Case Report

Cerebrotendinous xanthomatosis

Satyadev Vadapalli

Abstract

Cerebrotendinous xanthomatosis is a rare autosomal recessive lipid storage disorder affecting the biosynthetic pathway of bile acids, leading to increased cholestanol formation and its accumulation in various tissues. Patients can present with tendon xanthomas, gait abnormalities, osteoporosis with or without a pathological fracture, diminished vision, intractable diarrhoea, seizures, ataxia, psychosis, and mental retardation. We report a 20-year-old man who presented with multiple recurrent tendon swellings and seizures. The earlier diagnosis and treatment helps in preventing the devastating neurological sequalae of this sinister condition. Treatment with chenodeoxycholic acid is crucial in preventing the progression of this rare disorder.

Key words: Cerebrotendinous xanthomatosis, chenodeoxycholic acid, recurrent tendon xanthomas, serum cholestanol

Introduction

Cerebrotendinous xanthomatosis (CTX) is a rare cause of tendon xanthomas, which usually presents as bilateral fusiform swelling of the tendoachilles,[1] gait abnormalities, ataxia, and progressive neuropsychiatric manifestations.[1,2] It may also present early as juvenile cataract or intractable diarrhea.[3] The present case report is about a 20-year-old man who presented with multiple recurrent tendon xanthomas with other manifestations which were left unnoticed and the subject was left with permanent neurological sequelae.

Case Report

A 20-year-old male studying 8th standard presented with complaints of slowly progressive swellings over the left forearm, front of left knee, and behind the ankles bilaterally [Figure 1a, b] for last 10 years. The swellings were painless, but of late, he experienced pain in front of the left knee while squatting and on prolonged walk.

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He had similar swelling on the left forearm 5 years ago which recurred 1 year after surgery. He was operated for bilateral congenital cataracts at the age of five. He also had delayed milestones and decreased scholastic aptitude. He was taking Phenytoin before presentation for recurrent seizures. He was the third child born out of consanguineous marriage, others being normal.

On examination, he had short stature, bilateral pes cavus deformity, swellings of various sizes located near the ulnar border of left forearm, left infrapatellar region in the patellar tendon, and fusiform swellings bilaterally along the tendoachilles. The largest measured swelling was of 14 × 6 cm in the right tendoachilles. Terminal degree of flexion of left knee was restricted and painful with full range of motion at all other joints. Neurological examination revealed a decreased IQ (55). He also had bilaterally decreased muscle bulk with Grade 4 muscle power. Sensory system examination was normal. He had bilateral brisk reflexes with minimal cerebellar ataxia.

His renal and liver function tests, calcium, phosphorous, alkaline phosphatase levels, and fasting lipid profile were within normal limits. His complete blood picture and peripheral smear did not reveal any abnormality. Nerve conduction studies were normal. EEG showed diffuse slow wave activity with intermittent discharges at varied places. Magnetic Resonance Imaging (MRI) of the brain revealed minimal cerebral and cerebellar atrophy. MRI of both the ankles showed diffuse enlargement of bilateral tendoachilles and features of increased signal intensity in T1, T2 image sequences [Figure 2a–c] demonstrative of lipid deposits at their calcaneal attachments.

He underwent excision biopsy of swelling within the

left patellar tendon [Figure 3a, b]. Histopathologic examination of the specimen revealed foamy histiocytes, areas of fibrosis with plenty of cholesterol clefts, many foreign body and touton type of giant cells, and focal sparse chronic inflammatory cell collection. The features were suggestive of tendinous xanthomatosis [Figure 4]. He was started on chenodeoxycholic acid (CDCA) 250 mg TDS and atorvastatin 20 mg at HS daily and phenytoin was continued at 100 mg TDS. Patient was reviewed after an year, and on examination, he had developed new xanthomas on the chest wall over the ribs and there was minimal increase in the size of other xanthomas as he was noncompliant for treatment. Patient was counseled and his relatives were advised the need for regular treatment and followup.

Discussion

CTX is a rare inborn error of bile acid metabolism with autosomal recessive inheritance due to homozygous

