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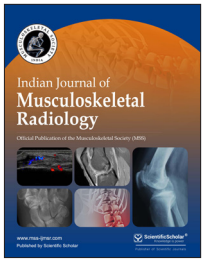

Case Report

Cerebrotendinous xanthomatosis: A multidisciplinary approach for early diagnosis

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ABSTRACT

Cerebrotendinous xanthomatosis (CTX) is a rare genetic disorder of bile acid metabolism which manifests in the form of variable neurological and non-neurological symptoms. Early recognition of the disease leads to a timely implementation of treatment and hence better prognosis. The early diagnosis of CTX depends on a multidisciplinary approach in which radiological imaging plays a pivotal role.

Keywords: Bile acid metabolic disorder, Xanthomatosis, Achilles tendon xanthoma

INTRODUCTION

Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive disorder of cholesterol metabolism that leads to reduced bile acid synthesis and accumulation of bile acid precursors in various tissues.[1] This condition leads to various neurological and non-neurological symptoms, for example, chronic diarrhea, juvenile cataract, tendon xanthomas, and progressive neurological dysfunction.[2] Due to marked variability in age of onset and severity of symptoms, the condition is prone to diagnostic delay.[3] A multidisciplinary approach is paramount for the early diagnosis of CTX which includes clinical examination, radiological imaging, biochemical parameters, and pathological confirmation. Since, early diagnosis leads to timely treatment and hence symptomatic improvement, this case report endeavors to evaluate efficacy of this multidisciplinary approach.

CASE REPORT

A 15-year-old young male presented in the orthopedic clinic with painless swelling of the posterior ankle bilaterally for 7 months. There was no history of any trauma. On clinical examination, an oblong-shaped non-tender lump was observed along the posterior aspect of both ankle joints, without any signs of inflammation. Ankle movement was restricted on plantar flexion; the rest of the movements were normal.

On further enquiry, it was noted that the patient was a school drop-out and had some neuropsychiatric symptoms too. This raised the suspicion of a multisystem disorder having musculoskeletal and neurological involvement. The patient was sent for a neurological examination, and it was found that all deep tendon reflexes were exaggerated.

Routine blood investigations (complete blood count and C-reactive protein) and the blood levels for ANA and other antibodies were normal. Total cholesterol level was 4.2 mmol/L (normal, <5.0 mmol/L).

The patient was referred to the radiology department for an ankle radiograph (anteroposterior and lateral view). The radiograph demonstrated soft-tissue opacity at the posterior aspect of ankle along the lower one-third of Achilles tendon bilaterally. The Kager fat plane was displaced anteriorly. The osseous structures and joints were unremarkable [Figure 1].

For further evaluation and characterization of posterior ankle soft-tissue lesion, a magnetic resonance imaging (MRI) ankle was performed on a 1.5 T MRI scanner. MRI images demonstrated well-circumscribed fusiform enlargement of lower one-third of tendon Achilles sparing the calcaneal attachment. The tendon fibers were thickened and demonstrated T1 hypointense signal. A focal area of T1 isointense (to muscle) and short-TI inversion recovery (STIR) hyperintense signal was demonstrated in the anteromedial aspect of swelling. The fibrillary architecture of the tendon was otherwise maintained. The calcaneal attachment was normal. No sign of enthesitis was demonstrated. Kager's fat pad was intact. The osseous structures and joints were unremarkable [Figure 2].

On the basis of MRI findings, metabolic or lymphomatous involvement of Achilles tendon was suspected, and an ultrasound (US)-guided biopsy was suggested for histopathological confirmation.

US demonstrated an oblong-shaped enlargement of the distal third of Achilles tendon. A focal geographical area of hypoechogenicity was observed on the anterior aspect of the tendon [Figure 3].

