28 mEq/L). His creatinine level was 0.7 mg/dL (normal range: 0.6–1.2 mg/dL), and his glucose level was elevated at 324 mg/dL (normal range: 70–99 mg/dL). His B-type natriuretic peptide was 128 pg/mL (normal range: <100 pg/mL), and his troponin-I level was significantly elevated at 1.04 ng/mL (normal range: <0.04 ng/mL). His thyroid-stimulating hormone level was 1.41 IU/mL (normal range: 0.4–4.0 IU/mL). His lipid profile revealed a total

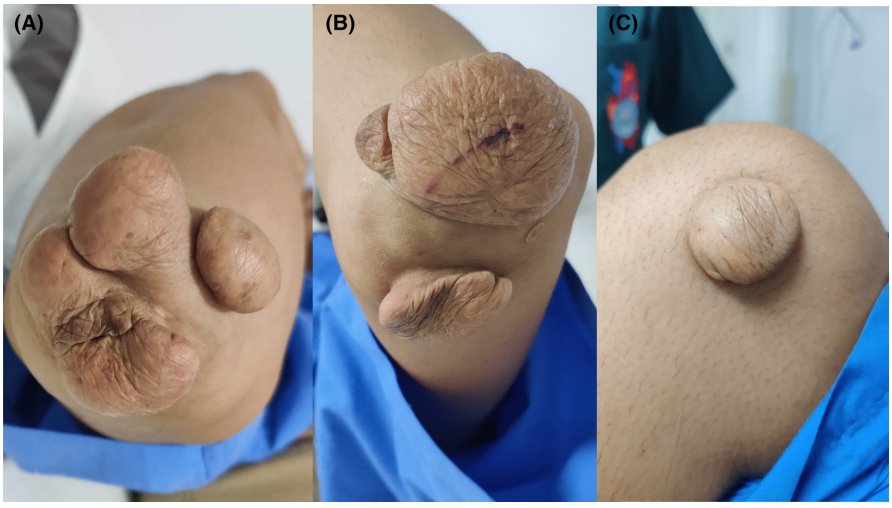

FIGURE 1 Tuberous xanthomas on bilateral elbow (A,B) and knee joint (C).

cholesterol level of 648 mg/dL (normal range: <200 mg/dL), LDL cholesterol of 504 mg/dL (normal range: <100 mg/dL), HDL cholesterol of 86 mg/dL (normal range: >60 mg/dL), and triglycerides of 135 mg/dL (normal range: <150 mg/dL).

Electrocardiography (ECG) showed ST-segment depression in the V3-V5 leads, indicating myocardial ischemia, and the quantitative troponin T test was significantly positive at 3.14 ng/mL. The patient was diagnosed with non-ST-elevation myocardial infarction (NSTEMI). Echocardiography revealed moderate mitral valve regurgitation, a left ventricular ejection fraction of 20%–22%, and severe left ventricular systolic dysfunction.

Given the worsening hypotension, the patient was stabilized by placing an intra-aortic balloon pump (IABP) in the proximal descending aorta via the right femoral artery (Figure 2A). Coronary angiography revealed triple-vessel coronary artery disease with 100%, 70%, and 80% occlusion of the right coronary artery, left main coronary artery, and left circumflex artery, respectively (Figure 2B). The patient and his family were informed of the need for urgent coronary artery bypass grafting (CABG), to which they consented. The surgery was successfully performed the following day.

Considering the poor response of HoFH patients to statins, the patient was also considered for combination therapy with PCSK9 inhibitors. However, due to financial constraints, lipoprotein apheresis, which remains a cornerstone treatment for HoFH, was not feasible in this case[11] After successful CABG, the patient was stabilized and prepared for discharge. He was prescribed a regimen including aspirin 75 mg orally once daily and atorvastatin 40 mg orally once daily at bedtime, both to be continued indefinitely. Additionally, metoprolol 50 mg orally twice daily and ramipril 5 mg orally once daily were prescribed for 6 months to manage his cardiovascular status. The patient was subsequently discharged with instructions for lifelong statin therapy, lifestyle modifications, the importance of medication adherence, and follow-up.

4 | CONCLUSION AND RESULTS (OUTCOMES AND FOLLOW-UP)

The patient had large, painless, flesh-colored masses throughout his body, known as tuberous xanthomas, present on the extensor surfaces of his hands, elbows, legs, and buttocks. He also exhibited corneal arcus and yellow-colored nodules on his eyelids, consistent with xanthelasmas (Figure 3A), as well as xanthomas on the extensor surfaces of his hands (Figure 3B). Post-CABG, the patient developed a decubitus ulcer over one of the xanthomas on his buttocks due to prolonged immobilization (Figure 3C). The patient reported that these masses had been present since childhood, gradually increasing in size and number with age. He had never sought medical consultation for these masses as they were asymptomatic. His family history was significant for his elder sister's similar presentation, who died of a myocardial infarction at the age of 45. The patient's parents and elder brother were alive, asymptomatic, and had no visible skin lesions.

