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Case Report

The 20-Year Diagnostic Odyssey of a Milder Form of Cerebrotendinous Xanthomatosis

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Abstract

Tendinous xanthomas are usually a sign of genetic dyslipidemias and are said to be pathognomonic for familial hypercholesterolemia. However, the differential diagnosis must also include rarer forms of genetic dyslipidemias such as cerebrotendinous xanthomatosis (CTX). In this report, we present the diagnostic odyssey of a French-Canadian patient presenting with Achilles tendon xanthomas and an unusual mild to moderate hypercholesterolemia. Comprehensive biochemical and genetic investigations confirmed the diagnosis of CTX, 20 years after the onset of her first symptoms. We also describe a new variant in the *CYP27A1* gene associated with this atypical case and expand the clinical phenotype of this rare genetic condition. CTX is thought to be underdiagnosed, and early diagnosis and treatment of this disease is essential as it has been shown to greatly improve the patient's symptoms and prognosis.

Key Words: Achilles tendon xanthoma, cerebrotendinous xanthomatosis, *CYP27A1*, cholestanol, chenodeoxycholic acid

Abbreviations: CDCA, chenodeoxycholic acid; CTX, cerebrotendinous xanthomatosis; FH, familial hypercholesterolemia; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; ULN, upper limit of normal; VUS, variant of uncertain significance.

Introduction

Xanthomas are lesions caused by the accumulation of fat in macrophages in the skin or tendons (1). Xanthomas are usually a sign of disorders of lipid metabolism and dyslipidemias. Tendinous xanthomas are more commonly associated with familial hypercholesterolemia (FH) (2, 3). FH is a semidominant genetic dyslipidemia associated with elevated low-density lipoprotein cholesterol (LDL-c) and increased risk of premature cardiovascular events (3). The worldwide prevalence of the heterozygous form of FH was recently estimated to be around 1:311 (4). However, the prevalence of FH is more frequent in some populations such as in French Canadians (1:80 to 1:250) (5). Tendinous xanthomas are widely said to be pathognomonic of FH and appear usually after the third decade (3). However, other rare genetic dyslipidemias, such as sitosterolemia and cerebrotendinous xanthomatosis (CTX), can also present with xanthomas (6-8). Here, we describe the diagnostic odyssey of an adult French-Canadian patient presenting with tendon xanthomas and unusual mild to moderate hypercholesterolemia.

Case Presentation

A 40-year-old French-Canadian woman was initially referred to the Genetic Dyslipidemias Clinic of the Montreal Clinical Research Institute in 2014 (Fig. 1). She presented with a 10-year history of progressive painful swelling of the Achilles tendons with no improvement with standard care. Investigations done prior to her referral, including magnetic resonance imaging and a biopsy, confirmed the presence of right Achilles tendon xanthomas. Interestingly, she also had excision of a possible right elbow tendinous xanthoma and left eyelid xanthelasmas 15 years ago. She was otherwise doing well with no history of ophthalmological, gastrointestinal, or neurological symptoms. Her physical examination was normal, except for the presence of a left Achilles tendon xanthoma. Her family history was remarkable for early coronary artery disease in her father, who died from myocardial infarction at age 54 years. Otherwise, her family history was negative for xanthoma and hypercholesterolemia. She did not have any siblings or offspring.

Diagnostic Assessment

Because of the presence of tendinous xanthomas, a lipid profile was obtained, showing mild to moderate hypercholesterolemia with total cholesterol ranging from 5 to 7 mmol/L (194-270 mg/dL; normal reference range, 3.16-7.00 mmol/L or 122-270 mg/dL) and LDL-c from 3.5 to 4.7 mmol/L (135-182 mg/dL; normal reference range, 1.60-3.40 mmol/L or

