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Other full case

Cerebrotendinous xanthomatosis associated with immune thrombocytopenia

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Summary

Cerebrotendinous xanthomatosis (CTX) is a lipid storage disease inherited in a autosomal recessive way. CTX is characterised by childhood-onset cataract, adolescent to young adult-onset tendon xanthomas and adult-onset progressive neurological dysfunction (dementia, psychiatric disturbances, pyramidal and/or cerebellar signs and seizures). Xanthomas appear in the second or third decade; they occur on the Achilles tendon, the extensor tendons of the elbow and hand, the patellar tendon and the neck tendons. The biochemical abnormalities that distinguish CTX from other conditions with xanthomas include high plasma and tissue cholestanol concentration, normal-to-low plasma cholesterol concentration and decreased chenodeoxycholic acid. Long-term treatment of individuals with CTX with chenodeoxycholic acid (CDCA) normalises bile acid synthesis, normalises plasma and cerebrospinal fluid concentration of cholestanol, and improves neurophysiological findings. Inhibitors of 3-hydroxy 3-methyl glutaryl coenzyme A reductase alone or in combination with CDCA are also effective in decreasing cholestanol concentration and improving clinical signs; however, they may induce muscle symptoms.

BACKGROUND

Cerebrotendinous xanthomatosis (CTX) is a rare disease due to metabolic disorders in cholesterol metabolism. The patient develops multiple skin swellings, cataract and neurological deficits. Early diagnosis during childhood helps early treatment that prevents progression of disease. Our patient was discovered accidentally at age of 43 years to have CTX when she was under investigation for bleeding tendency due to immune thrombocytopenia. She had below average mentality. Otherwise, her neurological examination was normal. MRI brain revealed no abnormalities, which was strange for the expected course of the disease by the age of 40 years.

CASE PRESENTATION

A 43-year-old female patient presented with an illness that had started in early childhood with the appearance of multiple progressively enlarging skin swellings over knees, ankles, elbows and hands. These swellings were painless. Medical advice was sought for but no specific treatment was given. The patient did not ever go to school as her parents noticed marked impairment of her learning abilities. At the age of 8 years she started to suffer from bilateral gradual diminution of vision. Six months ago the patient developed menometrorrhagia, gingival bleeding and ecchymosis but no peticheal rash or other orificial bleeding. Menarche was at the age of 12 years, she had regular menstruation and she had normal development of secondary sexual characters.

On examination, the patient's intelligence was below average (IQ:65). Her body mass index was 27.4. She had no xanthelasma or corneal arcus. There were multiple subcutaneous swellings over the extensor surfaces of the knees and ankles. These swellings were of variable sizes, firm and not tender, some were erythematous and they were not attached to overlying skin (figures 1–4). Acuity of vision was 6/60 in both eyes. She had spontaneous pendular horizontal nystagmus of both eyes and bilateral mature presenile cataract (figure 5). The rest of her neurological examination was normal. Psychiatric evaluation was normal. There was no similar condition in her family.

INVESTIGATIONS

Investigations revealed mild microcytic hypochromic anaemia with few target cells and severe thrombocytopenia (haemoglobin: 10 g/dl; total leucocyte count: 10 000/µl with normal differential count; platelets: 10 000/µl; reticulocytic count: 68 000/µl (1.5%); platelets count: 100%; international normalised ratio: 1). Bone marrow aspirate revealed hypercellular marrow with normal morphology and maturation of myeloid and erythroid series. Megakaryocytes were increased in number, showed defective budding, lobulation and many giant and dwarf forms. Iron stores of bone marrow were depleted. Total cholesterol: 3.88 mmol/l; triglycerides: 1.02 mmol/l; high-density lipoprotein cholesterol: 1.12 mmol/l; low-density lipoprotein cholesterol: 2.3 mmol/l. Serum cholestanol was elevated (3 ng/dl). Antinuclear antibody titre was 1/80 and anti-double stranded nuclear antibodies (ADNA) was negative. Skin biopsy revealed foamy histocytic cells (figure 6).

DIFFERENTIAL DIAGNOSIS

Other conditions with xanthomas[1]:

- Sitosterolemia—inherited sterol storage disease characterised by tendon xanthomas.
- Familial hypercholesterolaemia (especially type II a) in which plasma cholestanol level is normal.