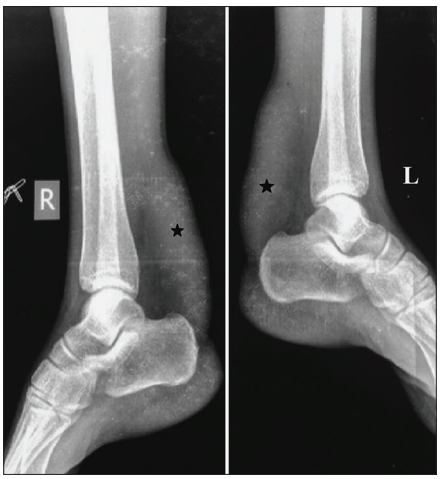

Figure 1: Lateral radiograph of the bilateral ankle demonstrates soft-tissue opacity posterior to the Kager's fat pad (black asterisk) along the lower third of both right and left Achilles tendons.

US-guided biopsy of the distal Achilles tendon lesion was done through in-plane approach, lateral to medial, and targeted at anterior hypoechoic area. Care was taken not to penetrate the Kager fat pad to prevent contamination of biopsy specimen with fatty tissue and to avoid false-positive histopathological reports [Figure 4].

Histopathological analysis of the biopsy sample confirmed the diagnosis of tendinous xanthoma [Figure 5].

MRI brain was done to rule out any organic lesion of the brain. MRI brain demonstrated T2 hyperintense signal in bilateral dentate nucleus of cerebellum and in bilateral peritrigonal white matter [Figure 6].

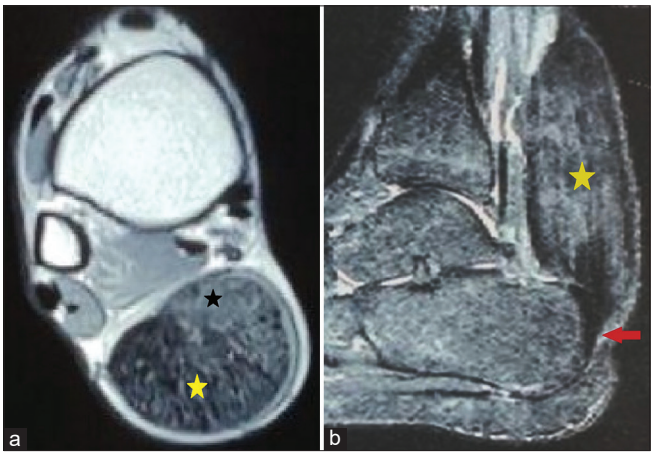

Figure 2: (a and b) Axial T1 (a) and sagittal short-TI inversion recovery (b) MR images of the ankle demonstrate fusiform enlargement of Achilles tendon with thickened fibers (yellow asterisk). A focal T1 isointense signal lesion (black asterisk) in the anterior medial aspect of the enlarged tendon. The calcaneal attachment of the Achilles tendon (red arrow) is normal.

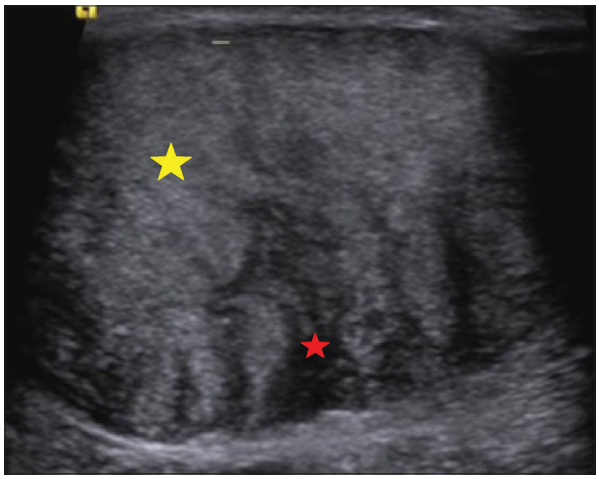

Figure 3: Axial ultrasound image of Achilles tendon demonstrates a fusiform enlargement of Achilles tendon (yellow asterisk). A focal hypoechoic area is demonstrated on the anterior aspect (red asterisk) (corresponding to the T1 isointense lesion of magnetic resonance imaging in Figure 2a).

