Normolipemic xanthomatosis

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Summary
A 20-year-old woman presented with tendon and tuberous xanthomas. Plasma lipid levels were normal. Xanthomatosis with normal lipid levels is rare.

Keywords: normolipemic xanthomatosis

Tendon and tuberous xanthomas are usually associated with familial hypercholesterolemia (type II hyperlipidemia) and broad beta disease (type III hyperlipidemia). Normolipemic xanthomatosis may be seen in several rare conditions.1-3 We report here a patient who did not fit into any of the known causes of normolipemic xanthomatosis.

Case report
A 20-year-old woman presented with a two-year history of multiple, painless swellings around her fingers, wrists, elbows and ankles. These swellings were preceded by itchy, bul- lous skin lesions which spontaneously subsided after a few weeks. Shortly thereafter the patient noticed the swellings which progressively increased in size. Physical examination was unremarkable except for the presence of mul- tiple tendon and tuberous xanthomas (figure). Xanthelasmas were absent. None of the family members had any such problem. Complete blood counts, blood sugar, urea, electrolytes, urinalysis, bone marrow aspirate, and serum and urine electrophoresis were within normal limits. Liver function tests revealed serum bilirubin of 10.26 mmol/l, alkaline phosphatase 90 IU/l, and aspartate and alanine aminotrans- ferases 18 IU/l and 20 IU/l, respectively. Lipid profile after overnight fasting revealed serum cholesterol 5.12 mmol/l, LDL cholesterol 2.71 mmol/l, HDL cholesterol 1.11 mmol/l, VLDL cholesterol 1.29 mmol/l, LDL/HDL ratio 2.4, serum triglycerides 1.73 mmol/l (all within the normal range). A repeat lipidogram was also within normal limits. The lipid profile was done as outlined in Vaisht et al.4 in the cardiacl biochemistry unit of the All India Institute of Medical Sciences, New Delhi, which employs both internal and external quality control programmes. Plasma choles- terol and stiosterol levels determined by gas liquid chromatography were within normal range. Excision biopsy from the lesion showed sheets of foamy macrophages interspersed with fibrovascular connective tissue and Touton giant cells, thus confirming the diagnosis of xanthomatosis in a normolipemic individual.

Causes of normolipemic xanthomas

<table>
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<th>Sitosterolemia</th>
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<td>rare genetic defect</td>
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<td>increased intestinal absorption of dietary plant sterols (phytosterols)</td>
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<td>tendon and tuberous xanthomas, xanthelasmas</td>
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<td>premature atherosclerosis</td>
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Cerebrotendinous xanthomatosis
- rare autosomal recessive disorder
- increased hepatic synthesis of cholesterol leads to its accumulation in brain, tendons and other tissues
- progressive cerebellar ataxia, dementia, corticospinal tract dysfunction, pulmonary insufficiency, tendon and tuberous xanthomas, cataracts, premature atherosclerosis, hypoadrenalism, and hypothyroidism

Xanthoma disseminatum
- rare benign histiocytic disorder
- extensive cutaneous and mucous membrane xanthomas
- immunohistochemical studies are needed to differentiate this disease from histiocytosis X

Juvenile xanthogranuloma
- papular xanthomas in infants and children, usually on face and scalp, and which often regress spontaneously

Eruptive histiocytosis
- benign condition affecting adults
- numerous, firm, discrete papular xanthomas appearing in crops. Spontaneous regression is the rule

Histiocytosis X
- benign or malignant proliferation of tissue macrophages (histiocytes)
- includes unifocal and multifocal eosinophilic granuloma, Hand–Schüller–Christian disease, and Littre–Siwe disease

Box 1

Discussion
Xanthomas are tumours characterised by collections of foamy histiocytes. Based on their clinical appearance they are classified into five principal types: eruptive, tuberous, tendinous, planar and xanthelasmas. Hyperlipoproteinemias, especially hypercholesterolemia, may result in the deposition of cholesterol in various tissues giving rise to xanthoma formation. Delineation of apo E subtypes is a useful diagnostic tool for type III hyperlipidemia, but is not widely available. Apo E 2/2 phenotype is seen in more than 90% of these patients.
Rarely, normolipemic patients have been described who present with planar, eruptive, or even tuberous xanthomas. It has been suggested that three pathogenetic processes could be responsible for normolipemic xanthomatosis. The first group includes disorders with accumulation of unusual lipids other than cholesterol such as cholestanol in cerebrotendinous xanthomatosis or plant sterols in betasitosterolemia. In the second group planar xanthomas may be seen over the face and upper trunk in patients with lymphoproliferative diseases such as multiple myeloma or lymphomas. Xanthoma formation may be due to cutaneous lymphoreticular hyperplasia with secondary xanthomatosis or to para-proteins interacting with lipoprotein receptors or blocking enzymes. The third group comprises patients in whom local abnormalities in the skin are thought to play a role. This includes xanthomas following distinct diseases such as erythromelalgia and epidermolysis bullosa dystrophica, generalised eruptive xanthomas, juvenile xanthogranuloma and xanthoma disseminatum. Our patient did not have any neurologic features suggestive of cerebrotendinous xanthomatosis. Cholestanol and plant sterol levels were within the normal range. There was no underlying lymphoproliferative disease and clinicopathologically there was no suggestion of xanthoma disseminatum, juvenile xanthogranuloma or generalised eruptive xanthomas. In view of the history of bullous lesions preceding the appearance of xanthomas it is possible that local dermal inflammatory lesions could have played a role in xanthoma formation. The case highlights the importance of looking beyond plasma lipids in a patient with tendon or tuberous xanthomatosis.


Learning/summary points

- Xanthomas are characterised by a collection of foamy histiocytes.
- Usually seen in hyperlipidemias.
- May occasionally be seen in normolipemic individuals.

Box 2

- Xanthomas are characterised by a collection of foamy histiocytes.
- Usually seen in hyperlipidemias.
- May occasionally be seen in normolipemic individuals.