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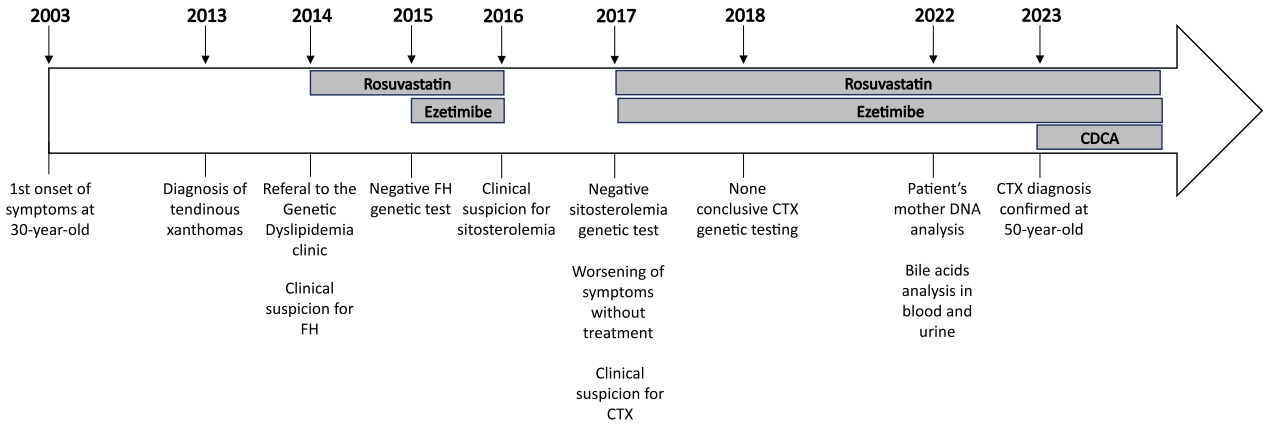

Figure 1. Diagnostic odyssey of the patient. CDCA, chenodeoxycholic acid; CTX, cerebrotendinous xanthomatosis; FH, familial hypercholesterolemia.

62-132 mg/dL) (Table 1). In light of her clinical picture, a diagnosis of FH was suspected. However, genetic investigation for common French-Canadian *LDLR* pathogenic variants associated with FH came back negative. Considering the negative genetic investigation and that LDL-c levels were only moderately elevated, other causes of xanthomas were investigated. A sterol profile was obtained, showing nonspecific elevation of 7-dehydrocholesterol (11.9 µmol/L, 23.8× upper limit of normal [ULN]; normal reference range, <0.5 µmol/L), cholestanol (23.5 µmol/L, 1.5× ULN; normal reference range, 2.5-15.4 µmol/L), lathosterol (14.6 µmol/L, 2.9× ULN; normal reference range, <5.0 µmol/L), lanosterol (1.5 µmol/L, 3.7× ULN; normal reference range, <0.4 µmol/L) (see Table 1). Based on the sterol profile, a diagnosis of sitosterolemia was also suspected in context of the mild nonspecific elevation of phytosterol levels. However, genetic investigation for sitosterolemia (*ABCG5* and *ABCG8* genes) was negative in 2017 (Laboratoire de diagnostic moléculaire, Institut de Cardiologie de Montréal). Cholestanol level was also elevated on the baseline sterol profile, and a diagnosis of CTX was therefore suspected. Sequencing of the *CYP27A1* gene (transcript NM_000784.3, genome built hg19/GRCh37) performed in 2022 identified that the patient was heterozygous for a pathogenic missense variant (c.1183C > T, p.Arg395Cys) and an intronic variant of uncertain significance (VUS; c.1017 + 5G > C) (Prevention Genetics). The c.1183C > T variant is located in the cytochrome P-450 domain and has been reported in other patients with CTX (9, 10). The c.1017 + 5G > C variant has not been reported in the literature in patients with CTX. This variant is reported in population databases, with a highest allele frequency of 0.0046% in Non-Finnish Europeans. It is located in intron 5 and within the consensus splice site of the intron. This variant is predicted to weaken the nearest canonical splice donor site on available splice prediction programs (Alamut Visual v2.11). The available evidence at that time was insufficient to determine the role of this variant in disease and a diagnosis of CTX could not be confirmed.

