Case report:

Familial xanthomatosis with type IIA familial hypercholesterolinemia

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Abstract:

Xanthomas are commonly caused by a disturbance of lipoprotein metabolism. Tuberous xanthomas present as yellow or reddish nodules located mainly on the extensor surface of the extremities and buttocks. They indicate a systemic alteration of cholesterol and/or triglyceride metabolism. Here we present a case of 6 year old boy with aymptomatic yellowish firm skin lesions on the elbows, knees and buttocks. Similar history was present in the elder two siblings. Investigations revealed elevated total cholesterol with elevated low density lipoproteins in all the family members. There were associated cardiac changes in the siblings. These features are suggestive of familial xanthomatosis with type IIa familial hypercholesterolinemia. This case highlights the importance of early recognition of the skin lesions by the dermatologist which will provide an opportunity for long term therapeutic efforts in a group at high risk for premature ischemic heart disease.

Key words: Xanthoma, cholesterol, ischemic heart disease

Introduction:

Lipoproteins are soluble compounds formed by the combination of insoluble circulating lipids (cholesterol, cholesterol esters, triglycerides and phospholipids) and proteins.[1] Any disorder of lipoprotein metabolism (dyslipidemia) confers on an individual, an increased risk of cardiovascular disease, pancreatitis or xanthoma.[1] Xanthomas are the characteristic cutaneous presentation in hyperlipoproteinemia. Type IIa hyperlipop-roteinemia or familial hypercholesterolemia usually presents with tendinous, tuberous or planar xanthomas (xanthelesma or intertriginous type).[2] Here we describe a case of familial xanthomatosis of the tuberous and tendinous type affecting three siblings of the family associated with familial hypercholesterolenemia.

Case report:

A 6-year-old boy presented with history of nodular skin lesions over the elbows, knees and buttocks for the past 1 year. The patient was apparently normal 1 year back when the parents noticed few, small yellowish nodules over the elbows. Gradually, the nodules increased in size and number, with new lesions appearing over the knees and buttocks. The lesions were asymptomatic. The child was born of a second degree consanguineous marriage. There was no family history of early myocardial infarction or stroke. A detailed history was taken. His other two siblingS had similar lesions.The elder brother, 9-year-old boy had asymptomatic skin lesions over the elbows, knees and buttocks for the past 2 years. The lesions were bigger in size. Additional lesions were present over the dorsum of hands, front and back of the ankle on both sides and over the upper eyelids. His elder sister aged 7 years also had similar lesions over the elbows, knees and buttocks, ankle and over upper eyelids for the past 2 years.

On clinical examination, the patient's general physical examination was normal. Cutaneous examination revealed multiple, small, yellowish

nodules measuring around 1-2 cm and plaques measuring 5-8cm in diameter, distributed over the elbows, knees and buttocks. The lesions were non-tender and firm in consistency. The surface was smooth. The lesions were not fixed to the underlying structures. The skin over the lesions was normal. The elder brother had similar yellowish non-tender, firm nodules measuring 2-3 cm and plaques measuring 8-10 cms over the elbows, knees and buttocks. Multiple small yellowish nodules measuring 1-2 cm were seen over the dorsum of the hands. Few yellowish nodules and plaques were seen over the front of the ankle and over the achilles tendon. The elder sister also showed similar lesions over the elbows, knees, buttocks, front of ankle and achilles tendon. She also had few yellowish coloured papules, coalescing to form plaques over the upper eyelids.

On systemic examination, a thrill was felt over the aortic area in our patient and on auscultation, pansystolic murmur heard in the tricuspid area. Ophthalmic examination revealed arcus juvenalis in all the three siblings. The other systems were normal.Routine investigations of the patient which included complete blood count, blood sugar, liver function test, renal function test, chest X-ray were within normal limits. Thyroid function tests were normal. Lipid profile was done for all members of the family and it revealed elevated total cholesterol and low density lipoprotein (LDL) cholesterol for all the family members. The detailed work-up is as shown in the table.

Echocardiography for our patient showed grade 2 aortic regurgitation, mild aortic stenosis, trivial mitral regurgitation and left ventricular hypertrophy. Carotid doppler study showed long segment stenosis of the left common carotid artery (44% stenosis) and left internal carotid artery (43% stenosis) by circumferential plaques causing significant hemodynamic disturbances. Abdominal ultrasonography and renal artery doppler study were normal. A biopsy from the nodule over the buttock was done, which showed dermal changes with sheets of histiocytes having small eccentric nuclei and abundant vacuolated cytoplasm with well defined cell borders, with occasional giant cells. These features were suggestive of xanthomas.Based on the history, clinical examination and investigations, a diagnosis of familial hypercholesterolenemia type IIa with tuberous and tendinous xanthoma was made. All members of the family were started on atorvastatin 20 mg/day.

