PICTORIAL CME

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Homozygous Familial Hypercholesterolaemia with Severe Aortic Stenosis

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A 24-year-old male patient presented with complaints of multiple nodular lesions on the body since the age of 5 years and exertional dyspnoea for 1 year. He was born to non-consanguineous parents and his developmental milestones were normal. His parents and one brother were healthy with no skin lesions or cardiac conditions. On examination, his BMI was 24 kg/m^2 and he had multiple tendinous/tuberous xanthomas on elbow, knuckles and achilles tendon, with polydactyly (Fig. 1-3). He also had cutaneous xanthomas over the body, xanthelasma palpebrarum and arcus juvenilis (Fig. 4-5). Systemic examination revealed grade 4 ejection systolic murmur in aortic area which was radiating to the carotids.

Blood investigations showed normal haemogram, blood glucose levels, thyroid, renal and liver function tests. However, lipid profile was grossly deranged with total cholesterol level of 730 mg/dL and LDL cholesterol level of 565 mg/dL. Echocardiography revealed severe supravalvular aortic stenosis. A diagnosis of homozygous familial hypercholesterolaemia was made and he was started on tablet rosuvastatin 40 mg, ezetimibe 10 mg, bempedoic acid 180 mg and aspirin 75 mg daily. Repeat lipid profile done after two months showed marginal change with total cholesterol level of 573 mg/dL and LDL-C of 483 mg/dL. He was advised lipoprotein apheresis, but could not be done due to financial constraints. His parents and sibling were also screened and all of them had LDL-C level of greater than 200 mg/dL without any skin manifestation, suggesting heterozygous familial hypercholesterolaemia.

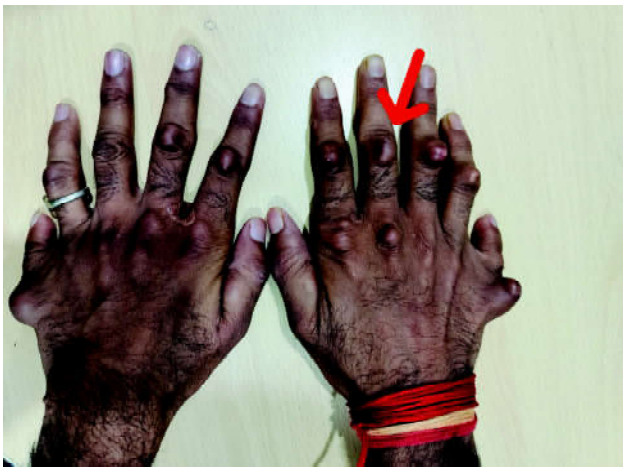

Fig. 1: *Tendinous xanthomas on knuckles with polydactyly.*

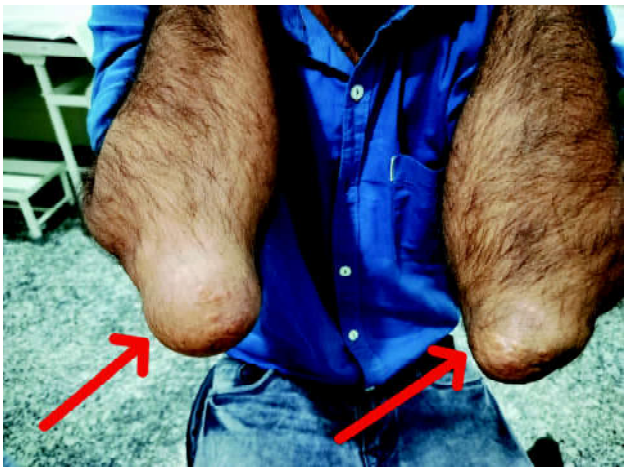

Fig. 2: *Tuberous xanthomas on elbow joints.*

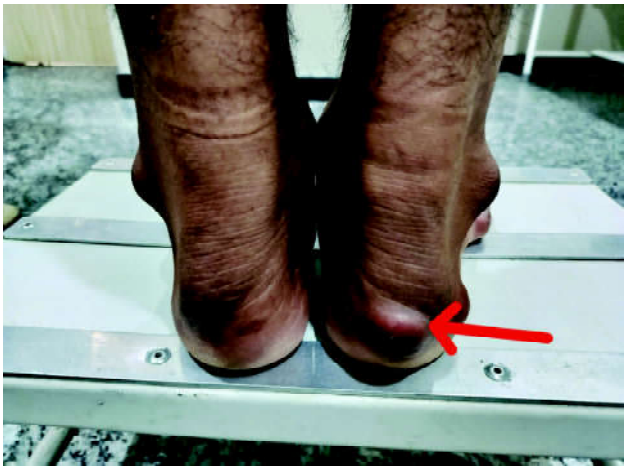

Fig. 3: *Tuberous xanthomas on achilles tendons.*

Familial hypercholesterolaemia (FH) is an inherited disorder characterised by severe elevation of serum LDL levels due

