Case Report

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A 37-year-Old Male Patient Presenting with Familial Hypercholesterolemia and Generalized Atherosclerosis

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ABSTRACT

A 37-year-old male undergoing preoperative cardiac evaluation before plastic surgery of lesions in both elbows, referred typical effort angina. His lipid profile showed excessive levels of Total Cholesterol and LDL Cholesterol and Cardiac Stress Test was strongly positive for angina. Subsequent Coronary Angiography revealed Triple-Vessel coronary artery disease and Carotid CTA revealed bilateral significant stenotic atherosclerotic plaques.

The patient underwent revascularization with CABG and Carotid Angioplasty and was put on lipid lowering therapy.

Abbreviations: FH: Familial Hypercholesterolemia; LDL: Low-Density Lipoprotein; PTA: Percutaneous Transluminal Angioplasty; HoFH: Homozygous HF; HeFH: Heterozygous FH; CHD: Coronary Heart Disease; LLT: Lipid Lowering Therapies

Background

Familial hypercholesterolemia (FH) is a genetic disorder characterized by high cholesterol levels, specifically very high levels of low-density lipoprotein (LDL cholesterol) in the blood and early cardiovascular disease. [1-3] The most common mutations diminish the number of functional LDL receptors in the liver. [4] Accelerated deposition of cholesterol in the walls of arteries leads to atherosclerosis in younger ages. [2,3] The most common problem in FH is the development of Coronary Artery Disease at a much younger age than what would be expected in the general population.

Case Presentation

A 37-year-old male patients was presented firstly at the plastic surgeon for evaluation of lesions in both elbows. The surgeon noticed tendon xanthomas and immediately referred the patient to a cardiologist. [4,5] During further assessment, the patients admitted having typical anginal chest pain, mainly exertion induced chest pain. The patient described the pain as a restrosternal squeezing sensation in the chest, which started when doing an exercise or a bit of work and vanished when the patient stopped the effort, grade II according to the CCS Angina Classification. The patient had been a smoker for about 10 years and referred for his uncle with familial dyslipidemia. He did not have hypertension or diabetes mellitus on presentation.

Physical Examination

The patient was alert, in good general condition, with normal vital signs (Blood Pressure 115/70, Heart Rate 62 bpm, SpO2 97%, Temperature 36.5° Celsius). Bilateral xanthelasmas and tendon xanthomas on elbows were the most prominent findings during physical examination. Auscultation of carotid arteries showed presence of bruits on both arteries. Pulmonary and cardiac examination was normal (Figures 1-4).

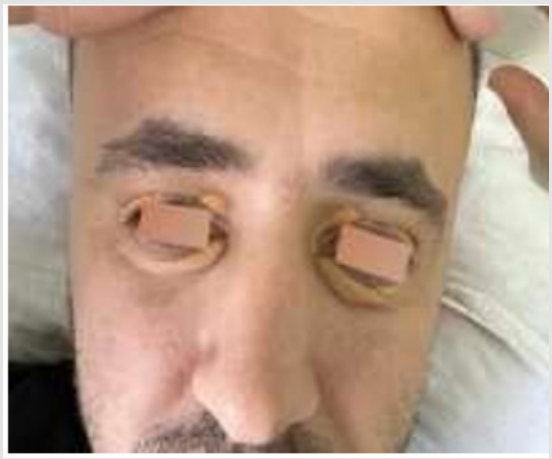

Figure 1: Patient's Xanthelasmas.

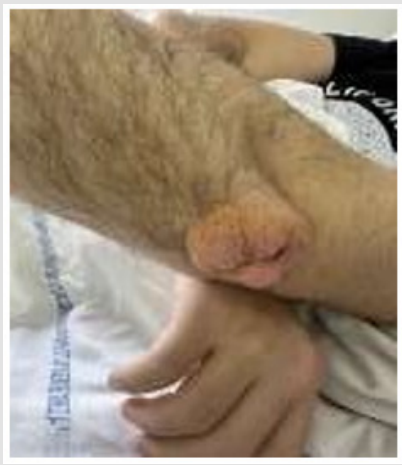

Figure 2: Patient's Tendinous Xanthomas.

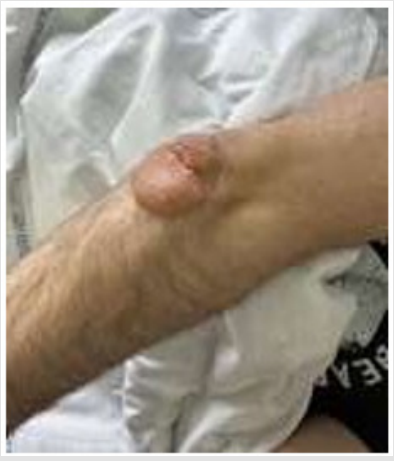

Figure 3: Patient's Tendinous Xanthomas.