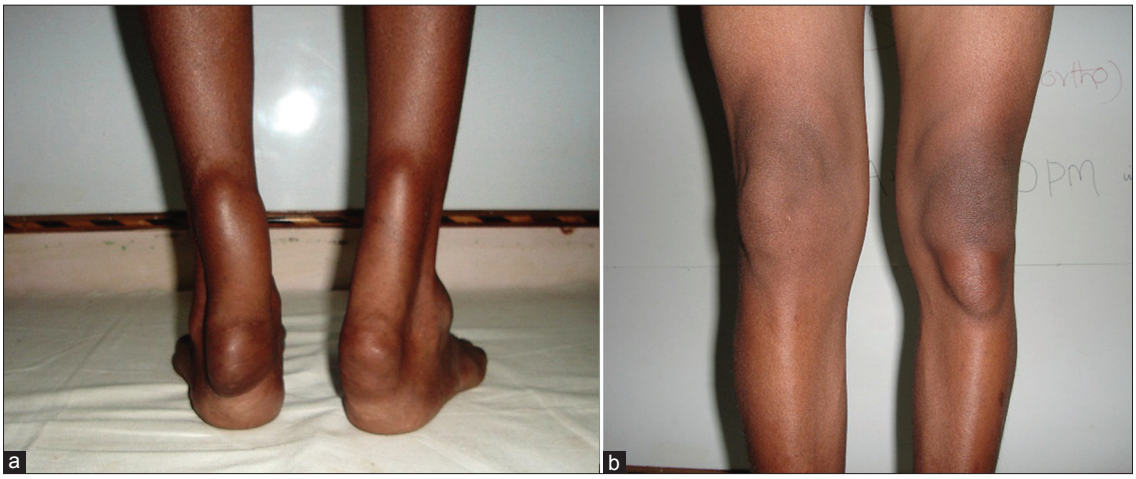

Figure 1: Clinical photographs showing (a) bilateral fusiform swellings of the tendoachilles. (b) xanthomas in the patellar tendon

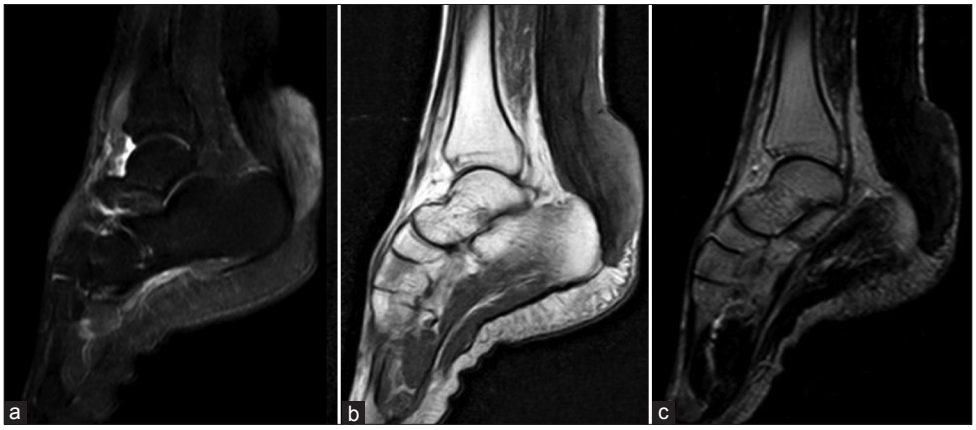

Figure 2: T1, T2, and STIR images of the tendoachilles showing (a) hyperintense signal in T1 (b,c) mixed intense signals in T2 and STIR

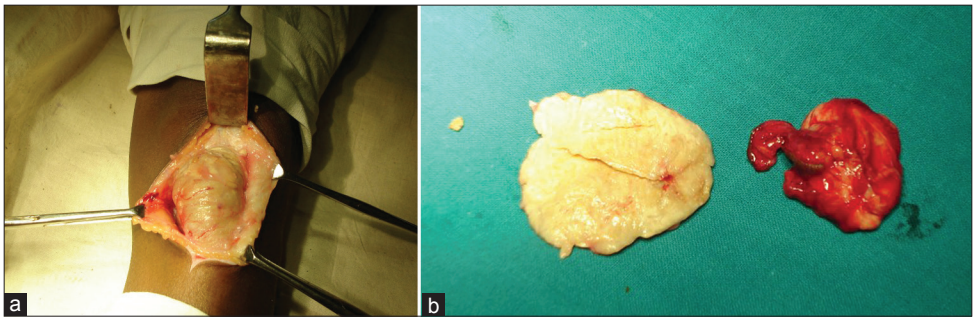

Figure 3: Intraoperative photograph showing (a) patellar tendon xanthoma before excision. (b) excised xanthoma

