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Case Report

A case of familial hypercholesterolaemia Type IIa presenting with tuberous xanthomas

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Introduction

The term Xanthoma originates from a Greek word “Xanthos” meaning yellow and is generically used to describe subcutaneous lipid deposits.¹ They do not represent a disease per se, but are cutaneous markers for lipoprotein disorders or may even arise without an underlying metabolic defect.² We report a case of multiple tuberous xanthomas with a lipid profile consistent with familial hypercholesterolaemia Type IIa.

Case Report

A 12-year-old male patient born of a nonconsanguineous marriage, presented with multiple asymptomatic skin coloured and yellowish raised lesions over the knees, elbows and

dorsa of fingers, since the age of 06 years. Lesions appeared spontaneously over the knees initially and subsequently spread to involve the elbows and fingers. No history of similar lesions in the family was elicited and there was no history of cardiovascular disease in the family. Examination revealed well circumscribed, firm and non tender nodules over the extensors of both elbows and knees and dorsa of fingers [Fig. 1A,B & C]. Systemic examination including cardiovascular system and screening for liver, renal and thyroid disorder was within normal limits.

Routine investigations including haemogram, blood sugar, liver and renal function tests were within normal limits. Chest radiography and electrocardiogram for cardiovascular status was normal. Histopathological examination of an incisional biopsy from a nodule over left elbow showed discrete collections of lipid laden macrophages with extracellular lipid and areas of dermal fibrosis [Fig. 2A & B]. Lipid profile showed

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Fig. 1 – A. Nodules over the extensors of both knees, B. Nodules over the extensors of both elbows, C. Nodules over dorsa of fingers.

Fig. 2 – A. H & E stain showing well circumscribed nodules in dermis, B. High power view showing lipid laden macrophages.

markedly elevated LDL cholesterol and total cholesterol, with normal triglycerides, VLDL and HDL levels, which confirmed Type IIa hypercholesterolaemia [Table 1]. Ophthalmological referral for corneal arcus and funduscopy were not contributory. He underwent a medical referral where he was screened for cardiovascular disease and started on dietary therapy along with lipid lowering agents in the form of oral atorvastatin at the dose of 10 mg daily with monthly follow up and three monthly lipid profile monitoring.

Discussion

Xanthomas are benign tumours characterized by skin coloured or yellowish plaques and nodules. Clinically, they can be classified as eruptive, tuberoeruptive or tuberous, tendinous and planar xanthomas.² Each of these characteristic clinical phenotypes are associated with specific metabolic defects which may be hereditary lipoprotein disorders or acquired defects of lipoprotein metabolism including those

Table 1 – Lipid Profile of the patient and both parents.

Lipid fraction	Patient (mg/dl)	Mother (mg/dl)	Father (mg/dl)	Normal range (mg/dl)
Total cholesterol	659	278	274	≤240
LDL	595	110	110	≤160
Triglycerides	126	137	124	≤200
VLDL	25	27	25	≤40
HDL	39	40	39	>40

VLDL: Very low density lipoproteins, HDL: High density lipoproteins, LDL: Low density lipoproteins.

secondary to hypothyroidism, biliary cirrhosis, diabetes mellitus, nephrotic syndrome, monoclonal gammopathy, and certain drugs.³ Particular forms like xanthoma disseminatum and verruciform xanthomas are known to occur in normolipemic individuals.⁴

Tuberous xanthomas are commonly found over the extensor aspect of elbows and knees. Although, rarely causing functional impairment, they can evolve into large exophytic lesions which maybe itchy and predisposed to trauma. They can also occur over pressure areas such as heels and plantar aspects of the feet. Corneal arcus which represent deposition of cholesterol esters in peripheral cornea may co exist in younger patients with familial hypercholesterolaemia.¹ In our case, characteristic firm nodules were found over extensors of elbows, knees and dorsa of fingers with no corneal arcus. Differential diagnosis includes cysts, neurofibromas and lipomas.² Histopathologically, they are characterized by discrete collections of lipid laden macrophages in the dermis and can show prominent fibrosis and cholesterol clefts.⁴ A similar picture was seen in histopathological examination of a representative lesion from our patient.

Familial hypercholesterolaemia (Fredrickson's Type II hyperlipidaemia) is an autosomal dominant condition characterized by high total and LDL cholesterol, slightly low HDL cholesterol and normal triglyceride concentrations and clinically by frequent tendon & tuberous xanthomata with premature onset of cardiovascular disease.¹ Two variants have been described: heterozygous with a prevalence of one per 500 and homozygous occurring with a prevalence of one per one million in the general population. The primary defect lies with genetic deficiency of the LDL receptors, which remove LDL cholesterol from the circulation. While in heterozygous form, the affected individuals have a two- to three-fold elevation in LDL cholesterol from the time of birth and xanthomatous lesions develop during the third to sixth decades; In the homozygous form, LDL cholesterol maybe raised by six to eight fold and xanthomas can appear as early as 20th week of intrauterine life.³ Subcutaneous planar and tuberous xanthomata may occasionally be seen in homozygotes, but not in heterozygotes. Other less common underlying gene defects include familial defective Apo B 100 lipoprotein and PCSK9 gene mutation. A small group of Autosomal recessive hypercholesterolaemia (ARH) has also been described in literature. Tuberous xanthomas can also occur in two other disorders of sterol metabolism, cerebrotendinous xanthomatosis and sitosterolaemia, both of which are extremely rare.¹ In our patient, the lipid profile was suggestive of Type IIa hyperlipidaemia, with markedly elevated total and LDL cholesterol levels and normal triglyceride levels. Homozygous familial hypercholesterolaemia was diagnosed on the basis of

the typical clinical features of tuberous xanthomas over extensors of elbows, knees and dorsa of fingers with early onset at six years of age. The diagnosis of familial hypercholesterolaemia is essentially based on clinical assessment and biochemical parameters. However, Apo B 100 Lipoprotein levels may help to further delineate the underlying heterogeneity of these phenotypically similar disorders. Dietary modification and drug therapy with statins form the initial treatment strategy. Pharmacotherapy, along with dietary modification generally suffices for patients with the heterozygous form, but LDL-apheresis and liver transplantation maybe required for those with the homozygous form.⁵ Our patient was exhibited dietary therapy along with lipid lowering agents in the form of oral atorvastatin and is on regular follow up. However, it is unlikely to have any significant effect on the cutaneous manifestations for which definitive measures in the form of surgical resection and debulking can be attempted for existing xanthomas. Placement of lesions over joints and unwillingness of the patient for surgical intervention precluded any such attempts in our case. Recent advances include genetic diagnosis in the form of polymerase chain reaction and fibroblast cell culture techniques for LDL receptor and ApoB 100 gene defects as all cases may not have classic features of xanthomas.⁶ As regards management, liver directed ex vivo gene therapy, could be the treatment of choice in the future.⁷

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