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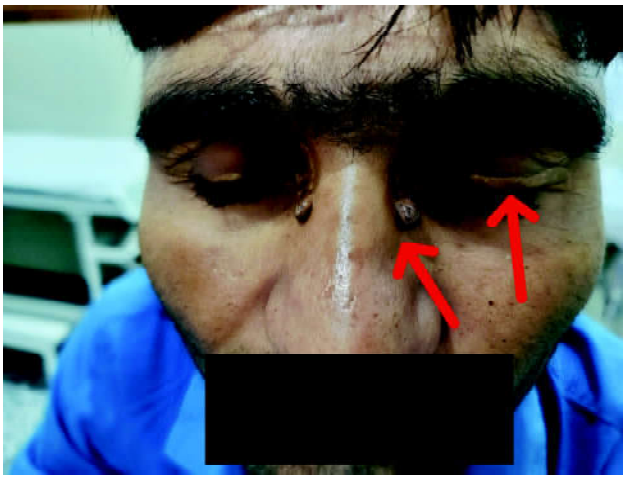

Fig. 4: *Xanthelasma palpebrarum on eyelids.*

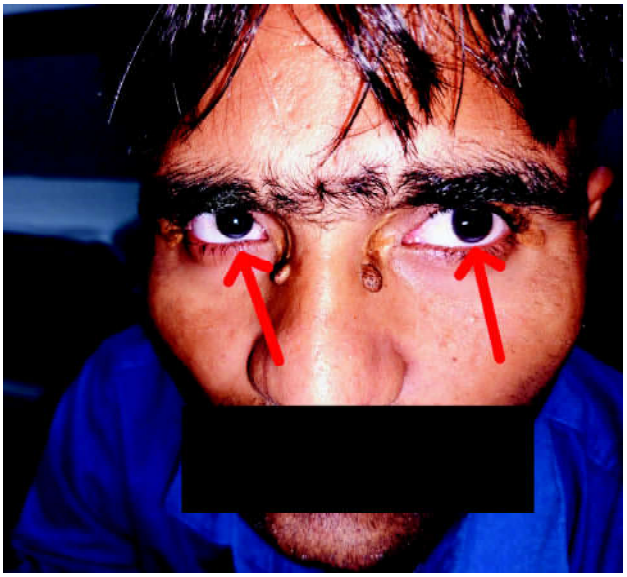

Fig. 5: *Arcus juvenilis.*

to mutations of the genes involved in the LDL receptor-mediated pathway for uptake of LDL[1]. There are three main genetic mutations in FH; defect in the LDL receptor (most common), apolipoprotein B (ApoB), or proprotein convertase subtilisin/Kexin type 9 (PCSK9). The severity of the disease and the age of onset of cardiovascular disease is determined by a homozygous or a heterozygous defect. Heterozygous FH (HeFH) patients have plasma LDL cholesterol (LDL-C) levels double the normal or higher and carry the mutated gene in a single allele. Homozygous FH (HoFH) exhibits LDL-C levels greater than five times of normal and have mutations in both alleles.

HoFH is a rare condition with prevalence of 1 in 1 million and is characterised by triad of very high LDL-C, cutaneous and/or tendon xanthomas and premature atherosclerotic cardiovascular disease (ASCVD). The LDL-C in HoFH is generally beyond 500 mg/dL, causing premature coronary artery disease and valvular/supravalvular aortic stenosis. Cutaneous xanthomas develop during infancy and are found on the extensor surfaces of elbow, knee, wrist and gluteal region. Tendon xanthomas manifest due to accumulation of cholesterol within macrophages in connective tissue of tendons[2]. Cholesterol deposition around corneal rim causes corneal arcus juvenilis and deposition on eyelids is called xanthelasma palpebrum.

Diagnosis of HoFH can be made by genetic or clinical criteria. An untreated LDL-C plasma concentration of ≥500 mg/dL, or a treated LDL-C concentration of ≥300 mg/dL and the presence of cutaneous or tendon xanthomas before the age of 10 years, or the presence of untreated elevated LDL-C levels consistent with HeFH in both parents is the clinical criteria for diagnosis of HoFH. The medical management of HoFH include lifestyle modifications with high dose statins, ezetimibe, bempedoic acid and PCSK9 inhibitors[3]. These medicines act by enhancing LDL receptor activity and are often ineffective due to near complete loss of LDL receptor activity in HoFH. Lipoprotein apheresis is the core therapy for HoFH as it directly removes LDL from plasma through selective absorption or filtration of LDL using an extra-corporal circulation system[4]. The prognosis of untreated HoFH is extremely poor as patients seldom survive beyond 30 years. The LDL-C accumulation increases risk of myocardial infarction and aortic stenosis, which may become the cause of death in these patients[5].

References

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