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Characterization of coronary atherosclerotic plaques in a homozygous familial hypercholesterolemia visualized by optical coherence tomography

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Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder, which resulted in severe elevations in low-density lipoprotein cholesterol (LDL-C) and a markedly increased risk of early-onset coronary disease.[1] It is most frequently caused by loss-of-function mutations in genes affecting the LDL receptor, which clears LDL particles from plasma.[2] FH accelerates atherosclerotic cardiovascular disease, especially coronary heart disease, with clinical manifestations often occurring after one to four decades of life.[3] The untreated patients with homozygous familial hypercholesterolemia (HoFH), which is caused by mutations in both alleles of the gene encoding the LDL receptor, developed overt atherosclerosis before the age of 20 years and generally do not survive past 30 years. Intravascular optical coherence tomography (OCT) has been proposed as a high-resolution imaging method for characterization of coronary atherosclerotic plaques.[4] Its utility in the evaluation of plaque composition can provide insights into the pathology of coronary arteries abnormalities.[5] However, little information about coronary atherosclerotic plaques of patients with FH has been presented.

A 29-year-old man presented with severe chest pain after performing physical activities for six months. His symptoms remained stable until three months before his hospitalization in the cardiovascular department in January 2018. At the age of 20 years, multiple xanthomas of about 1.0–3.5 cm in diameter had been found in his elbows and hip (Figure 1). Fasting measurement of lipid profiles revealed that his total cholesterol concentration was 22.31 mmol/L and LDL-C concentration was 12.25 mmol/L. Furthermore, his first-degree relatives had a history of elevated blood lipids and

Figure 1.   Multiple xanthomas in the elbows, about 1.0–3.5 cm in diameter.

sudden cardiac death. According to the Dutch Lipid Clinic Criteria, he was diagnosed with FH. Primary lifestyle modifications were established at that point, and lipid-lowering drugs were administered.

A long-term follow-up and LDL receptor gene mutation analysis were conducted to explore the relationship between the type of gene mutation and a variety of clinical phenotypes. The nucleotide sequence analysis revealed a homozygous W469X mutation in exon 10 of the LDL receptor gene. This mutation is a G1470A substitution that introduces the change from tryptophan to a premature stop codon and restricts protein synthesis after exon 10 (Figure 2). With reference to the United Kingdom FH mutation database (www.ucl.ac.uk/fh.), Leren, *et al*.[6] reported the presence of this mutation in the Norwegian population in 1997. The homozygous mutation of this locus can reduce the function of LDL receptor to < 2% of normal function, leading to

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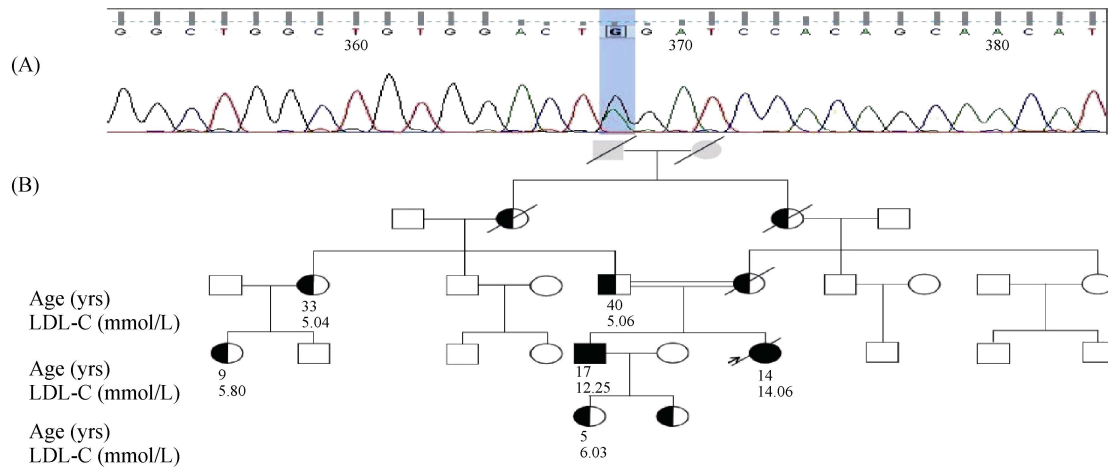13611078067@163.com (MENG K)

