

Case report

An unusual case of familial hyperlipidemia with statin induced rhabdomyolysis

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ABSTRACT

Familial hypercholesterolemia (FH), also known as Type 2 familial dyslipidemia is a genetic disorder characterized by high levels of low-density lipoprotein (LDL) cholesterol in the blood. Elevated LDL cholesterol levels leads to ischemic heart disease in younger age group. FH is well known to cause deposition of cholesterol in muscle tendons causing tendon xanthomas which present as nodules over Achilles' tendon. Familial hypercholesterolemia is treated with high dose of statins to bring down the LDL cholesterol. We hereby report an unusual case of familial hypercholesterolemia with very high LDL levels (504 mg/dl) and tendon xanthomas who developed statin induced rhabdomyolysis due to consumption of high doses of statins. Patient had consumed both atorvastatin and rosuvastatin by mistake which led to rhabdomyolysis. A clinician must look out for this complication in any patient who is started on high dose of statins. Anticipation of this complication, patient education and periodic checking of muscle enzyme creatine phosphokinase (CPK) and serum creatinine in a patient on high dose statins helps in tackling this complication effectively.

Keywords: Familial hypercholesterolemia; tendon xanthoma; rosuvastatin; rhabdomyolysis; ezetimibe.

INTRODUCTION

Familial hypercholesterolemia (FH) is an autosomal co-dominant disorder which is transmitted genetically. Patients with FH presents with raised low density lipoprotein (LDL) cholesterol levels in the blood affecting 0.2% population worldwide (1).

The abnormality is due to defect in the LDL receptors of the liver and other organs due to mutated LDL receptor gene located on chromosome 19. Defect in one mutant allele LDL receptor is more common than the defect in two LDL receptor alleles and the magnitude is approximately 1 in 500 individuals globally (2). Patients having FH are more prone to develop myocardial infarction (MI) and coronary artery disease (CAD). It is life threatening but can be brought under control with treatment. Very high LDL levels demand prompt treatment with cholesterol lowering drugs. Here, we report a patient with hypertension, type 2 diabetes mellitus (T2DM) and FH, who developed statin induced rhabdomyolysis due to use of low dose of statins and was treated successfully with hydration, ubiquinone and alkalization of urine. Patient had consumed both atorvastatin and rosuvastatin by mistake which led to myopathy and rhabdomyolysis. Patient was suggested to take PCSK 9 inhibitors which she couldn't afford due to poor economic status and was prescribed 5 mg of rosuvastatin with ezetimibe which

improved her renal parameters. She was restarted on low dose rosuvastatin with close monitoring of CK, renal functions and lipid profile levels.

Case presentation

A 57 year old female patient presented to a tertiary care hospital in Karnataka, south India with known case of ischemic heart disease (IHD), familial hyperlipidemia, T2DM and hypertension (HTN). Patient was brought conscious and oriented. She was febrile, had flank and low back pain and a history of joint pain and muscle cramps for the past 2 months. She was apparently few years back following which developed dyspnea on exertion. She also had occasional angina, mainly exertional. Gradually she developed fatigue, palpitations and chest pain, followed by giddiness, syncope and intermittent claudication. On examination, she had pitting pedal edema. She was previously started on high dose of rosuvastatin (40 mg) in view of very high LDL cholesterol levels (504 mg/dl). She presented with body aches, muscle tenderness and lab investigations showed elevated creatinine (1.76 mg/dl) and very high creatinine phosphokinase levels (2413 U/L). Rhabdomyolysis was diagnosed, which was presumed to be statin induced since there were no other risk factors for rhabdomyolysis. Prior informed consent was obtained from the patient for taking biopsy images and photographs.