Based on the clinical findings and laboratory data, the patient was diagnosed with HoFH, despite the lack of genetic confirmation due to financial constraints. The presence of widespread atherosclerosis, including severe triple vessel coronary artery disease, extensive xanthomas, and extremely elevated LDL cholesterol levels, was consistent with HoFH. Although genetic testing was not performed, the diagnosis was supported by "The Dutch Lipid Clinic Network Diagnostic Criteria for Familial Hypercholesterolemia". The patient was counseled about the need for ongoing pharmacotherapy, lifestyle modifications, and potential surgical excision of the xanthomas for cosmetic or functional reasons. Unfortunately, the patient

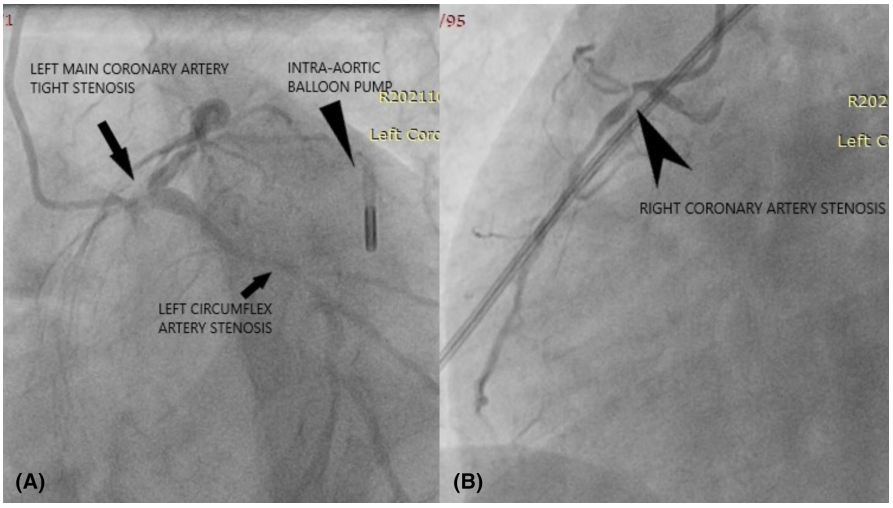

FIGURE 2 (A) Coronary angiography revealing 70% and 80% occlusion of the left main coronary artery and left circumflex artery, respectively. An intra-aortic balloon pump was placed in situ in the proximal descending aorta just below the origin of the left subclavian artery via the right femoral artery. (B) Coronary angiography showing complete occlusion of the right coronary artery, suggestive of triple-vessel coronary artery disease.

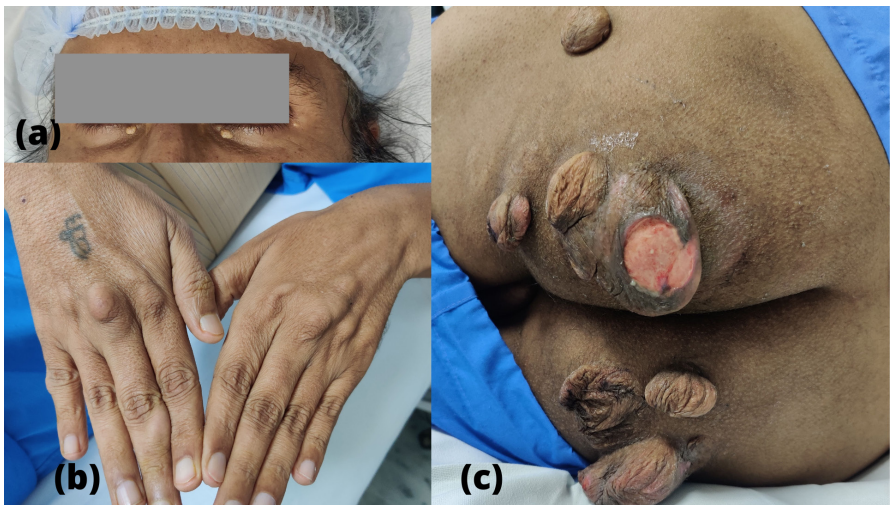

FIGURE 3 (A) Xanthelasmas on eyelids (a). (B) Multiple small tendinous xanthomas on bilateral hand joints (b). (C) Multiple giant tuberous xanthomas on the buttocks; decubitus ulcer on a tuberous xanthoma on the left buttock (c).

was lost to follow-up after discharge, highlighting the challenges in managing complex conditions like HoFH in resource-limited settings.