Figure 2. Sequence with mutation and pedigree of his family members. (A): The sequence of 1470 G >A nonsense mutation in exon 10 resulting in W469X; (B): the proband was indicated with an arrow. Squares indicate men; circles, women; deceased persons were indicated by a diagonal line drawn through the symbol. LDL-C: low-density lipoprotein cholesterol.

uncontrollable hyperlipidemia, premature coronary heart disease, and severe clinical manifestations.[7] The patient's sister was the homozygous proband carrying the same gene mutation. She died of severe aortic valve stenosis with insufficiency and severe heart failure at the age of 14 years. In addition, ten of patient's family members had also been diagnosed with FH by genetic testing and were all heterozygotes carrying the same gene mutation (Figure 2).

The patient began taking lipid-lowering drugs in 2009, when he was 20 years old. The patient was administered atorvastatin and ezetimibe. However, the treatment was discontinued for two years to avoid affecting his fertility. Considering the limited efficacy of lipid-lowering drugs, the

doses of his lipid-lowering drugs were continually increased, but his lipid level was not satisfactorily controlled. Eventually, the combined therapeutic strategy of high-dose statins, ezetimibe, and probucol was administered in 2014. His therapeutic management remained thereafter. Nine years later, a follow-up examination revealed that the patient's total cholesterol level had fallen by 3.5% and that his LDL level was 1.58 times higher than it had been in 2009 (Figure 3).

Echocardiography before hospitalization showed that the left ventricle ejection fraction was 68.9%. Severe aortic valve calcification was found but the function was not significantly abnormal (Figure 4). Coronary computed tomography angiography showed multiple mixed plaques
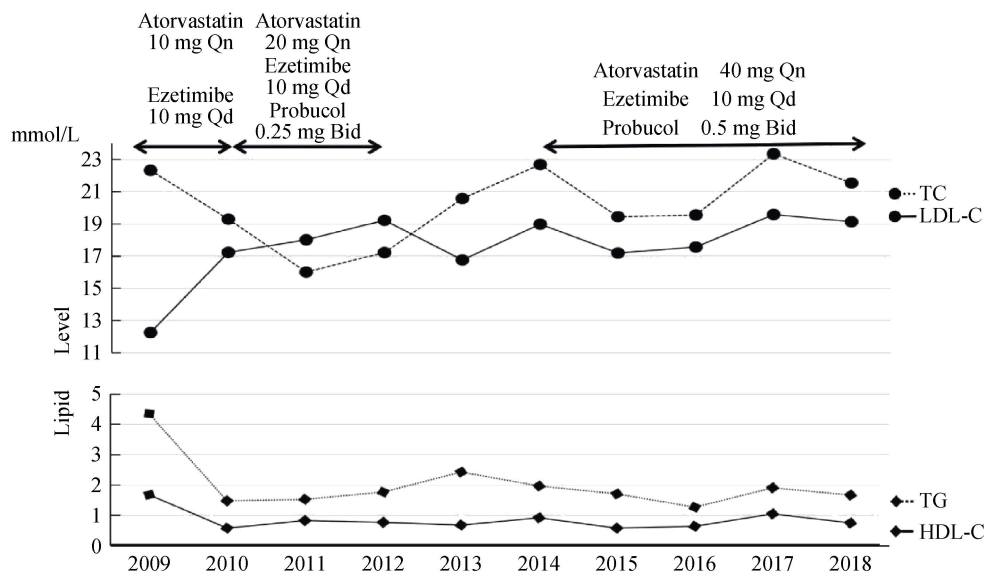

