

Rare Genetic Cerebrotendinous Xanthomatosis: A Case without Cholesterol-Elevation with Prominent Cholesterol-Rich Achilles Tendon Xanthoma

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ABSTRACT

Cerebrotendinous Xanthomatosis (CTX) is a rare inherited metabolic disease attributed to the mutation of the gene *CYP27A1*, resulting in sterol 27-hydroxylase deficiency characterized by deposition of cholestanol and cholesterol in several tissues, like the central nervous system and tendons. Accordingly, cataracts, gallstones, diarrhea and premature atherosclerosis have been reported. Nonetheless, clinical development is extremely heterogeneous in CTX. We report here one case of CTX genetic alteration occurring in the absence of cholestanol elevation in plasma and tendon, but with prominent xanthoma limited to severe inflammatory injury of the cholesterol-rich Achilles tendons. We propose that CTX may not be characterized by increased cholestanol production due to alteration in the sterol 27-hydroxylase gene, but is a more complex pathology that may result from additional genetic alterations that require further analyses.

Keywords: Cerebrotendinous xanthomatosis; Cholestanol; *CYP27A1*; Achilles xanthoma

INTRODUCTION

Cerebrotendinous Xanthomatosis (CTX) is a rare disease attributed to partial or complete loss of the enzyme sterol-27-hydroxylase leading to chenodeoxycholic acid and cholic acid production deficiency, and accumulation of sterol intermediates, mainly cholestanol, in plasma and in several other tissues. The clinical phenotype of CTX greatly varies among patients, and includes tendon Xanthoma, gallbladder stones, diarrhea, cataract, and neurological abnormalities [1]. The diagnostic identification typically is characterized by an elevated level of plasma cholestanol and identification of *CYP27A1* gene variants. However, there is a great diversity of phenotypes of this pathology so it is often difficult to identify the disease, and under diagnosis is frequent, but the treatment with chenodeoxycholic acid can prevent the unfavorable evolution of the disease. In his regard, a case of brain damage with absent tendon Xanthoma has been described [3]. We report here an opposite case, that is, alteration of the *CYP27A1* gene characteristic of CTX, without elevation of cholestanol in plasma and tendon, with extremely large Achilles tendon lesions

but absence of other clinical manifestations typical of the disease [2].

CASE PRESENTATION

A 68-year-old female patient, mulatto, rural worker from the countryside of the state of São Paulo, Brazil, since childhood presenting bulging in both Achilles' tendons. She was a smoker until 20 years ago. In the last 8 months, an ulcer appeared in the left Achilles tendon with significant local bleeding, which required blood transfusion. Biopsies of the left tendon lesion showed Xanthogranuloma with giant cells [3] abundant amounts of apparently cholesterol crystals surrounded by fibrous proliferation, and permeated squamous cells of the superficial layer of the epidermis without neoplastic cells, but containing keratinous material. Due to its size, the Xanthogranuloma was removed, which resulted in the impossibility of walking.

Her BMI was 23.73 kg/m² presence of bilateral cataract and in the retinal examination nonspecific atrophy of retinal pigment epithelium [4] Doppler examination of the lower limbs shows

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calcified atheroma without significant hemodynamic repercussions. Abdominal ultrasound shows aortoiliac atheromas and gallbladder presenting multiple images compatible with polyps. There are no gastrointestinal or neurological complaints or alterations in clinical examination [5] Carotid ultrasound shows atheroma in the bifurcation of the right and left internal and external carotid arteries, but all below 50%. Intima-media thickness is 0.15 cm. myocardial scientifically does not show significant changes.

Plasma and Achilles tendon sterol analyses by gas-liquid chromatography coupled to mass spectrometry (Shimadzu GCM-QP2010 Plus, Kyoto, Japan) are shown for the present case, healthy controls and for our two unpublished typical CTX patients characterized by the elevated plasma cholestanol [6] other authors have considered plasma cholestanol concentrations as normal below 5.0 µg/mL 4, elevated as 7.7 and 11.0 µg/mL in two CTX cases 5, or varying from 5.5 to 54.8 in several CTX cases.