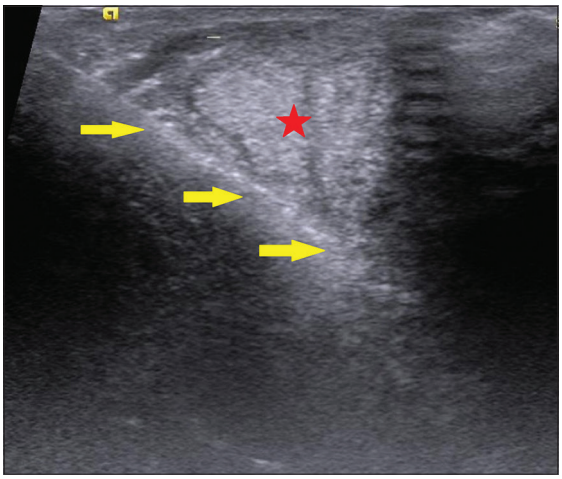

Figure 4: Ultrasound-guided biopsy of Achilles tendon lesion. The target was the hypoechoic area on the anterior aspect of Achilles tendon. (Yellow arrows: Biopsy needle trajectory, red asterisk: Achilles tendon). The targeted biopsy of the hypoechoic area was the advantage of image-guided biopsy over blind biopsy).

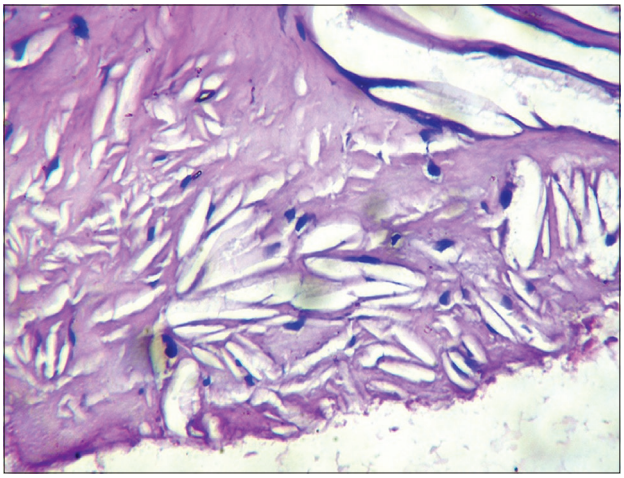

Figure 5: H and E stained section of Achilles tendon biopsy sample demonstrates numerous xanthoma cells and cholesterol clefts (×100).

Clinical findings, radiological imaging, and histopathological confirmation of CTX lead to early institution of treatment and marked improvement of gastrointestinal and neurocognitive symptoms on follow-up after 3 months.

DISCUSSION

CTX is a rare genetic disorder, first described by Van Bogart and his colleagues in 1937.[4] The estimated prevalence of the disease is <5/100,000.[5]

It shows autosomal recessive inheritance due to mutation in CYP27A1 gene which encodes for mitochondrial enzyme sterol 27-hydroxylase, an important enzyme in both classic and alternate pathway of bile acid synthesis. Deficiency

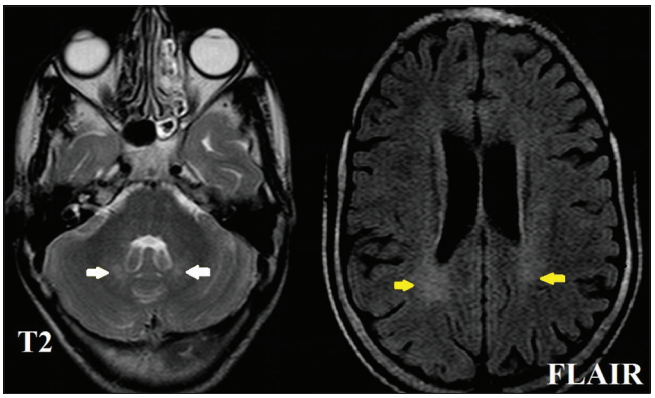

Figure 6: T2 and FLAIR axial section of magnetic resonance imaging demonstrate dentate nuclei hyperintensity (white arrows) and peritrigonal white matter hyperintensities (yellow arrows), respectively.

of sterol 27-hydroxylase leads to decreased production of chenodeoxycholic acid and elevated levels of cholesterol and other bile alcohols.[1] CTX presents with multiorgan involvement and a broad range of neurological and non-neurological symptoms.[2]

The mean age of onset of symptoms is 19 years, but the average age at the time of diagnosis is 35 years, thus representing a diagnostic delay of 16 years.[3] In our case, the patient presented at the age of 15 years.

