Familial hypercholesterolemia (FH) is an autosomal dominant condition caused by mutations in genes that regulate the clearance of plasma cholesterol. Left unattended, this leads to severe hypercholesterolemia, tendon xanthomas, and premature atherosclerotic cardiovascular disease, often at a young age. Therefore, early diagnosis and treatment of FH are critical in preventing avoidable catastrophic events, as exemplified by our case.

Case Report

A previously healthy 29-year-old Thai man suddenly collapsed while walking to the parking lot. He was taken to the hospital outpatient service nearby where ventricular fibrillation was documented (Figure 1). He was successfully defibrillated with return of spontaneous circulation and recovered well without neurological deficits. His first post-resuscitation ECG demonstrated sinus tachycardia with premature ventricular contractions (Figure 2). A subsequent ECG was completely normal (Figure 3). An echocardiogram demonstrated normal left ventricular size with preserved left ventricular systolic function and without regional wall motion abnormalities. His cardiac troponin T was elevated at 30.15 ng/L. Physical examination was remarkable for bilateral achilles tendon thickening with xanthomas (Figure 4A-C). To rule out an arrhythmogenic substrate, cardiac magnetic resonance imaging was performed and revealed no evidence of myocarditis, fatty infiltration, or fibrosis (Figure 5). Additionally, chamber sizes and biventricular systolic function were both normal. No significant valvular disease was noted.

A coronary angiogram demonstrated significant stenosis of the mid-left anterior descending (LAD) coronary artery with TIMI 1 flow. Minimal luminal irregularities were noted in the diagonal branch, distal left circumflex, and proximal right coronary artery (RCA) (Figure 6A-C). There was faint collateral supply from the posterior descending artery (PDA) to the distal LAD, suggestive of chronic LAD stenosis. After uneventful stent implantation, optical coherence tomography demonstrated excellent stent apposition without intimal edge dissection.
The patient is an only child. He is a non-smoker and does not use illicit drugs. His lipid profile demonstrated a total cholesterol of 356 mg/dl, low-density lipoprotein-cholesterol (LDL-C) of 286 mg/dl, high-density lipoprotein-cholesterol (HDL-C) of 76 mg/dl, and triglycerides (TG) of 57 mg/dl. The lipoprotein (a) was normal at 12 mg/dl. At least three family members had documented dyslipidemia. His paternal aunt, a thin, non-diabetic woman, was known to have an LDL-C of 328 mg/dl and TG of 337 mg/dl. His mother and paternal half-brother also had dyslipidemia and were treated with statin therapy (Figure 7). His father died in a motor vehicle accident at the age of 48, and his lipid levels were not known.

The patient was discharged and given atorvastatin 40 mg daily and dual antiplatelet therapy. Repeat lipid panel showed LDL-C of 136 mg/dl. Ezetimibe 10 mg daily was added to his regimen to achieve a more protective LDL target.

**Figure 1:** Rhythm strip at the time of his cardiac arrest revealed ventricular fibrillation requiring defibrillation.

**Figure 2:** After defibrillation, he had return of spontaneous circulation. His electrocardiogram revealed sinus tachycardia without obvious ST-T changes. Premature ventricular contractions were noted. His corrected QT interval was normal.
Figure 3: His second post-resuscitation electrocardiogram was unremarkable.

Figure 4: Xanthomas were noted in both Achilles tendons (A). Magnetic resonance image confirmed abnormal thickened left (B) and right (C) Achilles tendons with amorphous hyperintensity due to xantoma (fat laden histiocyte).

Figure 5: Delayed contrast enhancement of cardiac magnetic resonance image showed no evidence of prior myocardial fibrosis. (RV: right ventricle, LV: left ventricle).
Figure 6: Coronary angiogram demonstrated the culprit lesion in the mid-left anterior descending coronary artery (A, white arrow). He underwent successful stent implantation (5B). Diffuse atherosclerotic lesions (small black arrow) were noted along the origin of diagonal, distal circumflex, distal left anterior descending and proximal right coronary artery. Faint collateral supply from the posterior descending coronary artery to the distal left anterior descending was noted (5C, dashed arrow; suggestive of chronic LAD stenosis). LAD = Left Anterior Descending Artery, RCA = Right Coronary Artery, PDA = Posterior Descending Artery.

