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【 CASE REPORT 】

Prominent Tendon Xanthomas and Abdominal Aortic Aneurysm Associated with Cerebrotendinous Xanthomatosis Identified Using Whole Exome Sequencing

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Abstract:
A 63-year-old man was hospitalized due to an abdominal pulsatile mass. Computed tomography revealed a saccular type abdominal aortic aneurysm, the diameter of which was 52 mm. A physical examination revealed prominent Achilles tendon thickness and plantar xanthomas. He was born in a family of consanguineous marriage, where his parents were second cousins. He had no familial history of high low-density lipoprotein cholesterol, tendon xanthomas, or premature atherosclerosis. Whole-exome sequencing assuming recessive inheritance determined his genetic diagnosis to be cerebrotendinous xanthomatosis caused by homozygous mutations (c.410G>A or p.Arg137Gln) in the cytochrome P450 subfamily 27 A1 (*CYP27A1*) gene.

Key words: cerebrotendinous xanthomatosis, *CYP27A1*, exome sequencing, familial hypercholesterolemia, *LDLR*

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Introduction

Familial hypercholesterolemia (FH) is characterized by the clinical triad of primary hyper- low-density lipoprotein (LDL) cholesterolemia, tendon xanthomas, and premature coronary artery disease (CAD) (1) caused by genetic mutations in several genes associated with LDL metabolism, such as LDL receptor (*LDLR*), apolipoprotein B (*APOB*), and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) (2).

Recent studies have shown that FH is quite common, with an estimated frequency of approximately 1 in 200 in the general population (3-5). In addition, abdominal aortic aneurysm (AAA) has been shown to be one of the most common complications in patients with FH (6). Accordingly, when we encounter patients presenting with tendon xanthomas and AAA, we typically suspect them of having FH. However, there are other types of inherited diseases complicated by tendon xanthomas, such as autosomal recessive hypercholesterolemia (ARH), sitosterolemia, and cerebrotendinous xanthomatosis (CTX) (7-9).

We herein report a rare case of a patient with CTX born to consanguineous parents (second cousins) presenting with tendon xanthomas and AAA.

Case Report

A 63-year-old man presenting with prominent Achilles tendon thickness and plantar xanthomas (Fig. 1A-C) was referred to our hospital due to an abdominal pulsatile mass. Computed tomography revealed the existence of a saccular type AAA, the diameter of which was 52 mm (Fig. 1D). He had a history of hypertension for 5 years and a smoking habit (10 cigarettes/day). Coronary angiography revealed mild to moderate coronary atherosclerotic lesions (Fig. 1E and F).

He was initially suspected of having FH based on his physical findings as well as the presence of AAA with a modestly elevated LDL cholesterol level (166 mg/dL). He was born to consanguineous parents (second cousins). He had no familial history of high LDL cholesterol, tendon xanthomas, or premature atherosclerosis.

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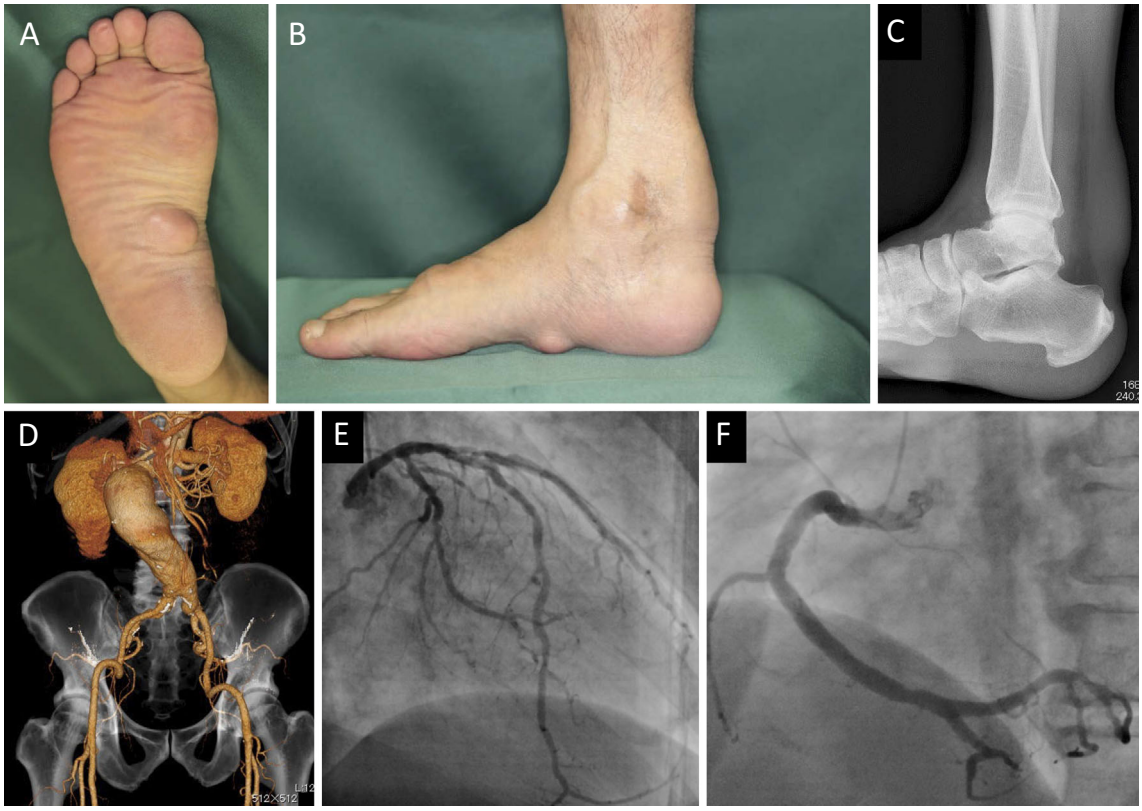