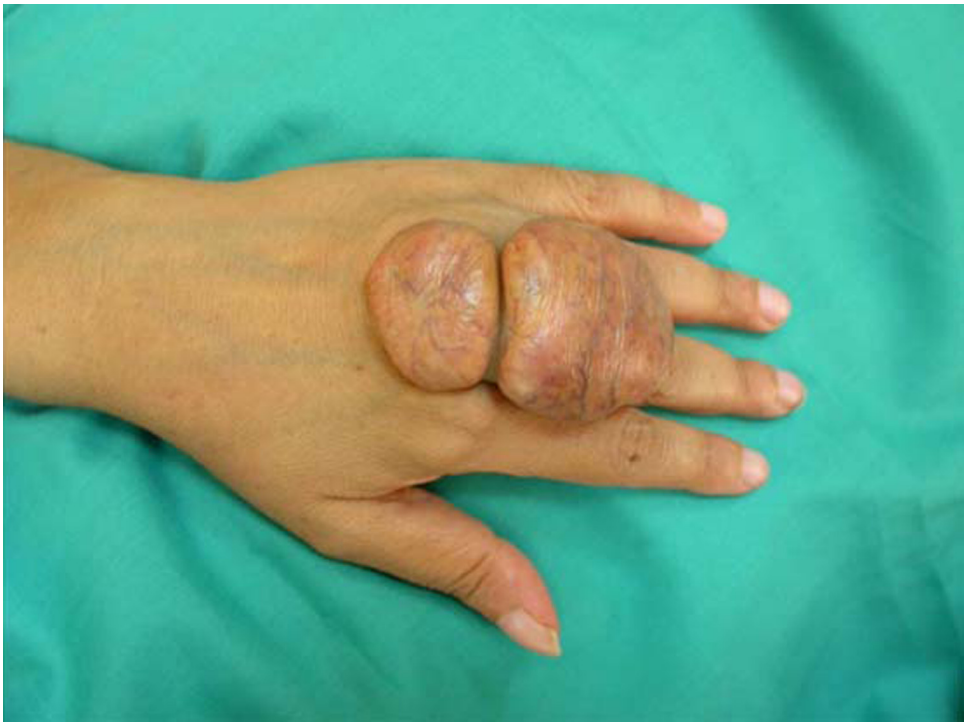

Figure 1 Xanthoma in left hand.

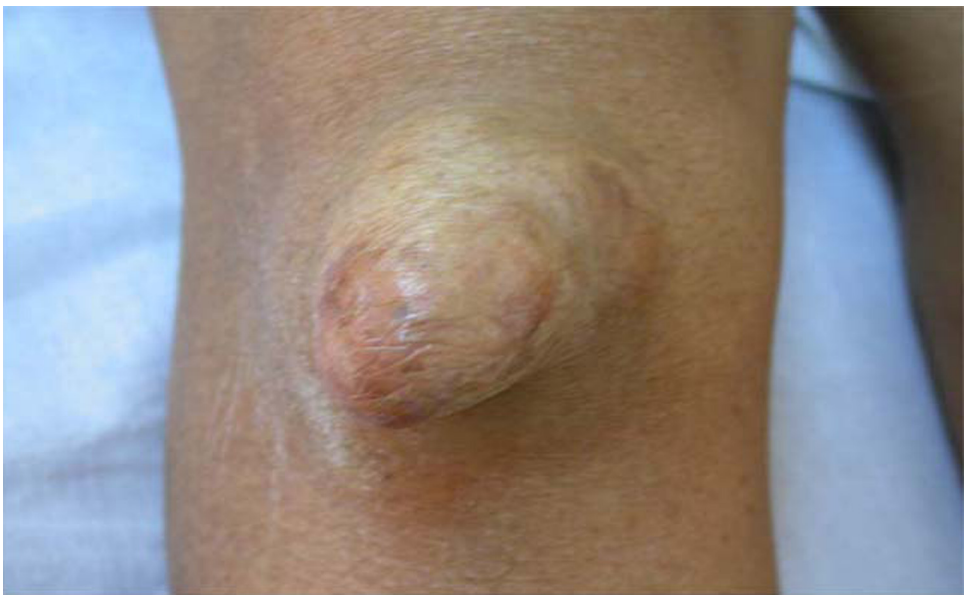

Figure 2 Xanthoma over right knee.

TREATMENT

Chenodeoxy cholic acid (CDCA) 750 mg daily has been commonly used as the standard treatment, which influences the negative feedback of cholesterol and bile acid synthesis. Also, a combination of CDCA with 3-hydroxy 3-methyl glutaryl coenzyme A reductase inhibitors is more effective in lowering the serum cholestanol levels.[2]

Treatment is ineffective as after the second or third decade of life the cholestanol would be extensively deposited in many tissues.