Figure 7: The patient’s family tree with partial knowledge of lipid levels in relatives. Although the information on lipid profiles in the family was incomplete, at least three members had documented dyslipidemia: his mother, his paternal aunt (LDLC 328, TG 337), and his paternal half-brother. All of them were on statin therapy.
Aborted Sudden Cardiac Death in Young Man with Familial Hypercholesterolemia: A Case Report and Review of The Literature

Discussion

We present a case of a young victim of acute myocardial infarction (AMI) where the known risk exposure was an exclusive and severe elevation in LDL-C, likely inherited as a heterozygous Familial Hypercholesterolemia (FH) trait. FH is commonly due to mutations in genes regulating clearance of plasma LDL via the LDL receptor (LDLR) pathway, including LDLR itself, APOB, and PCSK9. Ischemic events, such as AMI in individuals under the age of thirty, are uncommon. From multicenter registries and a prospective study, the mean age of AMI victims in Thailand ranges from 55 to 65 years old. AMI prior to the age of 45 accounts for only 6-10% of all cases. The development of cardiac ischemia in the young is not uncommon but predicting these unheralded events remains a significant challenge. Owing to the young age of our patient, all commonly-used risk scores would have classified him as a low risk prior to his event.

The most common risk factors found amongst those who sustain AMI in Thailand at young age are tobacco abuse and family history of coronary artery disease. Our patient did not smoke but was found to have severe hypercholesterolemia (LDL-C of 286 mg/dl). The absence of secondary causes to explain his severe hypercholesterolemia coupled with the absence of other lipid abnormalities, the presence of tendon xanathomas, and the family history of severe dyslipidemia allowed us to make a diagnosis of FH in the heterozygous state even though genetic testing was not performed.

FH is an inherited hypercholesterolemia, most commonly transmitted as an autosomal dominant trait that results from function-reducing mutations in genes encoding essential proteins for hepatic uptake of LDL-C. Mutations in LDLR are by far the most common and explain more than 90% of cases in which genetic confirmation is provided. Less often, mutations are found in either APOB, which codes for the major structural protein of LDL, a ligand for the LDLR; or in PCSK9, which codes for a secreted plasma protein that targets the LDLR for destruction in the lysosome. The mutations culminate in severe hypercholesterolemia, tendon xanathomas, and premature atherosclerotic cardiovascular disease. While most patients with FH have the milder heterozygous form, those with homozygous mutations are at risk of atherosclerotic events at a very early age. In Asian countries, more than 50 mutations have been reported in the literature, including two novel mutations in LDLR found in Thai patients (D151Y and M391T) that cause LDLR transport defects. Our patient is not likely to have the homozygous form since his LDL-C was below the range usually described for true homozygotes, which often is higher than 400 mg/dl. However, a homozygous state for a milder mutation(s) cannot be excluded on the basis of classic genetics, since affected family members included his mother and a paternal aunt and half-brother, and therefore his father may have been affected as well.

To prevent premature AMI in asymptomatic FH patients, US and UK guidelines recommend aggressive lowering of LDL-C, targeting a greater than 50% reduction from baseline. In a very high-risk case, i.e., post AMI victim like our patient, the desirable LDL-C should be less than 70 mg/dl. As a first step, therapeutic lifestyle changes (prudent diet, regular aerobic exercise, weight management, smoking cessation, etc.) are recommended. However, medical therapy is initiated at the same time. Currently, the HMG-CoA reductase inhibitors (statins) remain the cornerstone for treatment of FH, but frequently combination lipid-lowering therapy is required to achieve LDL-C goals. If high-intensity statin therapy fails to achieve LDL-C goals, then ezetimibe, a cholesterol absorption inhibitor, is added. Monoclonal antibodies targeting PCSK9 (e.g., PCSK9 inhibitors) were approved and brought to Western markets in 2015 and can be added if two-drug therapy is inadequate. With the advent of PCSK9 inhibitors, only the most severely affected FH patients do not achieve their LDL-C goals. In those cases, long-term LDL apheresis, a form of “cholesterol dialysis”, can be offered to physically eliminate LDL from the circulation in periodic sessions.

Conclusion

We report a case of aborted sudden cardiac death from AMI in a young man. FH was diagnosed by the presence of tendon xanathomas, severe hypercholesterolemia, and family history of similarly-affected individuals. At present, we are planning to send our patient for genetic testing of the FH-related genes (LDLR, APOB, PCSK9) to confirm our suspicion of FH and facilitate cascade screening of first-degree relatives. To the best of our knowledge, this is the first report of an aborted premature heart attack in a Thai FH patient. By reporting this case, we hope to raise awareness of and interest in this most common of monogenic disorders, which can cause premature cardiovascular disease, largely preventable if diagnosed and treated at an early age.

References

10. Acute Myocardial Infarction Registry, Cardiovascular Research and Prevention Center, Bhumibol Adulyadej hospital (unpublished data)