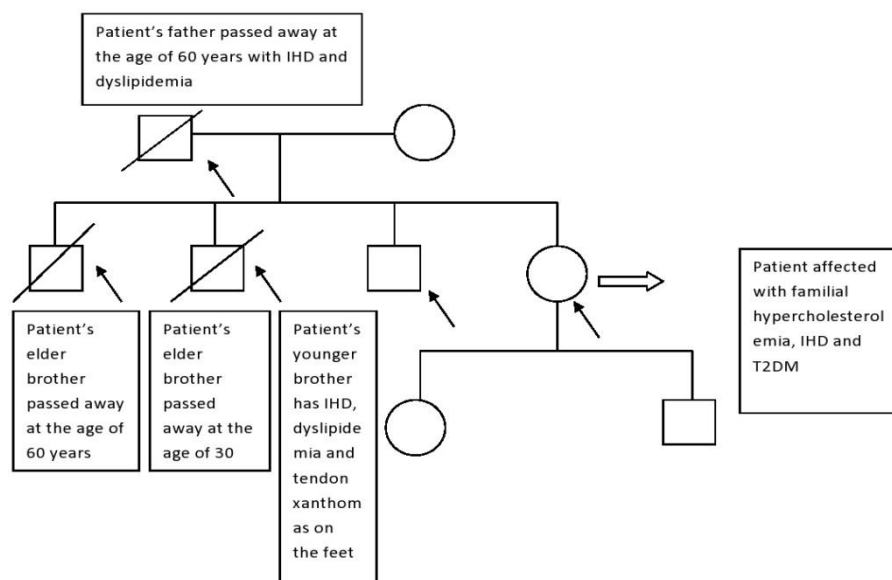


Fig 1: Flow chart describing the family tree of the patient

Family history and family tree

She had a significant family history of IHD and dyslipidemia. Her father (60), elder brothers of age 50 and 30 years all passed away with IHD and she has a younger brother who is suffering from IHD and dyslipidemia with swellings on his feet (Fig. 1).

Physical examination of the patient

On general physical examination, she was moderately built and nourished with BMI of 25.2 Kg/m², waist diameter of 79 cm and W/H ratio of 0.9. Her pulse rate was 80/min and a high blood pressure of 180/100 was recorded. She was found to have audible carotid and renal bruit with presence of pallor. Multiple xanthomas were present on the dorsum of her fingers, elbows, over Achilles' tendon and toes. Laboratory investigations for fasting lipid profile, creatine phosphokinase, renal function test (RFT) and blood sugars were done. Fasting blood sugar level of 118 mg/dl, CPK levels of 2413 U/L, LDL cholesterol levels of 163 mg/dl and creatinine levels of 1.76 mg/dl were recorded. Previously, biopsy of the swelling over the tendon of right little finger was done which showed presence of tendon/tuberous xanthoma (Fig. 2). Cut section showed grey white areas. Microscopic section showed hyperkeratotic overlying dermis with adnexal structures, deeper dermis showed nodules of lipid laden foam cells, occasional Touton giant cells along with mixed inflammatory infiltrate composed of lymphocytes, plasma cells, histiocytes and proliferating fibroblasts (Fig. 3-5).

Electrocardiogram (ECG) showed T inversions in anterolateral and inferior leads. The

echocardiography (ECHO) showed normal biventricular systolic function, absence of wall motion abnormality, sclerotic atrioventricular dissociation (AVD) with mild AS, trivial AR, trivial MR, mild TR, no pulmonary arterial hypertension (PAH), mild LV systolic dysfunction and absence of clot and pericardial effusion. The ejection fraction was observed to be approximately 67%. In view of positive ECG findings and history of angina, TMT was done which was positive for exercise induced ischemia. Coronary angiogram (CAG) was done which showed stenosis in the major arteries. Coronary artery bypass grafting (CABG) was done on elective basis on a later date. Bilateral carotid and vertebral artery doppler showed atherosclerotic changes in the form of increased intima media thickness in bilateral carotid arteries. Evidence could not be found regarding significant stenosis of hemodynamic nature or any occlusion.



Fig. 2: Prominent tendon xanthomas on bilateral ankles and feet

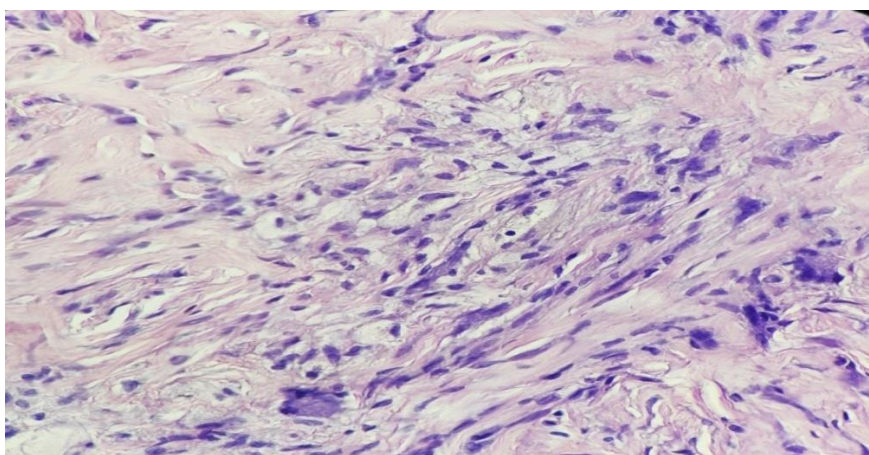


Fig. 3: Lipid laden macrophages in the centre with admixture of fibroblasts. Hematoxylin and Eosin, x400