Further biochemical and genetic investigations were conducted to confirm the diagnosis of CTX. Genetic analysis performed in the proband's mother in early 2022 showed that she was heterozygous for the pathogenic c.1183C > T variant. The VUS was not detected in her mother, suggesting that the 2 variants identified in the proband were in trans and that she is therefore a compound heterozygous for the 2 variants. Analysis of the serum bile acid concentration performed in 2022 revealed that it was extremely low (0.32 µmol/L; Cincinnati Children's), which was highly suggestive of reduced bile acid synthesis. A urine sample was also analyzed using fast atom bombardment ionization mass spectrometry (Cincinnati Children's). The profile indicated a lack of normal primary bile acid conjugates and a significant elevation of polyhydroxylated bile alcohol glucuronides that characterize the CYP27A1 deficiency. These complementary analyses confirmed the diagnosis of CTX in this patient (see Fig. 1).

Treatment

Considering the initial possible diagnosis of FH, the patient has been treated with rosuvastatin 10 mg and ezetimibe 10 mg since 2014. This regimen of treatment significantly reduced the total cholesterol (3.5-4 mmol/L [135-155 mg/dL]) and LDL-c levels (0.9-1.9 mmol/L [35-74 mg/dL]) and was associated with normalization of the sterol profile (see Table 1). Treatment with rosuvastatin and ezetimibe significantly improved her clinical status with resolution of the painful swelling of Achilles tendons. Interestingly, the patient stopped taking the rosuvastatin and ezetimibe in September 2016 for a few months. Cessation of treatment was associated with worsening of her pain, increase in the size of the xanthomas, and elevation of the total cholesterol and LDL-c levels.

Outcome and Follow-up

On the diagnostic confirmation of CTX, treatment with chenodeoxycholic acid (CDCA) was initiated in early 2023, considering this is the gold-standard treatment for this disease. Treatment with rosuvastatin and ezetimibe was continued as it was well tolerated and initially associated with significant clinical improvement. Other than the xanthomas, the patient did not have other clinical features of CTX. She had a normal bone mineral density scan, a normal electromyography/nerve conduction study, and had a normal stress echocardiography. Although she has not yet been evaluated in neurology, the patient does not report neurologic or psychiatric symptoms and had a normal neurological examination. She is currently on the waiting list for a baseline brain magnetic resonance imaging scan.

Table 1. Treatment, lipid and sterol profile of the patient from her initial visit until confirmation of the diagnosis

