Normolipemic xanthomatosis

R Handa, K Gupta, JP Wali

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.¹⁻⁵ 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 multiple tendon and tuberous xanthomas (figure). Xanthelasma 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 $\mu\text{mol/l}$, alkaline phosphatase 90 IU/l, and aspartate and alanine aminotransferases 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 Vasisht *et al*^{6,7} in the cardiac biochemistry unit of the All India Institute of Medical Sciences, New Delhi, which employs both internal and external quality control programmes. Plasma cholestanol and sitosterol 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

Sitosterolemia

- rare genetic defect
- increased intestinal absorption of dietary plant sterols (phytosterols)
- tendon and tuberous xanthomas, xanthelasma
- premature atherosclerosis

Cerebrotendinous xanthomatosis

- rare autosomal recessive disorder
- increased hepatic synthesis of cholestanol 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-Schuller-Christian disease, and Litterer-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 xanthelasma. 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.

Department of
Medicine, All India
Institute of Medical
Sciences, New
Delhi-110029, India
R Handa
K Gupta
JP Wali

Accepted 29 March 1995

Figure Tendon and tuberous xanthomas in a normolipemic individual

Rarely, normolipemic patients have been described who present with planar, eruptive, or even tuberous xanthomas.^{5,8-10} It has been suggested that three pathogenetic processes could be responsible for normolipemic xanthomatosis.¹⁰ 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

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

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 xanthomatization or to paraproteins interacting with lipoprotein receptors or blocking enzymes.⁴ The third group comprises patients in whom local abnormalities in the skin are thought to play a role.¹⁰ This includes xanthomas following distinct diseases such as erythroderma and epidermolysis bullosa dystrophica, generalised eruptive xanthomas, juvenile xanthogranuloma and xanthoma disseminatum.⁵ 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.

- 1 Bhattacharya AK, Connor WE. β -Sitosterolemia and xanthomatosis. *J Clin Invest* 1974; 53: 1033-43.
- 2 Salen G. Cholestanol deposition in cerebrotendinous xanthomatosis. *Ann Intern Med* 1971; 75: 843-51.
- 3 Wilson DE, Flowers CM, Hershgold EJ, Eaton RP. Multiple myeloma, cryoglobulinemia and xanthomatosis. *Am J Med* 1975; 59: 721-9.
- 4 Feingold KR, Castro GR, Ishikawa Y, Fielding CJ. Cutaneous xanthoma in association with paraproteinemia in the absence of hyperlipidemia. *J Clin Invest* 1989; 83: 797-802.
- 5 Weiss N, Keller C. Xanthoma dissemination: a rare normolipemic xanthomatosis. *Clin Invest* 1993; 71: 233-8.
- 6 Vasishth S, Narula J, Awtade A, Tandon R, Srivastava LM. Lipids and lipoproteins in normal controls and clinically documented coronary heart disease patients. *Ann Indian Natl Acad Med Sci* 1990; 26: 57-66.

- 7 Vasishth S, Pant MC, Srivastava LM. Effect of alcohol on serum lipids and lipoproteins with special reference to high density lipoprotein subfractions and apoproteins in human male drinkers. *Indian J Med Res* 1992; 96: 333-7.
- 8 Fleischmajer R, Tint GS, Benett HD. Normolipemic tendon and tuberous xanthomas. *J Am Acad Dermatol* 1981; 5: 290-6.
- 9 Mulholland RS, Freiberg A. Normolipidemic xanthomata of the hand extensor tendons. *J Rheumatol* 1989; 16: 242-4.
- 10 Parker F. Normocholesterolemic xanthomatosis. *Arch Dermatol* 1986; 122: 1253-7.