Our case has no elevation of cholestanol in plasma and tendon, but the latter is rich in cholesterol crystals. Sitosterolemia was excluded by the very low concentrations of campesterol and sitosterol [7].

Two genetic variants in compound heterozygosity were identified in the *CYP27A1* gene. One variant found in exon5, c.C1016T:p.T339M (rs121908102) has been related in several individuals with clinical signs of CTX, being considered a pathogenic variant 8,9,10. The other variant was found in intron 4, c.844+4A>G (rs1016174396) not directly altering the amino acid sequence of the *CYP27A1* protein and described as uncertain significance (Figures 1a-1c) [8].



Figure 1: (A) Great thickening of both Achilles tendons with extensive necrosis on the left; Panel (B) CT scan of the left Achilles tendon; Panel (C) histology of the left tendon biopsy showing Xanthogranuloma with giant cells, and abundant amount of cholesterol crystals surrounded by fibrous proliferation permeated with squamous cells of the epidermal layer without neoplastic cells, but containing keratinous material.

RESULTS AND DISCUSSION

Due to the extensive necrosis of one of the tendons, [9] our case could have been confounded with an unusual case of aspergilloma reported in the Achilles tendo, however, the latter occurred in only one tendon, not in both, as typically described in the metabolic alterations of familial hypercholesterolemia, CTX and sitosterolemia [10].

CTX is often accompanied by several clinical manifestations that include neuropsychiatric, gastrointestinal, premature atherosclerosis and cataract. Nevertheless, the presence of cataracts and atherosclerosis in our patient could be indistinctly attributed to her age as well as to the fact that she was a former cigarette smoker. However, it is unusual for the CTX patient to have large Achilles tendon injuries, apparently sparing other tendons, in addition to massive tendon necrosis and absence of any other manifestations, notably neurological. Cases of necrobiotic Xanthogranuloma have been described, but all are

Lipids	Healthy controls (n=6)	Case	CTX 1	CTX 2
-	Plasma	-	-	-
Cholesterol (mg/dL)	148 ± 24	109	142	154
Cholestanol (µg/mL)	2.60 ± 1.33	2.11	10.11	19.97
Desmosterol (µg/mL)	0.529 ± 0.239	0.45	1.505	1.701
7-Dehydrocholesterol (µg/mL)	0.151 ± 0.065	0.247	1.936	2.479
Lathosterol (µg/mL)	1.011 ± 0.327	0.015	0.083	0.089
Campesterol (µg/mL)	1.397 ± 0.669	0.017	0.086	0.077
Sitosterol (µg/mL)	2.829 ± 0.690	0.165	0.24	0.163
Tendon				
Cholesterol (µg/g)	nd	16,280	48,472	91,506
Cholestanol (µg/g)	nd	139	3,253	2,195

Table 1: Plasma and Achilles tendon sterol analyses.

characterized by multiple body lesions not limited to the Achilles tendons, nor showing typical genetic alteration of CTX as in our patient [11].

Our case presents an alteration in the *CYP27A1* gene characteristic of the Cerebrotendinous Xanthomatosis (CTX) disease. However, it is also noteworthy that the patient, as in other reported cases [6], did not present neurological involvement or elevation of cholestanol in the plasma and in the Achilles' tendons. On the other hand, the extreme [12-14] variability of manifestations in CTX is also exemplified by a recent case of a typical genetic alteration with elevated plasma cholestanol and neurological changes, but no xanthomata.