Figure 3. The results of lipid levels among nine years follow-up. HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride.
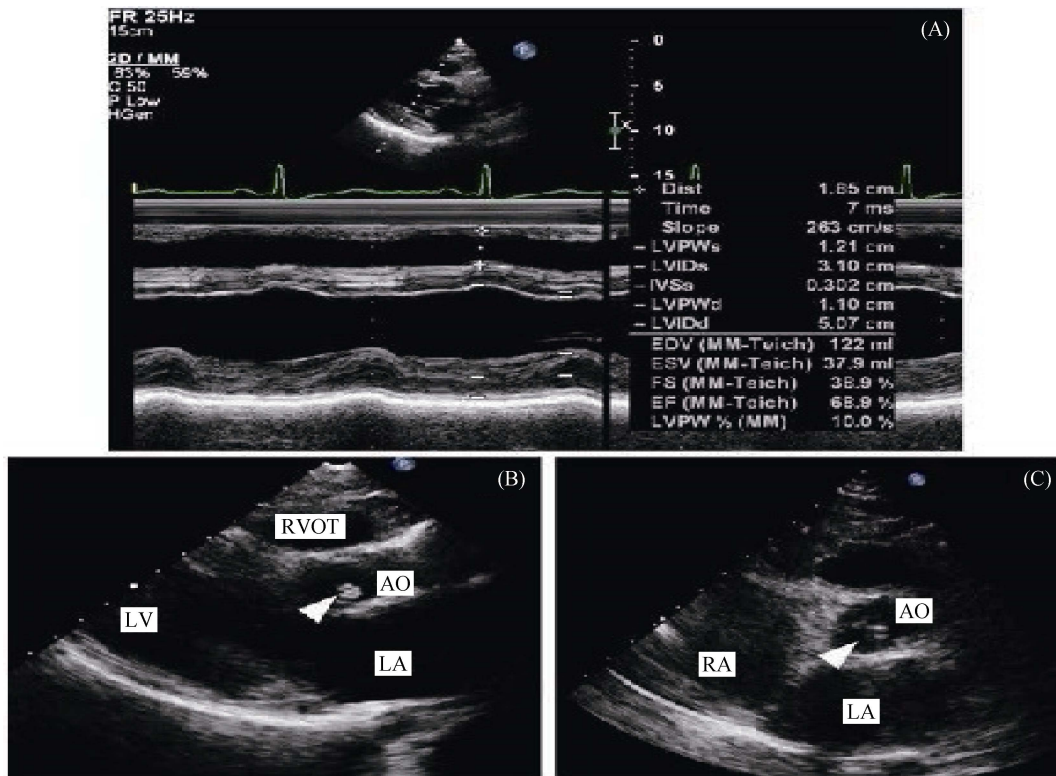
Figure 4. The result of echocardiography. (A): Left ventricle ejection fraction was 68.9% with no wall motion abnormalities; (B): severe aortic valve calcification was found in non-coronary cusp (white arrow head); (C): severe aortic valve calcification was found in Left coronary cusp (white arrow head).
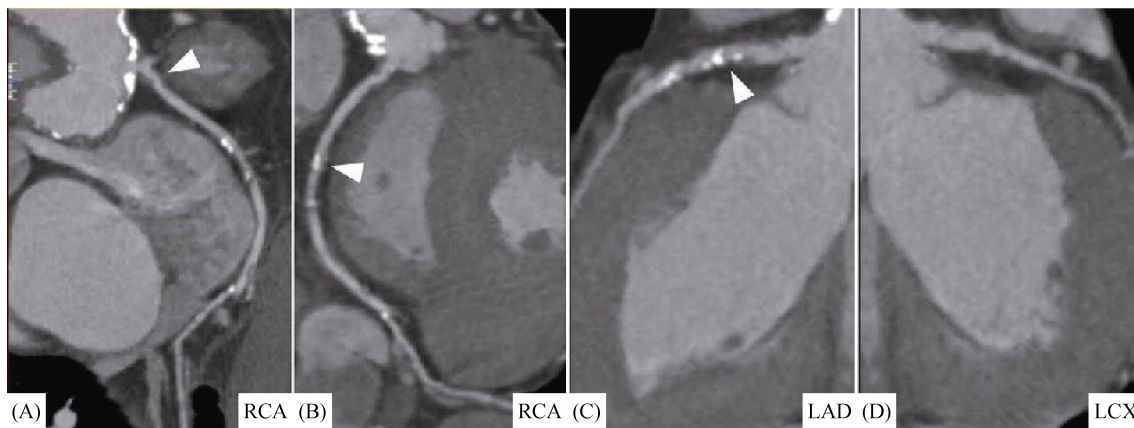