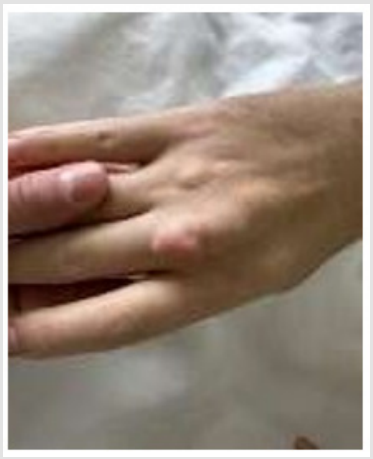

Figure 4: Patient's Tendinous Xanthomas.

Further Investigations

Admission Echocardiography demonstrated a normal size LV, normal LV function (EF~0.60) and no regional wall motion abnormalities. Rest ECG was normal, showing Sinus Rhythm, a HR of 60 bpm, no significant ST-T abnormality. Lipid Profile confirmed very high cholesterol levels. Total Cholesterol was 484 mg/dL, LDL-C 428 mg/dL, Triglycerides 117 mg/dL and HDL-C 33 mg/dL. Complete Blood Count and Biochemistry Panel resulted in normal range. Other endocrine system indicators resulted also normal: HbA1c 5.0% and TSH 1.462 mIU/L. The patient underwent invasive examinations, where Coronary Angiography revealed 3 (Triple) Vessel Coronary Artery Disease + Secondary branches,). The stenotic segments were significant: RCA: 100% ostial stenosis / CTO with intercoronary collaterals; Left Main: 25-50% stenosis; LAD: 75% ostial, 75% mid, 100% apical tract with collaterals; LCx: 75% proximal, 75-90% OM1, 90% distal. Coronary Artery Bypass Grafting (CABG) was recommended (Figures 5-8). Based on patient history, clinical examination and his tendency to form atherosclerotic plaques, we also did Carotid CT Angiography which unfolded significant stenoses of its segments. Most significant were Left ICA: 99% proximal sub occlusive stenosis and Left ECA: 75% ostial stenosis. Right Carotid Artery and its branches had no significant stenoses, but Right Vertebral Artery had a 80% ostial stenosis (Figures 9 & 10).

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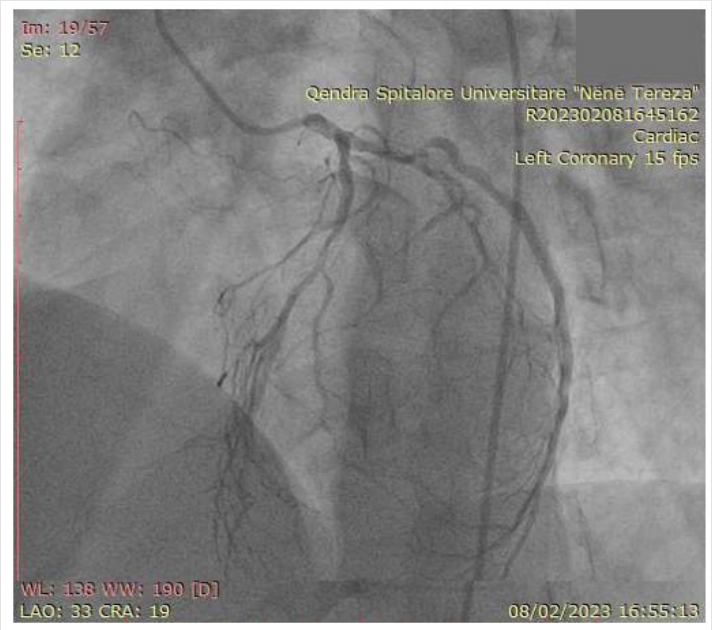

Figure 5: Coronary Angiography LAO 30 CRA 20 – Stenoses of LAD segments.