OUTCOME AND FOLLOW-UP

The patient's thrombocytopenia improved on steroid treatment and she is off steroids after 2 months of use.

DISCUSSION

CTX was first described by Van Bogaert *et al*. It is a rare lipid metabolic disorder inherited in an autosomal recessive way.[3] Review of the literature revealed 176 patients with documented CTX of which 56% were females.[2] The primary biochemical defect is deficiency of hepatic mito-

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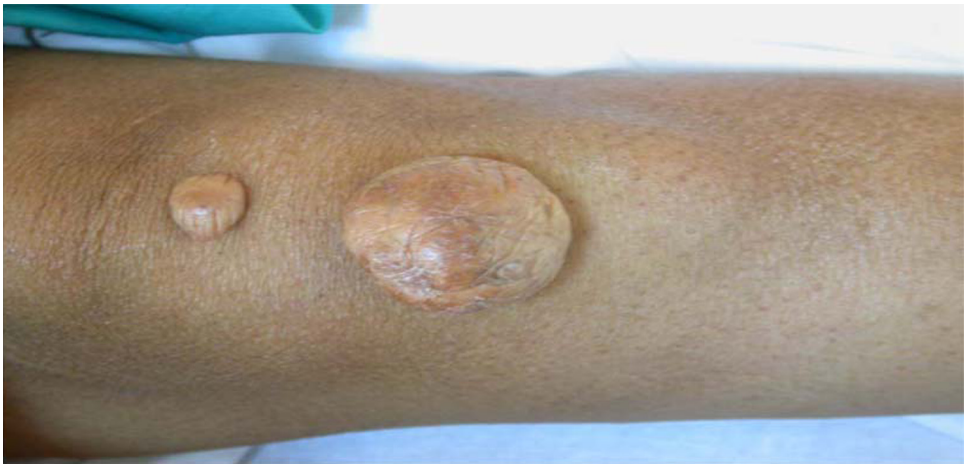

Figure 3 Xanthoma over left knee.

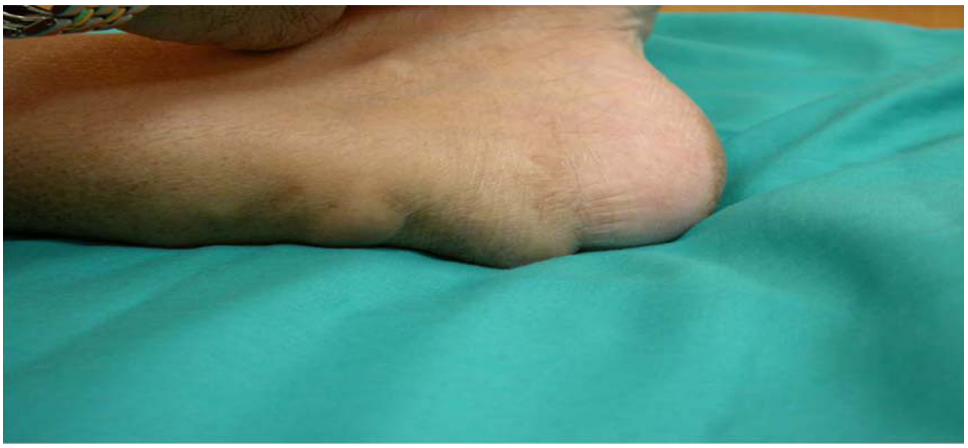

Figure 4 Xanthoma over tendoachilles of left leg.