Accumulation of cholesterol and cholestanol in body tissues, notably the tendons, brain (primarily white matter), and lens leads to tendon xanthomatosis, neurologic dysfunction, and cataract, respectively, all of which are characteristics of CTX.[6] The earliest symptoms are primarily non-neurological, as in our case, the patient presented with tendon swelling, which he had for the past 7 months, but the retrospective history revealed that the patient had neurocognitive and bowel symptoms for 5 years.

Chronic diarrhea and cataract are the usual initial presentations during the first decade of life, followed by tendinopathy in the second decade. Mild neurological symptoms may occur at an early age but mostly undergo undiagnosed (as in our case) and present later with full-blown symptoms.[7]

Tendon xanthomas mostly involve Achilles tendon; however, xanthomas may also develop on fingers, tibial tuberosity, triceps, and plantar surface of feet.[8]

The radiograph is usually the first imaging modality for any ankle swelling to look for underlying osseous abnormality. Soft-tissue abnormality on radiograph necessitates further imaging through ultrasonography (USG) or MRI.

On MRI, the tendon xanthomas have higher signal intensity on T1 and T2 sequences in comparison to normal tendons,

with a speckled or reticulated appearance due to deposition of fat in between the tendon fibers.

Both are equally efficacious for the characterization of soft-tissue lesions, with USG having edge over MRI because of its widespread availability, cost-effectiveness, repeatability, higher spatial resolution, and dynamic nature. However, subtle signal changes picked on STIR images may not be detected on USG.

A biopsy is often needed for the confirmation of tendon xanthoma because other conditions such as lymphoma can also involve Achilles tendon and present with posterior ankle lump.[9] Periventricular white matter hyperintensities at the level of posterior body of lateral ventricles in fluid-sensitive sequences of MRI are one of the imaging features demonstrated both in CTX and lymphoma.

A US-guided biopsy is preferred over blind biopsy. Injury to Achilles tendon, particularly at the hypoxic zone, is notorious for delayed healing. US-guided biopsy prevents injury to adjacent neurovascular structures. Under US guidance only, interfiber space biopsy is possible.

The characteristic imaging findings demonstrated on MRI brain are T2/FLAIR hyperintensities in the bilateral dentate nuclei and adjacent cerebellar white matter. T2/FLAIR high signal intensities can also be seen in periventricular white matter, basal ganglia, and spinal cord. The accumulation of cholesterol within the neurons with resultant demyelination and neuronal loss leads to these signal abnormalities.

CTX is one of the few rare genetic disorders, where an early diagnosis can have a significant impact on the disease progression. In our case, the patient presented with bilateral Achilles swelling and detailed multidimensional diagnostic workup helped to reach the diagnosis of CTX. The diagnosis of CTX is made only when tendon xanthoma is associated with cerebral symptoms and associated changes in brain MRI. Hence, a multidisciplinary approach is needed to differentiate CTX from simple tendon xanthoma and to rule out lymphoma too. MRI can suggest xanthoma by its classical appearance. Since tendinous lymphoma can have similar imaging features, tendinous biopsy is mandatory. The biopsy can obviate the need for genetic analysis for definitive diagnosis. USG-guided biopsy prevents contamination of biopsy specimens with Kager fat.

The initial symptoms are generally non-specific, hence, the disease usually remains undiagnosed until the advanced stage and unlikely to show significant improvement after initiation of therapy. This signifies the importance of early diagnosis and early treatment to reduce the morbidity and mortality associated with the disease. Differential diagnoses for CTX are mainly the disorders that are associated with xanthomas. Sitosterolemia is an inherited sterol storage disease characterized by tendon xanthomas and premature atherosclerosis and increased serum plant sterols. Neurocognitive symptoms are absent but the patient may present with paraparesis due to cord compression from intradural extramedullary xanthomas.