Figure 5. The results of CTCA. (A): Multiple calcified plaques were noted in the aortic root and a non-calcified plaque was noted in the origin of RCA (white arrow head); (B): multiple mixed plaques and calcified plaque were noted all across RCA. The calcified plaque located in the middle of the RCA resulted in severe stenosis (white arrow head); (C): the main segment of the left coronary is normal. Multiple calcified plaques and non-calcified plaques were noted in the proximal segment of LAD, which resulted in severe stenosis (white arrowhead); (D): multiple non-calcified plaques were noted in the proximal. CTCA: computed tomography coronary angiography; LAD: left anterior descending; LCX: left circumflex artery; RCA: right coronary artery.

and calcified plaques in the three coronary arteries, resulting in severe stenosis. The distal of left circumflex artery (LCX) was totally occluded (Figure 5). It mainly showed the calcification plaque, which would hinder the composition of

coronary plaques and affect the precision of severity assessment.

After exclusion of valvular and supra-valvular aortic diseases, the invasive angiography and coronary revascu-

larization were recommended for the unstable angina resulting from a reduced oxygen supply. Coronary angiography showed severe triple-vessel disease (Figure 6). OCT was performed immediately after coronary angiography (Figure 7). The images of the LCX showed an intact three-layer structure of the vessel wall and the intimal was
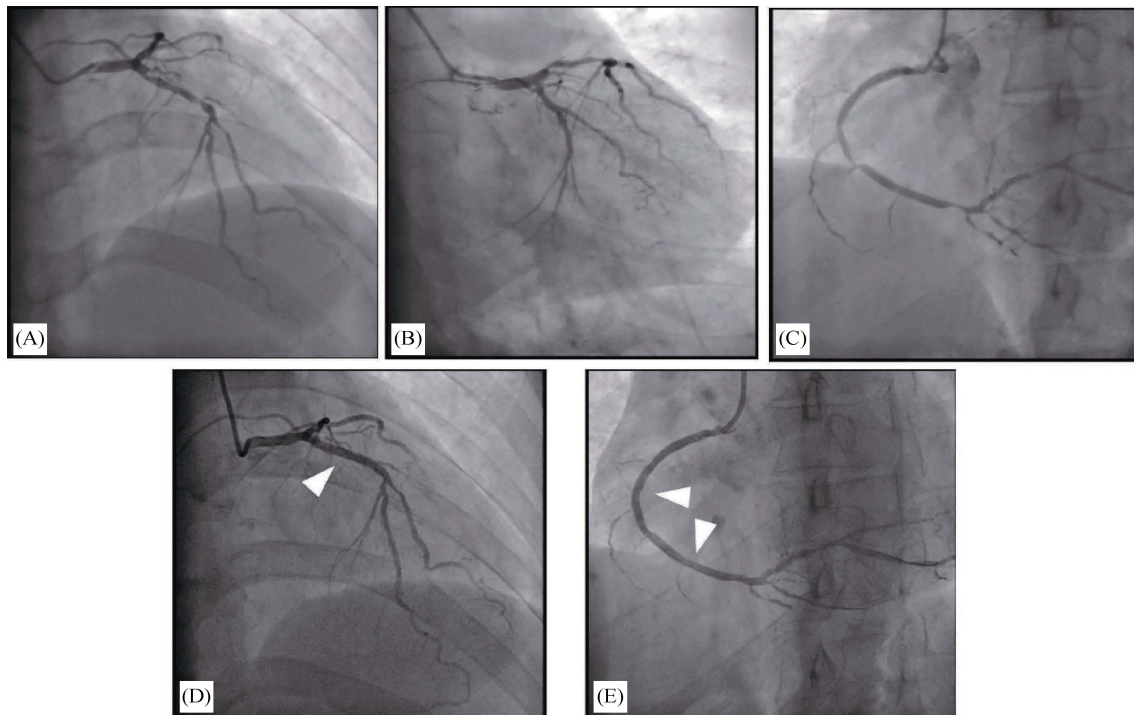