Parameters	Reference range	Initial visit (Jan 2014)	May 2014	2015	2016	2017	2018	2022
Treatment	—	None	Rosuvastatin	Rosuvastatin Ezetimibe	Rosuvastatin Ezetimibe	None	Rosuvastatin Ezetimibe	Rosuvastatin Ezetimibe
Lipid profile								
Cholesterol	3.16-7.00 mM (122-270 mg/dL)	**7.14 mM (276 mg/dL)**	5.39 mM (208 mg/dL)	3.55 mM (137 mg/dL)	3.56 mM (138 mg/dL)	4.88 mM (189 mg/dL)	3.98 mM (153 mg/dL)	3.89 mM (150 mg/dL)
Triglycerides	0.49-2.82 mM (43-250 mg/dL)	1.26 mM (112 mg/dL)	1.00 mM (89 mg/dL)	1.19 mM (105 mg/dL)	1.32 mM (117 mg/dL)	1.15 mM (102 mg/dL)	1.14 mM (101 mg/dL)	0.96 mM (85 mg/dL)
HDL-c	0.80-1.81 mM (31-70 mg/dL)	**1.90 mM (74 mg/dL)**	1.71 mM (66 mg/dL)	1.64 mM (63 mg/dL)	**2.02 mM (78 mg/dL)**	**1.85 mM (72 mg/dL)**	**1.82 mM (70 mg/dL)**	1.58 mM (61 mg/dL)
LDL-c	1.60-3.40 mM (62-132 mg/dL)	**4.66 mM (180 mg/dL)**	3.22 mM (124 mg/dL)	1.37 mM (53 mg/dL)	0.94 mM (36 mg/dL)	2.51 mM (97 mg/dL)	1.64 mM (63 mg/dL)	1.87 mM (72 mg/dL)
Sterol profile								
7-Dehydrocholesterol	<0.5 µM (<20 µg/dL)	—	**11.9 µM (476 µg/dL)**	0 µM (0 µg/dL)	—	—	—	0 µM (0 µg/dL)
Cholestanol, µM	2.5-15.4 µM (100-615 µg/dL)	—	**23.5 µM (940 µg/dL)**	12 µM (480 µg/dL)	—	—	—	7.5 µM (300 µg/dL)
B-sitosterol, µM	<24 µM (<960 µg/dL)	—	10.2 µM (408 µg/dL)	4.8 µM (192 µg/dL)	—	—	—	7.5 µM (300 µg/dL)
Campesterol, µM	<24 µM (<960 µg/dL)	—	15 µM (600 µg/dL)	4.7 µM (188 µg/dL)	—	—	—	7.8 µM (312 µg/dL)
Desmosterol, µM	<6.5 µM (<260 µg/dL)	—	1.5 µM (60 µg/dL)	1.2 µM (48 µg/dL)	—	—	—	0.8 µM (32 µg/dL)
Lathosterol, µM	<5.0 µM (<200 µg/dL)	—	**14.6 µM (584 µg/dL)**	3.5 µM (140 µg/dL)	—	—	—	2.9 µM (116 µg/dL)
Lanosterol, µM	<0.4 µM (16 µg/dL)	—	**1.5 µM (60 µg/dL)**	0 µM (0 µg/dL)	—	—	—	0 µM (0 µg/dL)
24-Dihydrolanosterol	0 µM (0 µg/dL)	—	**0.7 µM (28 µg/dL)**	0 µM (0 µg/dL)	—	—	—	0 µM (0 µg/dL)

Results out of reference range are shown in bold. Values in parenthesis are conventional units.
Abbreviations: HDL-c, high-density lipoprotein cholesterol; Jan, January; LDL-c, low-density lipoprotein cholesterol; mM, mmol/L; µM, µmol/L.

Discussion

We presented the diagnostic odyssey for a French-Canadian patient with a milder form of CTX presenting with Achilles tendinous xanthomas and mild to moderate hypercholesterolemia (see Fig. 1). CTX is a rare recessive genetic disease characterized by disruption of bile acid synthesis due to inactivation of the *CYP27A1* gene (11). More than 250 cases have been described in the literature, and more than 100 different *CYP27A1* disease-causing variants have been reported worldwide in patients of different ethnic origins (12). Severity of the disease is highly variable and phenotypic variability has been described even within the same family (13). CTX may present early in life with neonatal-onset cholestasis, infantile-onset diarrhea, or childhood-onset cataract (11). Tendinous xanthomas usually appear in the second or third decade. They may sometimes present with long-standing history of tendinopathy and progressive swelling of the tendons involved, as described in our patient (12). Adult-onset progressive neurologic dysfunction can also be observed, such as dementia, psychiatric disturbances, and pyramidal or cerebellar signs and seizures. Some individuals show cognitive impairment from early infancy, whereas the majority have normal or only slightly impaired intellectual function until puberty. Dementia with slow deterioration in intellectual abilities occurs in the third decade in more than 50% of individuals (14). To date, our patient has not presented with evidence of neurological manifestations. Interestingly, nonneurologic forms of CTX have also been described, which clearly expand the phenotypic variability seen in this condition (15). Other complications include premature atherosclerosis predisposing to myocardial infarction, osteoporosis predisposing to bone fractures, and respiratory insufficiency (16).