Xanthomas are also seen in hypercholesterolemia and hyperlipidemia (especially type IIa), however, plasma cholestanol concentration and MRI brain are normal.

Clinically, CTX resembles Marinesco-Sjogren syndrome, an autosomal recessive disorder characterized by the cerebellar ataxia, bilateral cataract, and non-progressive mental retardation. Skeletal deformities and variable neuromuscular manifestations are also present. On MRI brain scan, T2 hyperintensity in the cerebellar cortex and cerebellar atrophy predominantly involving the vermis are characteristic. The absence of tendon xanthomas helps to differentiate this condition from CTX.

Dentate nucleus T2 hyperintensity is seen in metronidazole toxicity and decompensated maple syrup urine disease, however, patients with these diseases present with acute encephalopathy. Tendon xanthomas are absent and serum cholestanol levels are normal.

Oral chenodeoxycholic acid is the mainstay of treatment; when started early, it has shown to improve the clinical symptoms.[10] Surgical removal of xanthomas is not recommended as xanthomas may regrow rapidly in patients with uncontrolled CTX.[8]

CONCLUSION

The possibility of CTX should be considered in every person with Achilles tendon swelling and associated neurological symptoms. This demands a multidisciplinary approach for early diagnosis of this condition. Early initiation of treatment will not only relieve the symptoms but can also prevent further progression of the disease. Imaging findings, although, are non-specific but a multimodality imaging assessment of Achilles tendon and of brain is of great help in guiding the differential. Imaging modalities, especially USG and MRI, are the key stones in diagnosis. If a biopsy is needed, it should always be done under US guidance for the confirmation of this diagnostically challenging condition.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Nie S, Chen G, Cao X, Zhang Y. Cerebrotendinous xanthomatosis: A comprehensive review of pathogenesis, clinical manifestations, diagnosis, and management. Orphanet J Rare Dis 2014;9:179.
2. Keren Z, Falik-Zaccai TC. Cerebrotendinous xanthomatosis (CTX): A treatable lipid storage disease. Pediatr Endocrinol Rev 2009;7:6-11.
3. Pilo-de-la-Fuente B, Jimenez-Escrig A, Lorenzo JR, Pardo J, Arias M, Ares-Luque A, *et al*. Cerebrotendinous xanthomatosis in Spain: Clinical, prognostic, and genetic survey. Eur J Neurol 2011;18:1203-11.
4. van Bogaert L, Scherer HJ, Epstein E. Une Forme Cerebrale de la Cholesterinose Generalisee, Dissertation/Master's Thesis. Paris: Masson et Cie; 1937.
5. Lorincz MT, Rainier S, Thomas D, Fink JK. Cerebrotendinous xanthomatosis: Possible higher prevalence than previously recognized. Arch Neurol 2005;62:1459-63.
6. Salen G, Steiner RD. Epidemiology, diagnosis, and treatment of cerebrotendinous xanthomatosis (CTX). J Inherit Metab Dis 2017;40:771-81.
7. Sastri VR, Ravindranath VS, Metikala S, Kumar M. Bilateral xanthomas of tendoachilles in A patient of cerebrotendinous xanthomatosis-a rare case report and review of literature. J Orthop Case Reports 2014;4:40-3.
8. Berginer VM, Salen G, Patel SB. Cerebrotendinous xanthomatosis. In: Rosenberg RN, Pascual JM, editors. Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease. London: Elsevier; 2015. p. 589-98.
9. ter Braak BP, Guit GL, Bloem JL. Case 111: Soft-tissue lymphoma. Radiology 2007;243:293-6.
10. Berginer VM, Salen G, Shefer S. Long-term treatment of cerebrotendinous xanthomatosis with chenodeoxycholic acid. N Engl J Med 1984;311:1649-52.

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