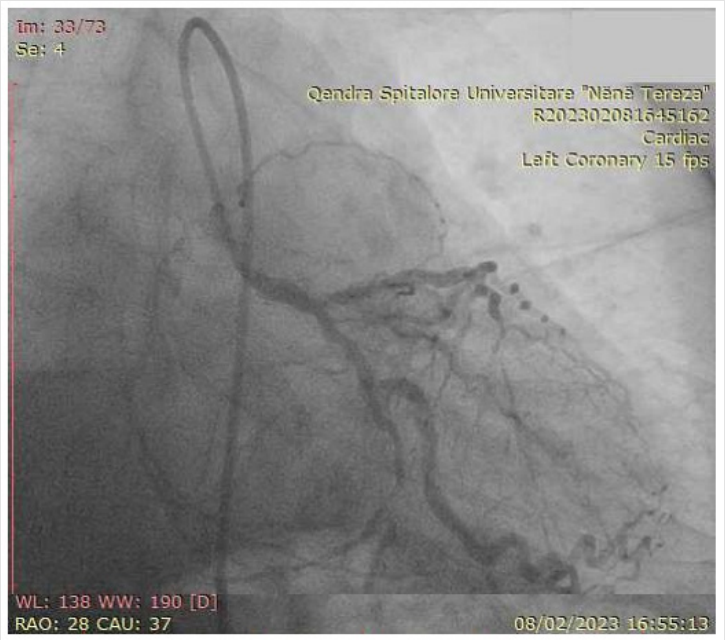

Figure 6: Coronary Angiography RAO 30 CAU 40 – Stenoses of LCx segments.

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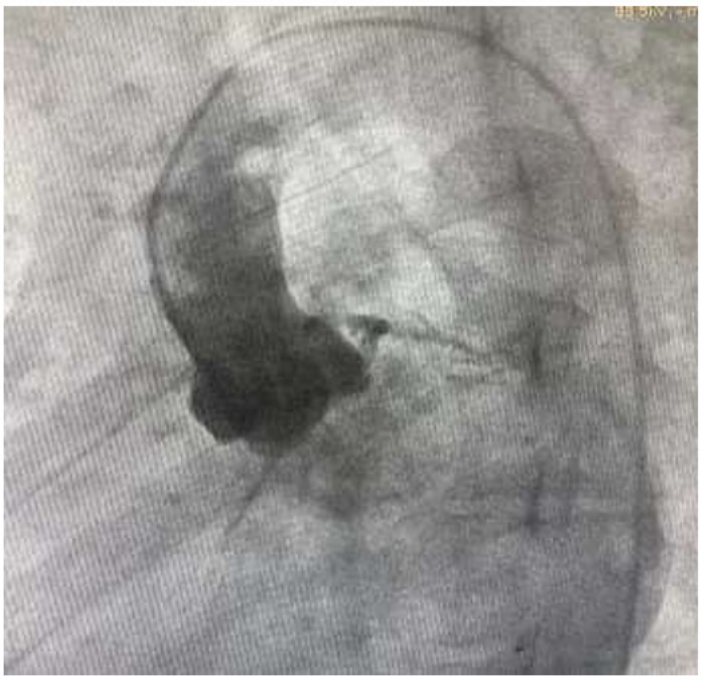

Figure 7: Aortography was performed and RCA was not visualized (CTO).

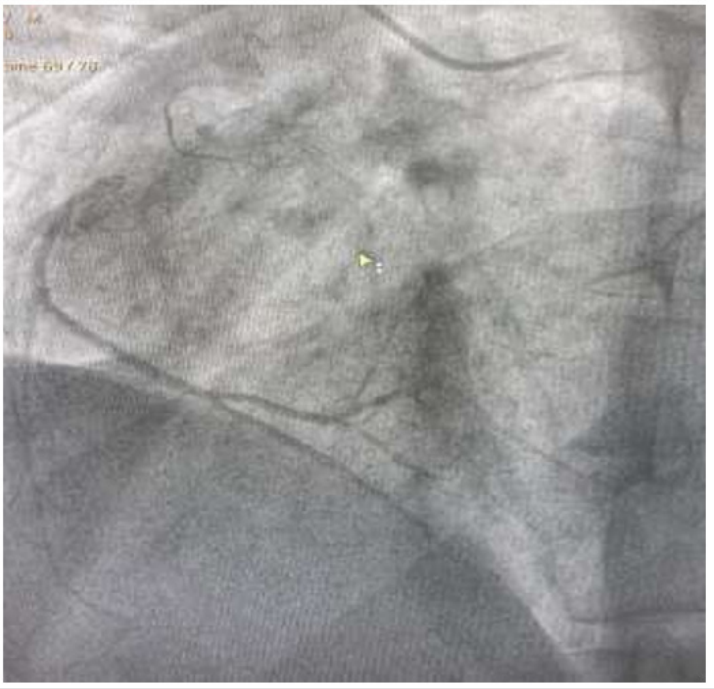

Figure 8: On this frame is seen visualization of RCA by catheterization of Left Main (collaterals from LAD).