Figure 6. The results of CAG. (A): Diffuse stenosis in proximal and middle LAD, with the uttermost of 90% stenosis; (B): the distal of LCX was total occlusion; (C): diffuse stenosis all across RCA, with 90% stenosis in middle and distal RCA; (D): a stent was implanted in the culprit lesion of LAD (arrow head); (E): two stents were implanted in the RCA (arrow head). LAD: left anterior descending; RCA: right coronary artery.
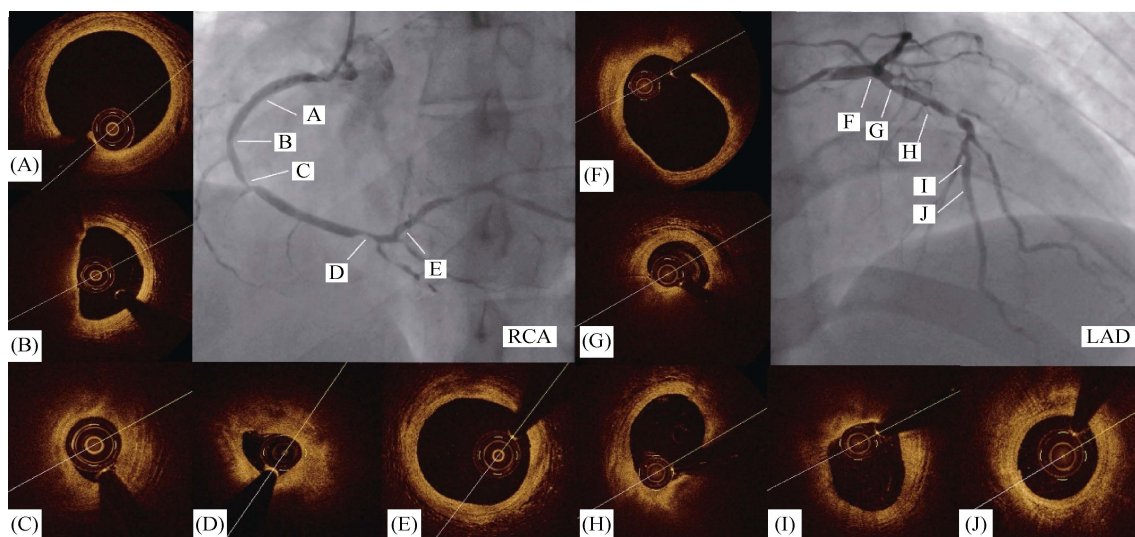

Figure 7. OCT finding of RCA and LAD. (A): An intact three-layer structure of the vessel wall; (B): a thin-cap fibroatheroma was located in the middle segment of RCA. The least fibrous cap thickness was 40 μm and the lipid core occupied two quadrants; (C): fibrous hyperplasia mixed with calcification in the narrowest part of RCA; (D): severe fibrous hyperplasia; (E): an intact three-layer structure of the vessel wall; (F): lipid plaque accompanied with inflammatory cell infiltration; (G): a large lipid plaque in the narrowest site of LAD; (H): mixed plaque accompanied with inflammatory cell infiltration; (I): calcified plaque; (J): normal vessel. LAD: left anterior descending; OCT: optical coherence tomography; RCA: right coronary artery.