5 | DISCUSSION

The clinical management of HoFH remains a significant challenge due to the limited efficacy of traditional lipid-lowering therapies.[12] As Nohara et al. emphasized, early initiation of aggressive treatment, including lipoprotein apheresis and Microsomal triglyceride transfer protein (MTP) inhibitors, is crucial for reducing the burden of atherosclerosis and preventing premature death.[13] Lipoprotein apheresis has been the cornerstone of treatment for HoFH, as it selectively removes atherogenic lipoproteins, including those containing apolipoprotein B, such as LDL cholesterol, thereby reducing the risk of cardiovascular events.[14] However, access to lipoprotein apheresis is often limited by financial and logistical constraints, particularly in resource-limited settings.[15] This highlights a critical gap in the equitable management of HoFH across different populations.

Recent advances in pharmacotherapy have provided new options for managing HoFH, especially in patients who are refractory to statins. PCSK9 inhibitors, such as alirocumab and evolocumab, have shown efficacy in lowering LDL cholesterol levels in patients with HoFH, particularly in those with residual LDL receptor activity.[16–21] However, the effectiveness of PCSK9 inhibitors varies among patients with HoFH, as their mechanism of action depends on the presence of functional LDL receptors.[22,23] This underscores the importance of individualized treatment strategies for managing HoFH.

Emerging therapies, such as siRNA drugs (e.g., inclisiran), represent a promising avenue for patients who do not respond to conventional treatments.[13] Inclisiran works by inhibiting the production of PCSK9, leading to increased LDL receptor recycling and enhanced clearance of LDL cholesterol from the bloodstream. This long-acting therapy, which requires only twice-yearly administration, offers a convenient option for patients who struggle with adherence to more frequent dosing regimens.[24] Clinical trials have demonstrated significant reductions in LDL cholesterol levels with inclisiran, even in patients with HoFH.[24–26] However, access to this novel therapy remains limited, particularly in low-resource settings.

Another promising therapeutic option is evinacumab, an anti-ANGPTL3 antibody that lowers LDL cholesterol levels independently of LDL receptor activity.[13] Evinacumab has been shown to significantly reduce LDL cholesterol levels in patients with HoFH, including those with minimal or no LDL receptor function.[27–29] The availability of such receptor-independent therapies is particularly important for patients with HoFH, who often have severely impaired or absent LDL receptor activity. However, like other emerging therapies, evinacumab is not yet widely available and may be cost-prohibitive for many patients.

In addition to these pharmacologic advances, gene therapy represents a potential future direction for the treatment of HoFH.[30] Although still in the experimental stage, gene therapy aims to correct the underlying genetic defect responsible for the disease. Early studies have shown promise, but significant challenges remain, including the delivery of the therapy and long-term safety.[30] The potential of gene therapy to provide a one-time cure for HoFH is exciting, but its practical application is likely years away.

In this case, the patient exhibited many of the hallmark features of HoFH, including extremely elevated LDL cholesterol levels, extensive xanthomas, and premature coronary artery disease. Despite the lack of genetic testing,

the clinical diagnosis of HoFH was strongly supported by the patient's presentation and family history. This case underscores the importance of recognizing the signs and symptoms of HoFH early, particularly in resource-limited settings where access to advanced therapies may be restricted.

For this patient, ongoing statin therapy and lifestyle modifications were the primary means of managing his condition. However, as highlighted by recent studies, statins alone are often insufficient to achieve the necessary LDL cholesterol reductions in patients with HoFH. Combination therapies, including the use of PCSK9 inhibitors or newer agents like inclisiran or evinacumab, should be considered when available. Unfortunately, due to socioeconomic constraints, the patient was lost to follow-up, which limits our ability to assess the long-term outcomes of his treatment.

In conclusion, this case highlights the need for early recognition and intervention in HoFH patients, particularly in resource-limited settings where access to advanced therapies may be challenging. The limitations faced by our patient underscore the ongoing need for accessible healthcare solutions to manage rare and severe conditions like HoFH. Continued research and advocacy are needed to ensure that all patients, regardless of their socioeconomic status, have access to the life-saving treatments they need. Additionally, the development and implementation of new therapeutic options, such as siRNA drugs, anti-ANGPTL3 antibodies, and gene therapy, offer hope for more effective and equitable management of HoFH in the future.

AUTHOR CONTRIBUTIONS

Harsimran Kalsi: Conceptualization; project administration; writing – original draft; writing – review and editing. **Ankur Singla:** Conceptualization; project administration; writing – original draft; writing – review and editing. **Sukhjot Kaur:** Conceptualization; project administration; writing – original draft; writing – review and editing. **Amogh Verma:** Supervision, Validation, Investigation, Writing – original draft; writing – review and editing. **Nathnael Abera Woldehana:** Writing – original draft; writing – review and editing. **Sarvesh Rustagi:** Writing – original draft; writing – review and editing. **Mahendra Pratap Singh:** Writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All relevant data, including figures and additional information, are provided within the manuscript. Any further details can be obtained by contacting the corresponding author.

ETHICS STATEMENT

Ethical approval was not required for this case report.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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