Table 1: A detailed work up of laboratory parameters of family members

Relation to case 1	Age (yrs)	Sex	Blood sugar (mg/dl)	LDL	TGL	Total cholesterol	HDL	Thyroid function
Self	6	M	Normal	571.7	84.9	640	44.3	Normal
Brother	9	M	Normal	505	102.3	599.2	42.1	Normal
Sister	7	F	Normal	536.8	97.9	646	39.9	Normal
Mother	38	F	Normal	220	90	325	62.8	Normal
Father	45	M	Normal	168.3	128	300	73	Normal

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WHO/Fredrickson's classification of hyperlipoproteinemia/hyperlipidemia

Type I	Hyperchylomicronemia
Type IIa	Elevated LDL (familial hypercholesterolemia)
Type IIb	Elevated LDL and VLDL (familial combined hypercholesterolemia)
Type III	Broad β-VLDL (Familial dysbetalipoproteinemia)
Type IV	Elevated VLDL (Familial hypertriglyceridemia)
Type V	Elevated chylomicrons and VLDL (mixed hyperlipidemia)

WHO: World Health Organization, LDL: Low density lipoprotein, VLDL: Very low density lipoprotein

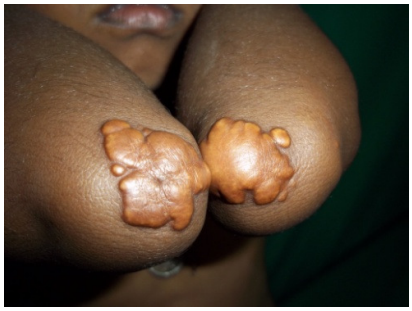

Figure 1: Yellowish nodules and plaques over elbows

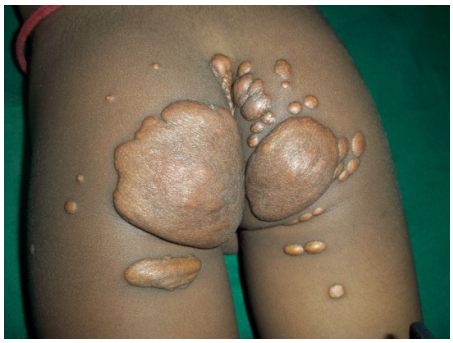

Figure 2: Yellowish papules, nodules and large plaques over buttocks

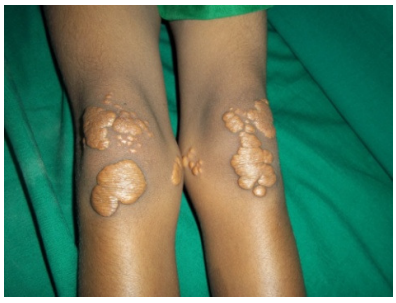

Figure 3: Yellowish papules and plaques over knees

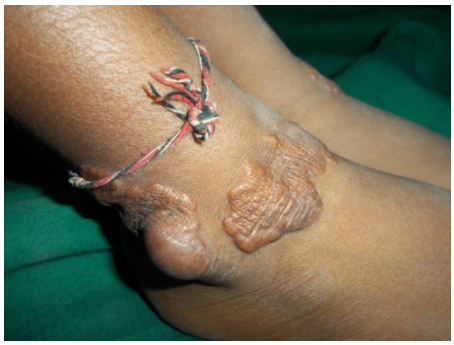

Figure 4: Yellowish plaques and nodules over the front and back of ankle, and over the lateral malleolus

Discussion:

Hyperlipidemias are common metabolic disorders of plasma lipoproteins that are often associated with an increased risk of atherosclerosis. Occasionally, they lead to other abnormalities, especially xanthomatous deposits and pancreatitis.[3] Xanthomas are plaques or nodules consisting of accumulation of lipid-rich macrophages known as foam cells.[4] The term 'Xanthoma' is derived from the greek word meaning 'yellow tumour'.[5] They are non-neoplastic, tumor-like lesions, which occur in essential hyperlipidemia, diseases with secondary hyperlipidemia, like primary biliary cirrhosis and diabetes mellitus and occasionally in normolipidemic states.[6] They do not represent a disease but rather are symptoms of different lipoprotein disorders or arise without an underlying metabolic defect. Clinical presentations of xanthomas include eruptive, tuberous, tubero eruptive, tendinous, planar, verruciform and papular forms.[4] Tuberous xanthoma, present as yellowish or reddish nodules, mainly located on the extensor surface of the extremities and buttocks. When they occur in children and adolescents, a more severe form of hyperlipidemia should be suspected. Early diagnosis and treatment may help in preventing the development of early coronary artery disease and pancreatitis.[3]

There are many case reports of familial hypercholesterolemia presenting with xanthomata.[7,8,9] The hyperlipoproteinemias which manifest in early childhood are type -1 and type II a.[10]

Familial hypercholesterolemia is a common autosomal dominant disorder affecting appr-oximately one in 500 of general population.[7] It is characterized by the finding of hypercholesterolemia and hypertriglyceridemia within the same kindred and with-kindred members having either one of these abnormalities or both.[3] The primary defect is due to a reduction in L D L catabolism because of an abnormality in the L D L receptors. Heterozygotes express half the numbers of LDL receptors and homozygotes have between 0 and 25%.

Homozygotes for familial hypercholesterolemia have markedly elevated cholesterol and LDL at birth. In early years a unique yellowish xanthoma may develop in the interdigital webs of the hands and in the cleft between the buttocks and tuberous xanthomas on the elbows, knees and buttocks.

These xanthomas do not appear in the heterozygous adult with familial hypercholesterolemia.[7] Statins are effective in the treatment of Type IIa hyperlipoproteinemia. They inhibit HMG CoA reductase, a rate-limiting enzyme in cholesterol synthesis. The other treatment modalities include lifestyle modifications like regular exercise and avoidance of smoking.[2] The clinical importance in

the present homozygous case was to highlight the need for immediate measures to halt the further progression of coronary artery disease by medications and life style modifications. This will go a long way in improving the quality of life of the patient and in prevention of further atherosclerotic complications.

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