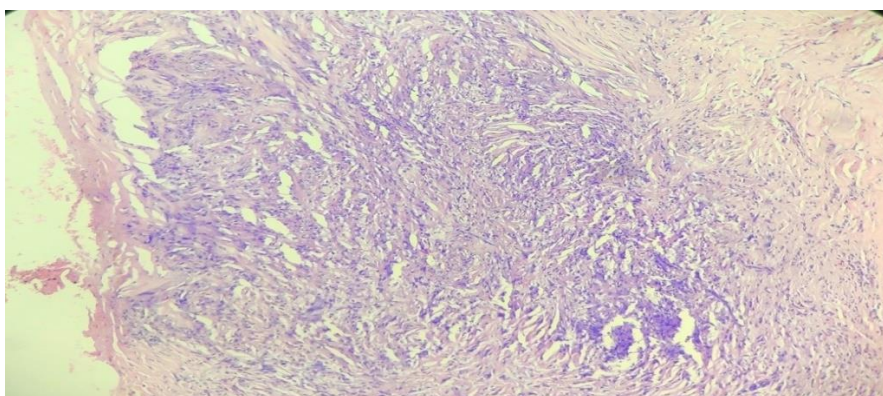


Fig.4: Dermal infiltrate composed of nodules of foamy histiocytes, Touton giant cells and fibroblasts. Hematoxylin and Eosin, x100

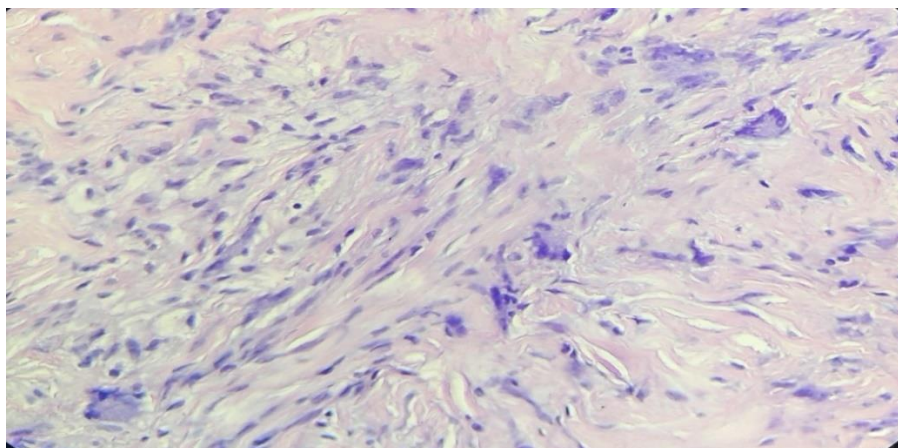


Fig.5: Admixture of foamy histocytes and Touton giant cells. Hematoxylin and Eosin, x400

Treatment at the Hospital

In view of onset renal failure (1.76 mg/dl) and very high CPK levels (2413 U/L) rhabdomyolysis was diagnosed which was presumed to be statin induced since there were no other risk factors for rhabdomyolysis. Patient was started on symptomatic management with NaHCO_3 and IV fluids.

CPK levels came down to 129 U/L over a period of one week. Patient was suggested to take PCSK 9 inhibitor which she could not afford due to financial conditions. Statins were stopped temporarily and ubiquinone (Coenzyme Q) was administered in view of statin induced myopathy and rhabdomyolysis. Medications were optimized for the control of T2DM and HTN (Table 1).

Table 1: Laboratory reports of the patient

Parameters	Initial Lab reports	Lab reports during discharge	Normal Ranges
Fasting blood sugar (mg/dl) (During recent admission)	118	107	70-100 mg/dl (Hexokinase method)
CPK (U/L) (During recent admission)	2413	129	Adult female- 20-180 U/L (UV NAC activated method)
Creatinine (mg/dl) (During recent admission)	1.76	1.38	0.5-0.9 mg/dl (Jaffe rate blanked method)
Total cholesterol (mg/dl)	575 (5 years back)	253 (During recent admission)	140-200 mg/dl (CHOD-POD method)
Triglyceride (mg/dl)	157 (5 years back)	181 (During recent admission)	60-150 mg/dl (GPO Trinder method)
HDL cholesterol (mg/dl)	40 (5 years back)	53 (During recent admission)	40-60 mg/dl (Direct homogenous)
LDL cholesterol (mg/dl)	504 (5 years back)	163 (During recent admission)	50-130 mg/dl (By Friedwald's formula)
TC/HDL	14 (5 years back)	4.7 (During recent admission)	<5