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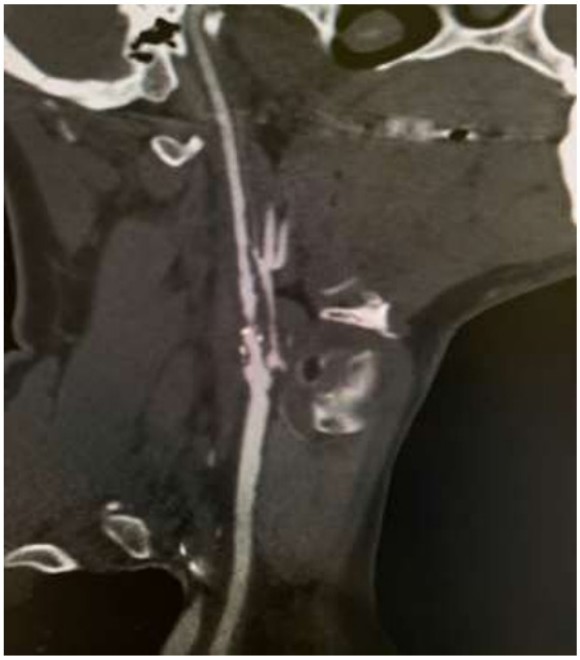

Figure 9: Left Carotid CTA: Left ICA: 99% proximal stenosis; Left ECA: 50-75 % ostial stenosis.

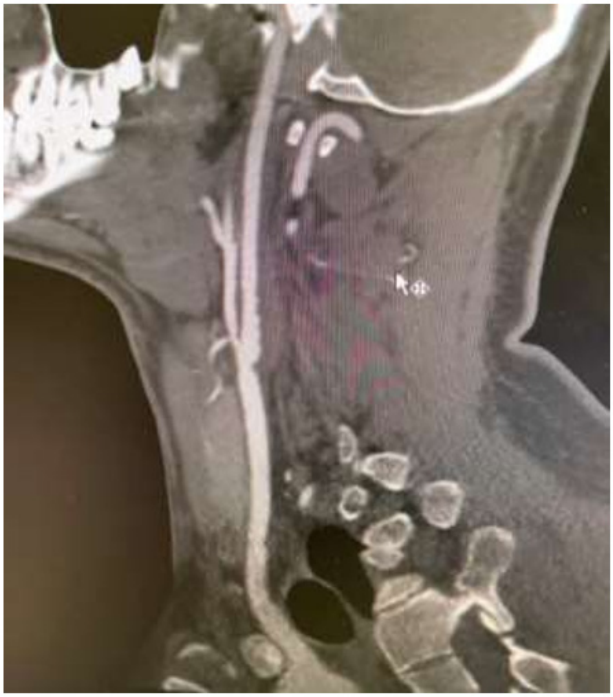

Figure 10: Right Carotid CTA: Right Common Carotid Artery: 50% stenosis Right ICA: 25% proximalstenosis Right ECA: 30% ostial stenosis.

Clinical Course and Treatment

Because of the complexity of the patient, with different comorbidities a multidisiplinary consultation was done, including Cardiologist, Cardiac Surgeon and Vascular Surgeon. The patient was put on lipid lowering therapy with Rosuvastatin/Ezetimibe in high dosages and anti-ischemic therapy was optimised. 1 month after starting lipid-lowering therapy (Rosuvastatin 40 mg + Ezetimibe 10mg), LDL was decreased to ~190 mg/dL. During further hospitalization, complete revascularization with CABG was performed and then the patient underwent Percutaneous Transluminal Angioplasty (PTA) with stent for the Left Internal Carotid Artery. On discharge, we recommended treatment with Dual Antiplatelet Therapy (Aspirin + Clopidogrel), Beta Blockers, Rosuvastatin/Ezetimibe in high dosages.