Figure 1. **Achilles tendon thickness, plantar xanthomas, and abdominal aortic aneurysm. A: Planter xanthoma (Right). B: Achilles tendon thickness and plantar xanthoma (Right). C: X-ray of the Achilles tendon (Right). D: Three-dimensional reconstructed computed tomography image of abdominal aortic aneurysm. E: Coronary angiogram (Left). F: Coronary angiogram (Right).**

Recessive inherited disease was speculated at this point, so we investigated his genetic background using whole-exome sequencing, assuming a recessive form of inheritance. The mean depth was 99.9× per base across the whole exome. The percentage of on-target reads was 84.6%. Also, the coverage rate of target coding lesions (10×) was 99.0%. Bioinformatics analyses and segregation pattern matching followed by exome sequencing were performed for the patient to identify causative variants. The number of aligned variants in the patient that passed the standard quality control was 142,508. Of those, 15,335 were missense, nonsense, splice site, and frameshift variants. After removing "common" variants [MAF >1% using the Asian cohort in the Exome Aggregation Consortium (ExAC) project] (10), 3,042 variants were detected. Subsequently, filtering against the segregation pattern assuming the recessive form of inheritance with the use of an *in silico* annotation prediction tool (scaled C-score >20) reduced the candidate variants to homozygous mutations in the cytochrome P450 subfamily 27 A1 (*CYP27A1*) gene (c.410G>A or p.Arg137Gln, Fig. 2A). This mutation was confirmed by Sanger sequencing (Fig. 2B and C), and it has previously been reported to cause such a condition in other patients (9).

Accordingly, an increased serum level of cholestanol was found (5.2 μg/mL, reference range 1.62-3.08). The patient did not show any neuropathy, although T2-weighted and fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging showed periventricular white matter. Other classical phenotypes of CTX, such as juvenile cataract, chronic diarrhea, and intellectual disability, were not found. Endovascular repair (EVAR) was successfully performed for the treatment of his saccular type AAA. Atorvastatin 10 mg was used to reduce his LDL cholesterol, although chenodeoxycholic acid was not used due to the lack of neuropathy.

Discussion

We herein report a rare case of a patient with CTX born to consanguineous parents, where his parents were second cousins, presenting with tendon xanthomas and AAA. To our knowledge, this is the first case report of CTX exhibiting AAA.

A number of symptoms of CTX have been reported, including neuropathy, tendon xanthomas, neonatal jaundice, skeletal abnormalities, atherosclerosis, cardiovascular disease, chronic diarrhea, and hypothyroidism (11). Neuropathy and tendon xanthomas are considered the most frequently observed symptoms, although the clinical symptoms are quite heterogeneous in this disease. In the present patient, who was born to consanguineous parents, prominent Achilles tendon thickness and plantar xanthomas were identified as the typical features of CTX. No case presenting with