CONCLUSION

In summary, our case reported here shows that the CTX genetic alteration can occur in the absence of cholestanol elevation but with prominent xanthomata limited to the cholesterol-rich Achilles tendons causing severe inflammatory injury. This case leads us to admit that CTX is not necessarily characterized by increased cholestanol production due to alteration in the sterol 27-hydroxylase gene, but is a more complex pathology that may result from increased uptake or decreased cellular excretion of cholesterol. Molecular characterization of affected CTX families provides early diagnosis and treatment of homozygotes in the presymptomatic state as well as identification of heterozygotes, which is crucial for treatment and genetic counseling and for prenatal diagnosis. The patient is scheduled to be treated with chenodeoxycholic acid.

REFERENCES

- DeBarber AE, Duell PB. Update on cerebrotendinous xanthomatosis. *C. opin. lipidol.* 2021;32(2):123-131.
- Duell PB, Salen G, Eichler FS, DeBarber AE, Connor SL, Casaday L, et al. Diagnosis, treatment, and clinical outcomes in 43 cases with cerebrotendinous xanthomatosis. *J. clini lipidol.* 2018;12(5): 1169-1178.
- Stenos C, Kalafatakis K, Constantoulakis P, Zekiou K, Margoni A, Kardara P, et al. A case of cerebrotendinous xanthomatosis with brain and spinal involvement without tendon xanthomas: Identification of a novel mutation of the *CYP27A1* gene. *J. clini lipidol.* 2022;16(03): 281-285.
- Guenzel AJ, DeBarber A, Raymond K, Dhamija R. Familial variability of cerebrotendinous xanthomatosis lacking typical biochemical findings. *JIMD reports.* 2021;59(1):3-9.
- Nozue T, Higashikata T, Inazu A, Kawashiri MA, Nohara A, Kobayashi J, et al. Identification of a novel missense mutation in the sterol 27-hydroxylase gene in two Japanese patients with cerebrotendinous xanthomatosis. *Intern. Medici.* 2010;49(12): 1127-1131.
- Stelten BM, Raal FJ, Marais AD, Riksen NP, Roeters van Lennep JE, et al. Cerebrotendinous xanthomatosis without neurological involvement. *J. Int.Medi.* 2021;290(5):1039-1047.
- Tada H, Nomura A, Ogura M, Ikewaki K, Ishigaki Y, Inagaki K, et al. Diagnosis and management of sitosterolemia 2021. *J. Atheros, thromb.* 2021.
- Verrips A, Hoefsloot LH, Steenbergen GCH, Theelen JP, Wevers RA, Gabreels FJM, et al. Clinical and molecular genetic characteristics of patients with cerebrotendinous xanthomatosis. *Brain.* 2000;123(5):908.
- Appadurai V, DeBarber A, Chiang PW, Patel SB, Steiner RD, Tyler C., et al. Apparent under diagnosis of Cerebrotendinous Xanthomatosis revealed by analysis of ~ 60,000 human exomes. *Molec. gene. metab.* 2015;116(4):298-304.
- Meiner V, Meiner Z, Reshef A, Björkhem I, Leitersdorf E. Cerebrotendinous xanthomatosis: molecular diagnosis enables presymptomatic detection of a treatable disease. *Neurology.* 1994;44(2):288.
- Park YH, Kim YH, Kim JY, Choi GW, Kim HJ. Aspergilloma clinically mimicking Achilles tendon xanthoma in a non-immunocompromised patient: A case report. *Foot. Ank. Surg.* 2020;26(8):943-945.
- Oben JE, Ngondi JL, Momo CN, Agbor GA, Sobgui CS. The use of a *Cissus quadrangularis/Irvingia gabonensis* combination in the management of weight loss: a double-blind placebo-controlled study. *Lipi. Heal. Disease.* 2008;7(1):1-7.
- Nelson CA, Zhong CS, Hashemi DA, Ashchyan HJ, Brown-Joel Z, Noe MH, et al. multicenter cross-sectional study and systematic review of necrobiotic Xanthogranuloma with proposed diagnostic criteria. *JAMA derma.* 2020;156(3):270-279.
- Björkhem I. Cerebrotendinous xanthomatosis. Current opinion in lipidology. 2013;24(4):283-287.