Discussion

Hyperlipidemias are classified either as Primary Hyperlipidemia (also called familial) when caused by genetic mutations or Secondary Hyperlipidemia (also called acquired) when caused by an underlying disorder such as Diabetes, Hypothyroidism or Obesity. Familial Hypercholesterolemia (FH) is a subtype of Primary Hyperlipidemia. It is the most commonly inherited metabolic disease and has an autosomal dominant mode of inheritance. [5,6] FH, either Homozygous HF (HoFH) or Heterozygous FH (HeFH), emerges due to a genetic mutation that disrupts the pathway of the LDL Receptor (LDLR). The primary pathological genes responsible for encoding LDLR encompass apolipoprotein B (ApoB), proprotein convertase subtilisin kexin-9 (PCSK9), and low-density lipoprotein receptor adaptor protein 1 (LDLRAP1). As of now, over 400 distinct mutations contributing to the FH phenotype have been documented [4]. HoFH is characterized by the existence of two detrimental mutations in both alleles of the responsible genes and its prevalence is notably scarcer. Recent genetic studies suggest that the prevalence of HoFH is now estimated to range between 1 in 250,000 and 1 in 500,000 individuals. [4] While the prevalence of Heterozygous FH (HeFH) is noted to be approximately 1 in 100 to 250 individuals, yet only a small fraction of these patients receive diagnosis or treatment. [4] Patients afflicted with FH typically exhibit elevated levels of low-density lipoprotein-cholesterol, along with xanthomas and premature coronary artery disease.

Using Dutch lipid clinic network criteria, even in the absence of genetic data, we can confirm about the presence of HeFH (which our patient with 17 points fulfill the criteria of HeFH). The treatment should be started without delay. [7] Coronary Heart Disease (CHD) stands as the primary cause to mortality and morbidity among individuals identified with FH. Premature CHD is an established phenomenon of FH, with the average mean age of onset of coronary symptoms shown to be 45 years in men and 55 years in women. [2] But beyond LDL-C, other cardiovascular risk factors, as in our case smoking and lifestyle, and also Lp(a) levels, metabolic or inflammatory risk, may contribute to a more broad diffusion and the earlier presentation of the atherosclerosis disease. Data from the Simon Broome Registry [2,5,6] (UK Register of patients with Familial Hypercholesterolemia) showed that the cumulative risk of a fatal or non-fatal coronary event in the patients with FH by the age of 60 years without effective treatment is at least 50% in men and 30% in women, with a marked increase in postmenopausal women. [2] This means that early diagnosis and management of Familial Hypercholesterolemia will prevent coronary artery disease and improve clinical cardiovascular outcomes. SAFEHEART Study (Spanish Familial Hypercholesterolemia Cohort Study) concluded that identifying ~9000 cases of FH could lead to prevention in 10 years of 847 coronary events and 203 coronary deaths. [3] Treatment of FH consists of medical therapy and lifestyle changes (diet, weight loss, smoking cessation, physical activity). Although lifestyle changes are important and have a positive impact, the main treatment of Familial Hypercholesterolemia is medical therapy.

[1] Lowering LDL-C levels to normal in patients with FH is challenging, especially in most patients with HoFH, but a combination of multiple lipid lowering therapies (LLT) is strongly recommended. High- intensity statins and ezetimibe are the first –line therapy of LLT used by the majority of FH patients. [8] These drugs are easily available, low cost, well tolerated and have been shown to reduce cardiovascular mortality in patients with FH. [9] Last decade there has been innovation regarding the available cathegories of cholesterol-lowering drugs. A range of promising novel medications comprises PCSK9 Inhibitors (alirocumab and evolocumab), MTP Inhibitors, Inclisiran, and Bempedoic Acid. [1] Alirocumab and evolocumab are indicated for homozygous and heterozygous FH patients who persist with elevated LDL-C despite the use of statins and ezetimibe therapies. [1] Therapies acting independently of the LDL receptor pathway, such as lomitapide and evinacumab, are very promising drugs for many patients with HoFH, and may reduce the need for lipoprotein apheresis in future. [10-12] Gene therapy strategies, either aiming to permanently replace or knock out key lipid-related genes are very promising and potentially definitive lifelong treatment option [1,6,13,14].

Conclusion

FH is challenging in many directions. The first one is prompt identification of the disease and screening of first –degree relatives to identify asymptomatic individuals, because the diagnosis of FH is frequently missed or made with a considerable delay. The second one is treatment using multiple lipid lowering therapies to achieve optimal LDL -goals, and modification of other risk factors, that strongly determine survival and also quality of life. Besides the considerable advancements that have been made in the development of innovative medications for addressing FH, there are several barriers to defeat like cost and availability, treatment adherence and also the low responsiveness to medical therapy. In order to make these possible, a national strategy is required for the early identification, screening of the population, optimal treatment, and crossing the financial barriers of this condition, to modify and prevent premature onset of atherosclerosis as well as cardiac and cerebrovascular accidents.

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