The biochemical abnormalities that distinguish CTX from other conditions with tendinous xanthomas include high plasma and tissue cholestanol concentration, decreased CDCA, increased concentration of bile alcohols and their glycoconjugates, and increased concentrations of cholestanol and apolipoprotein B in cerebrospinal fluid (11). A sterol profile is therefore highly clinically indicated when we suspect CTX as elevated cholestanol levels are part of the key biochemical abnormalities seen in this rare genetic condition (11). In addition to the increase in cholestanol levels seen in our patient, other sterols can be elevated in CTX patients. Indeed, we observed an increase in 7-dehydrocholesterol, lathosterol, and lanosterol levels as previously described in other patients with CTX (17). CTX may also be confirmed by the identification of pathogenic variants in the *CYP27A1* gene and analysis of urine and blood bile acid profiles (11). As illustrated by our case, the identification of a VUS can increase the complexity of obtaining a clinical diagnosis. Comprehensive biochemical and genetic investigations often help determine the pathogenicity of these VUS. Clinical opinion from a medical geneticist with experience in biochemical genetics can often help in the interpretation of the genetic investigations.

The initial mild to moderate hypercholesterolemia identified in our patient has also contributed to her diagnostic odyssey. Patients with CTX usually present with normal cholesterol levels (9). Moreover, the combination of tendon xanthomas and hypercholesterolemia in a French-Canadian patient was highly suspicious for a diagnosis of FH (2, 3). However, few cases of CTX patients described in the literature also presented with mildly elevated total cholesterol and LDL-c levels (18). As illustrated by our case, CTX should therefore be considered in patients presenting with tendinous xanthomas, even in the occurrence of mild to moderate hypercholesterolemia.

Long-term treatment with CDCA has been shown to normalize cholestanol concentration and improve neurophysiologic findings in CTX patients (19). Statins alone or in combination with CDCA are also effective in decreasing cholestanol and improving clinical signs (20). In our case, statin and ezetimibe were well tolerated and associated with normalization of the sterol profile, including cholestanol levels. Although the patient had substantial clinical and biochemical improvement after treatment with statin and ezetimibe alone, CDCA was initiated after the diagnostic confirmation of CTX since it is considered the gold-standard treatment for this rare condition. However, there is no clear evidence that a milder form of CTX would clinically benefit from further treatment with CDCA. CDCA is a costly medication, and perhaps a more affordable treatment option with statin and ezetimibe would be sufficient in milder forms of CTX. Additional research is needed to determine the best treatment option for milder forms of CTX.

The prevalence of CTX has been estimated to be less than 5/100 000 worldwide, but it varies according to country and ethnic group (21). Recent studies suggest that CTX is probably underdiagnosed (22) and that improved detection strategies are needed. A clinical diagnostic algorithm for CTX has been developed and should be used to help in the diagnostic process (11). A recent pilot study has also shown a promising option of screening for CTX as part of newborn screening (23). Increased awareness of CTX is important for early diagnosis, which is important for patients as early treatment considerably slows or prevents disease progression (24).

Learning Points

- CTX may present initially with a milder phenotype, such as long-standing history of tendinopathy with progressive swelling of tendons and mild to moderate hypercholesterolemia
- CTX is characterized by a bile acid synthesis defect and accumulation of cholestanol
- Biochemical and genetic testing are complementary to confirm the diagnosis
- Treatment with CDCA may improve symptoms and prognosis
- Treatment with statin and ezetimibe may normalize the cholestanol levels in milder forms of CTX, and perhaps not all cases require treatment with CDCA

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Contributors

All authors made individual contributions to authorship. S.B., A.B., and S.P.G. were involved in the diagnosis and management of this patient. A.L. and V.P. were involved in the genetic and biochemic analysis and interpretation of the data. M.P. was involved in analysis and interpretation of the data.

S.P.G. drafted the article and all other authors revised it critically for important intellectual content and approved the final version to be submitted.

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Original data generated and analyzed for this case report are included in this published article.

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