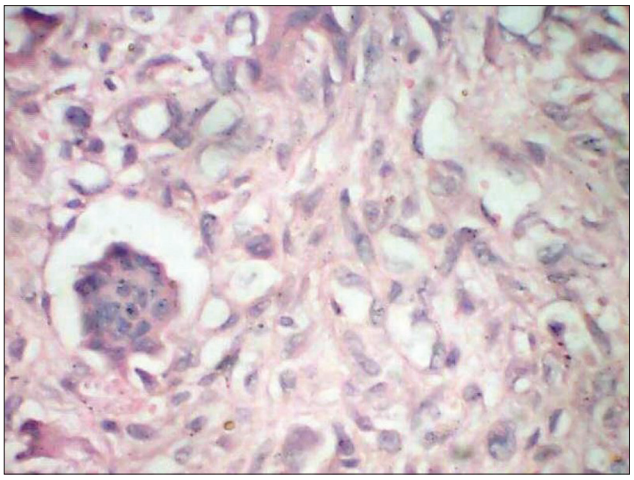

Figure 4: Light photomicroscopic examination of the tissue showing foamy histiocytes, areas of fibrosis with plenty of cholesterol clefts, many foreign body and Touton type of giant cells

mutation of the hepatic mitochondrial enzyme 27-sterol hydroxylase (CYP 27).[4] This enzime catalyzes the oxidation of side chain of cholesterol, an intermediate step in the formation of cholic acid and CDCA (bile acids). Bile acid synthesis is blocked due to the deficiency of 27-sterol hydroxylase, resulting in increased production of bile acid intermediates, which in turn leads to increased cholestanol formation which gets deposited in various tissues. The laboratory in restigations for of CTX include elevated plasma cholestanol and increased urinary bile alcohols.

CTX is clinically characterized by myriad manifestations such as juvenile cataracts, chronic diarrhea, tendon xanthomas, and progressive neuropsychiatric manifestations.[1,3] Bilateral cataracts usually present in the first decade of life and eventually obstructive coronary artery disease develops. Patients report with tendon xanthomas during the second or third decades as massive Achilles tendon xanthomas.[1] Other areas include quadriceps, triceps, extensor tendons, and neck muscles. Xanthomatous deposition is also seen in CNS, bones, and lung. Osteoporosis and repeated fractures are also seen in patients with CTX. Patients have normal serum calcium, phosphorous, and alkaline phosphatase levels. Mental retardation and progressive intellectual deterioration are the prime neurological manifestations.[2] Other neuropsychiatric symptoms include behavioral changes, agitation, depression, and hallucinations. Seizures are common and may be the presenting feature in more than 50% of the patients. Peripheral neuropathy resulting in atrophy of muscles and pes cavus also occurs. Electrophysiological studies reveal decreased nerve conduction velocities and abnormal sensory, motor, visual, and brainstem evoked potentials. Accumulation of cholestanol in brain and CSF is an important feature leading to spasticity and cerebellar signs by the second decade.[5] Because patients with CTX have brain atrophy, it is postulated that the adverse effects of cholestanol may be caused by increased apoptosis pathways. Cholestanol also gets deposited in the bones, leading to early osteoporosis, and the risk of pathological fractures increases manifold.[6]

The diagnosis of CTX is mostly clinical as most of biochemical parameters are normal. Diagnosis depends on finding elevated serum cholestanol levels. Neuroimaging with computed tomography (CT) and MRI shows evidence of cerebral and cerebellar atrophy. T2-weighted image may show focal or diffuse high signal intensities in vertebral and cerebellar white matter. Dentate nuclei could be hyperintense on FLAIR images. Spinal cord atrophy may be seen. MRI of the Achilles tendon shows soft tissue swelling. Histopathologic examination reveals the dense connective tissue of the tendon being replaced by an infiltrate of foamy histiocytes, multinucleated giant cells, and elongated cholesterol clefts. The differential diagnosis for a patient presenting with xanthomas of Achilles tendon and other tendons includes familial hypercholesterolemia and sitosterolemia. Patients have accelerated atherosclerosis with tendon xanthomas, but absence of neurological symptoms and diarrhea differentiates them from CTX. The other differential, Marinesco–Sjogren syndrome, also has features of cerebellar ataxia, congenital cataracts, and mental retardation, but the patients rarely have tendon xanthomas.

Early diagnosis of CTX is imperative as pharmacological management with CDCA and HMG COA reductase inhibitors (Simvastatin) has shown to slow or even reverse the progression of disease.[7,8] Longterm treatment with CDCA at dose of 750 mg/day normalizes plasma and CSF concentrations of cholestanol and leads to improvement in neurological status and peripheral neuropathy and regression of xanthomas. Cataracts need surgical treatment and xanthomas may be removed for cosmetic reasons, but may lead to worsening of gait in neurologically affected patients.

This case is presented in view of rarity to increase suspicion index for the presence of multiple tendinous xanthomas.[6] Early detection of CTX as drug therapy can limit further damage to CNS and can prevent progression of tendon xanthomas and in early cases may even lead to regression in some.[3,7,8] Family members should be screened and the benefits of genetic testing should be given to asymptomatic subjects for the early diagnosis of this rare disease.

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