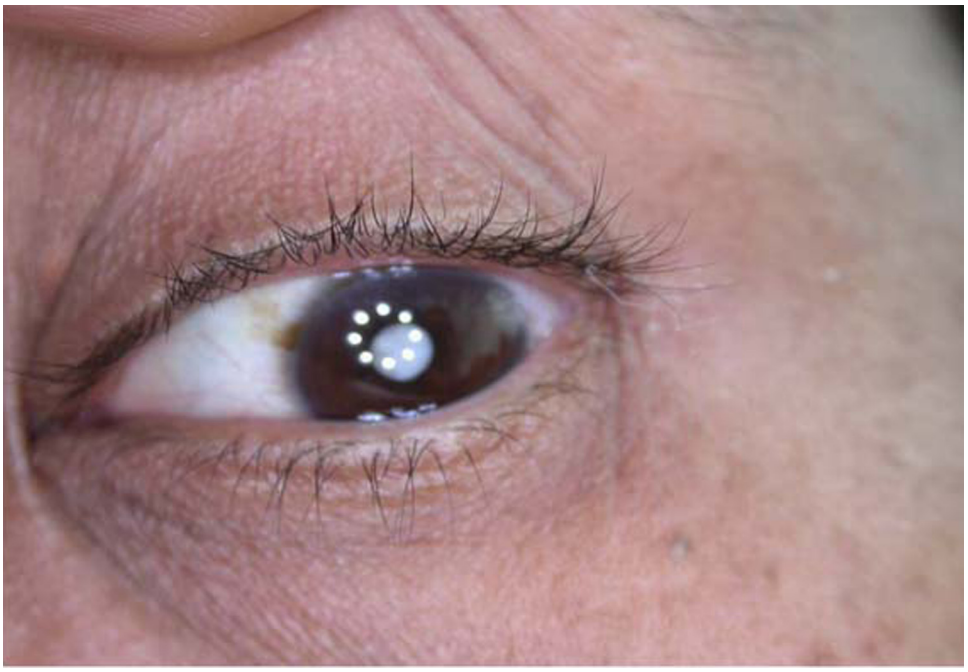

Figure 5 Eye cataract.

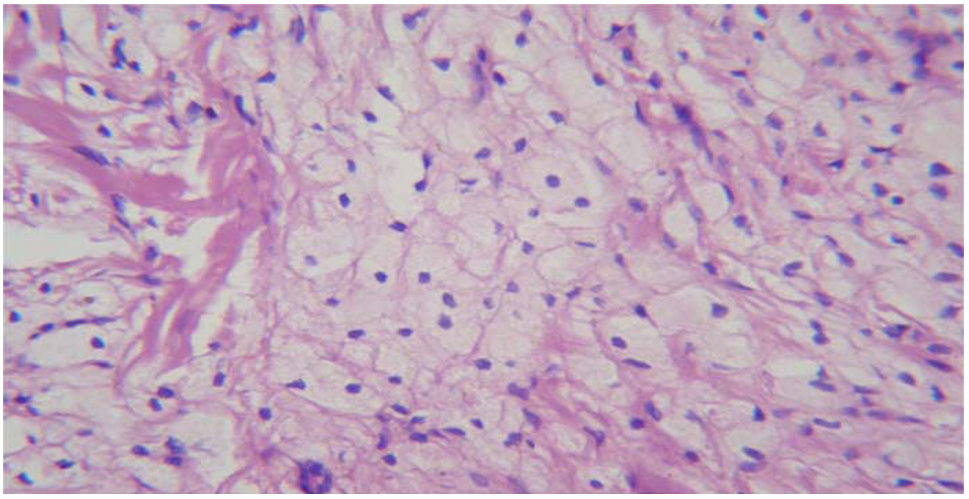

Figure 6 Skin biopsy showing multiple histocytic foamy cells.

chondrial enzyme sterol-27-hydroxylase, which catalyses the hydroxylation of cholestanol (5-α-dehydro derivative of cholesterol) and its deficiency decreases bile acid synthesis. This reduces feedback inhibition on cholesterol 7-α-hydroxylase, which is the rate-limiting enzyme, resulting in synthesis and accumulation of more cholestanol (normal <1 ng/dl).[4] In approximately 75% of affected individuals, cataracts are the first finding often appearing in the first decade of life. Xanthomas appear in the second or third decade; they occur on the Achilles tendon, the extensor tendons of the elbow and hand, the patellar tendon and the neck tendons. Some individuals show mental impairment from early infancy, whereas the majority has normal or only slightly subnormal intellectual function until puberty; dementia with slow deterioration in intellectual abilities occurs in the 20s in over 50% of individuals. Neuropsychiatric symptoms such as behavioural changes, hallucinations, agitation, aggression, depression and suicide attempts may be prominent. Pyramidal signs (ie, spasticity) and/or cerebellar signs are almost invariably present between the age 20 and 30 years. Other findings include extrapyramidal manifestations (dystonia and atypical parkinsonism), seizures and peripheral neuropathy.[5]

Learning points

- In our patient the subcutaneous swellings and the cataract with decreased mentality were the evident symptoms of CTX.
- This is the first case of CTX and immune thrombocytopenia with no correlation between immunothrombocytopenia and this syndrome.

Competing interests None.

Patient consent Obtained.

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