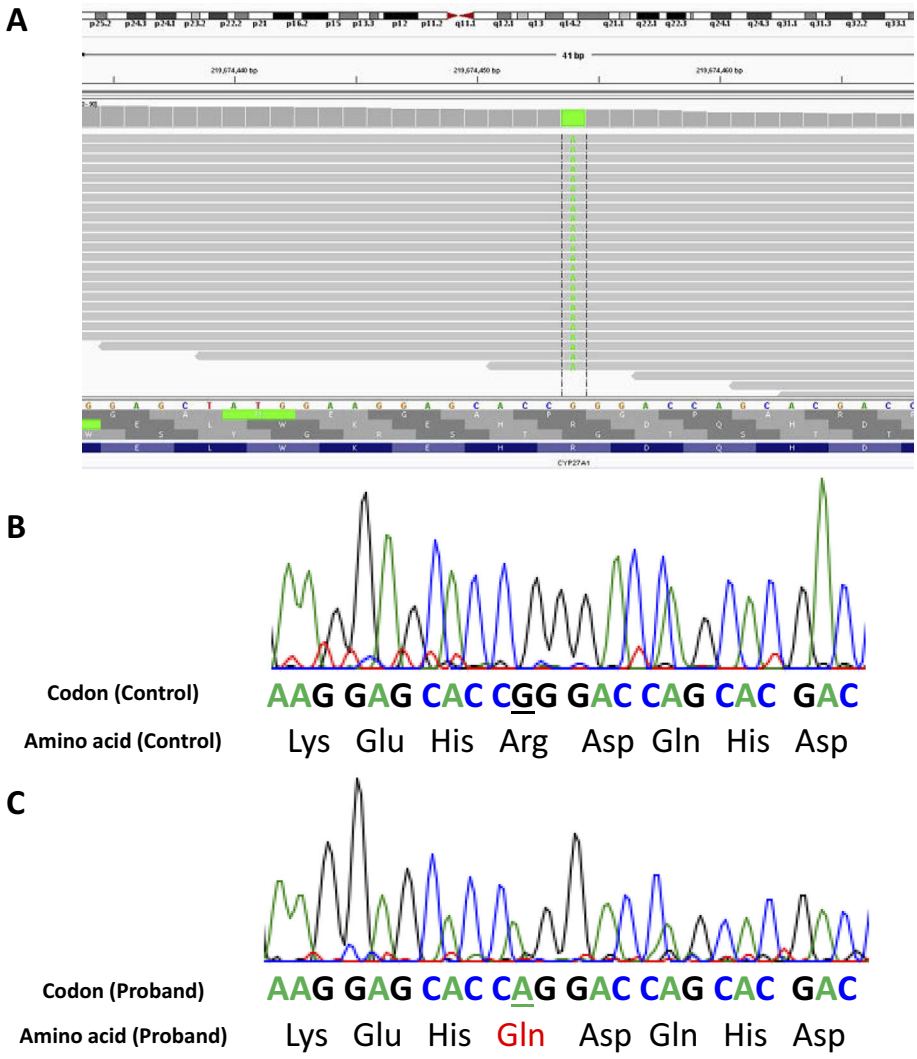

Figure 2. Genetic mutations in *CYP27A1* gene. A: Integrative genomics viewer (IGV). The alignments of the *CYP27A1* locus for the proband, focusing on the mutation site, are illustrated. The gray bars indicate that the sequence is the same as the reference allele. The green bar indicates the alternate allele at the mutation site. B: Genetic sequence of control. C: Genetic sequence of proband.

AAA as a concurrent disease of CTX has yet been reported, although AAA may have coincidentally coexisted with CTX in this case, since there were no obvious specific findings of AAA. The combination of tendon xanthomas and AAA is often observed in patients with FH, which has recently been shown to be a relatively common inherited disorder. However, other recessive forms of inherited diseases, such as ARH, sitosterolemia, and CTX, should be considered in cases like our own, based on the presence of plantar xanthomas as well as the family history. In addition, a comprehensive genetic analysis using whole-exome sequencing was quite useful for determining the genetic diagnosis in our patient. In this way, we were able to rule out the possibility of other recessive as well as dominant forms of diseases, such as ARH, sitosterolemia, and FH.

Our patient did not exhibit several symptoms known to be associated with CTX, such as cataract, diarrhea, and neuropathy. It has been reported that the clinical symptoms are quite heterogeneous in this disease, and phenotypes have even been shown to differ in identical twins (12). Accordingly, it is not yet clear if there are any associations between phenotypes and genotypes in this rare disease.

In conclusion, we herein report a rare case of a patient with CTX born to consanguineous parents (second cousins) and presenting with tendon xanthomas and AAA. The physical findings, family history, and comprehensive genetic analyses led to his accurate diagnosis, which might lead to a good prognosis.

The authors state that they have no Conflict of Interest (COI).

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