generally thickened in the remaining segment. The minimum lumen area (MLA) of the LCX was 3.74 mm². Multiple lipid-rich plaques accompanied by inflammatory cell infiltration leading to lumen irregularity were noted in the right coronary artery (RCA). The fibrous hyperplasia was most severe at the narrowest site of the RCA. Fibrous plaques were found mixed with calcification. A thin-cap fibroatheroma (TCFA) was located in the middle segment of RCA, 13 mm proximal to the narrowest part. The thinnest part of the fibrous cap of the thin-cap fibroatheroma was 40 μm, and the lipid core occupied two quadrants. A fibrous plaque mixed with a large lipid core was located in the narrowest part of the proximal left anterior descending (LAD), and the MLA was 1.88 mm².

According to result of coronary angiography and OCT images, the MLA indicated that the LAD and RCA were the culprit vessels. Percutaneous coronary intervention was performed to treat the culprit lesions located in LAD and RCA. Measurement of the normal lumen diameter was provided useful information for choosing the stent size and model. Considering the severe fibrous hyperplasia in the RCA, a cutting balloon was applied to dilated stenotic coronary artery before the stent implantation. Drug-eluting stents were implanted in the RCA and LAD to cover the culprit lesion and re-angiography revealed that the blood supply had improved. OCT was performed after the implantation, and the stent malposition was found. High-pressure balloons were applied until good the stents adherence was obtained.

The patient was discharged from the hospital three days later, and was prescribed aspirin and ticagrelor along with lipid-lowering drugs were. He didn't complain of severe chest pain or chest tightness and regained the ability to perform mild to moderate labor activities when he returned to outpatient clinic at three and six months.

In the present case, the patient was diagnosed and treated with high dose of lipid-lowering drugs in a timely manner. However, the efficacy of lipid-lowering drugs is not obvious. This patient's severe aortic valve calcification, which had evolved through lipid accumulation, was very similar to the histopathological changes noted in non-FH populations with age-related aortic calcification. In addition, the early onset and severe coronary artery disease in this patient indicated that the progression of atherosclerosis had greatly accelerated under the conditions of uncontrolled hypercholesterolemia.

To our knowledge, this is the first report to present OCT images of a patient with HoFH. As the highest resolution intravascular imaging technique, OCT showed the microstructural characteristics of coronary plaques. The high plasma LDL-C concentrations contributed to the initiation and the progression of atherosclerosis. Lipid-rich plaques have been considered to represent the early stage of atherosclerosis, which is characterized by an accumulation of lipid in the intimal layer of the artery. Inflammatory cell infiltration and instability of arteriosclerosis plaques occurred in this patient, which resulted in the expression of a proteolytic enzyme that weakens the fibrous cap and ultimately promotes plaque disruption.[8] The composition of the culprit lesion was fibrous hyperplasia mixed with calcification. The patient was in the advanced stage of atherosclerosis, which might have been the result of repeated plaque rupture and healing responses.

The utility of OCT not only clarified the structural characteristics of plaques, but also provided evidences for optimization of surgical strategies, thereby increasing the success rate of surgery and reducing complications. Sudden adverse coronary outcomes are usually caused by vulnerable plaques and that the severity of stenosis is of less importance than the composition and the size of these plaques. The presence of lipid-rich plaques in the non-culprit regions of the target vessel may also increase the risk of revascularization for recurrent ischemia in the future.[9] Care must be taken with the stents and non-culprit regions during long-term management.

Various diagnostic imaging methods, including OCT, showed the characterization of coronary atherosclerotic plaques in this patient with HoFH. We found that multiple types of coronary atherosclerotic plaques coexist in patients with HoFH, suggesting that the revascularization and clinical management in the homozygous group are more complicated. The utility of OCT has certain guiding significance for percutaneous coronary interventions and long-term management.

Acknowledgment

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