FBS- fasting blood sugar, TC- total cholesterol, TG- triglycerides, HDL – High Density lipoprotein cholesterol, LDL- Low Density lipoprotein cholesterol, CPK- creatine phosphokinase

Once CPK levels and creatinine levels decreased, she was started on low dose of rosuvastatin(5mg), along with ezetimibe. Treatment was continued with regular monitoring of RFT, FLP and CPK levels which eventually returned to normal levels and the patient was discharged after her condition symptomatically improved.

DISCUSSION

FH is a condition which is transmitted genetically and is caused by more than 900 mutations in the LDL receptor gene which is located on the 19th chromosome. This leads to decrease in number of LDL receptors which are of functional nature on the cell surface. This disease is inherited as an autosomal dominant trait. In this condition the body fails to remove the LDL cholesterol and as a result of which it gets deposited in the arteries leading to an increase in the serum LDL cholesterol levels. Patho-physiologically there is impairment in LDL cholesterol levels clearance and internalization. This results in uninhibition of synthesis of cholesterol which is intracellular in nature (2). In this condition narrowing of arteries from atherosclerosis take place from an early age. Even though FH is an inherited condition, alcoholism, obesity, diabetes and hypothyroidism can worsen the condition. These patients develop several types of xanthomata including tuberous, tendon xanthomas, sub periosteal with increased number of xanthomatous plaques. The term xanthoma is referred as nodules or plaques consisting of deposition of lipids in the foam cells and collagen which are not normal in nature. Xanthomas develop due to the leakage of lipid from

the vesicle to the adjacent tissue where the lipids are phagocytosed by the macrophages as the cholesterol remains un-degraded and keeps on accumulating in the cells developing foamy macrophages. Induction of an inflammatory reaction and crystallization into the cleft takes place by the extracellular cholesterol with giant cells and finally results into fibrosis (3). In the arterial walls excess plasma LDL cholesterol get accumulated. Macrophages take it up and initiate the development of atherosclerotic lesion after they become engorged with modified LDL cholesterol. It later develops into atherosclerotic plaques which are composed of cellular debris, cholesterol and fibrous tissue. The artery can be obstructed completely by a blood clot if there is a rupture in the plaque and thus resulting in myocardial infarction. Patients who have two-to-three-fold rise in LDL cholesterol levels have a 50% chance of developing MI before the age of 60. It was found that due to constant therapy of statins, FH patients tend to develop diabetes because of the elevated cholesterol levels in the cells which are responsible for proper functioning of the beta cell of the pancreas. Mabuchi et al found that the combination of pharmacotherapy and LDL-apheresis facilitated the reduction of LDL-C levels by 60%. Experiments are still going on for gene therapy. An anti-PCSK9 (proprotein convertase subtilisin/kexin type 9) antibody diminishes the levels of LDL cholesterol on top of a statin and is under trials. Few studies have found a nascent cholesterol absorption inhibitor known as ezetimibe along with the statins which impairs the intestinal reabsorption of hepatically excreted biliary cholesterol and dietary cholesterol (4). Ezetimibe when used alone or in

combination with fibrates and niacin becomes a noteworthy drug to achieve the normal levels of fasting lipid profile as there remains a risk of statin induced myopathy when only statins are used alone (5). In this case the patient was given ezetimibe, coenzyme Q along with 10 mg rosuvastatin which became an attractive choice for successfully treating the condition.

CONCLUSION

FH is a condition that causes abnormal elevation in LDL cholesterol levels and leads to accelerated atherosclerosis and ischemic heart disease at relatively young age which requires treatment by statins. However, high dose of statins can cause myopathy and rarely rhabdomyolysis and acute kidney injury. Though not common, every patient on high dose statins should be monitored for statin induced myopathy and rhabdomyolysis. Educating patient regarding the symptoms of statin induced myopathy and periodic screening of RFT and CPK can help to diagnose this condition at an early stage. Treatment is withdrawal of statins and hydration and alkalization of urine. Generally, patients respond well to conservative treatment, but severe cases require hemodialysis.

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CONFLICT OF INTEREST

All the authors declare that the study has no conflict of interest.

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