

Early onset and persistent progression of coronary artery disease of unknown etiology in a 30-year-old man

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The prevalence of coronary artery disease (CAD) in young patients is difficult to establish as most cases remain subclinical.¹ The etiology and pathogenesis of atherosclerosis is complex. Its progression is particularly rapid when environmental factors coexist with genetic ones. An early and accurate identification of individuals at increased risk of CAD is critical for effective prevention and intervention, such as statin treatment.² Nevertheless, young smokers with hypertension and high fasting glucose levels have a higher probability of unsatisfactory results of lipid-lowering therapy.³

A 29-year-old man with risk factors of hypertension and smoking was diagnosed with

a non-ST-segment elevation myocardial infarction in March 2011. He also suffered from paroxysmal atrial fibrillation and preexcitation syndrome. A family history of cardiovascular diseases and diabetes was negative. The predicted 4-year mortality assessed with the SYNTAX II score was 6.4% for percutaneous coronary intervention and 0.7% for coronary artery bypass grafting (coronary angiography is presented in [FIGURE 1A](#) and [1B](#)). The patient thus underwent emergent coronary artery bypass surgery with 3 arterial grafts, using the left and right internal mammary arteries (LIMA and RIMA) and the radial artery (RA): RIMA to the LAD, LIMA to the first

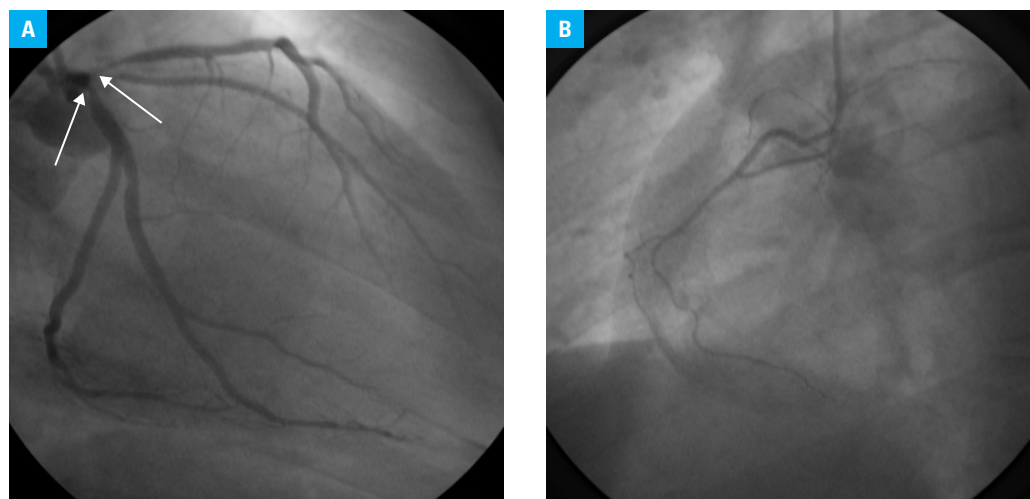


FIGURE 1 Preoperative and follow-up imaging of the coronary arteries (arrows); **A** – coronary angiography showing left artery dominance with significant ostial stenosis of the left anterior descending (LAD) artery (99%), first marginal branch (99%), and circumflex artery (80%); **B** – coronary angiography showing the right coronary artery with no atherosclerotic lesions

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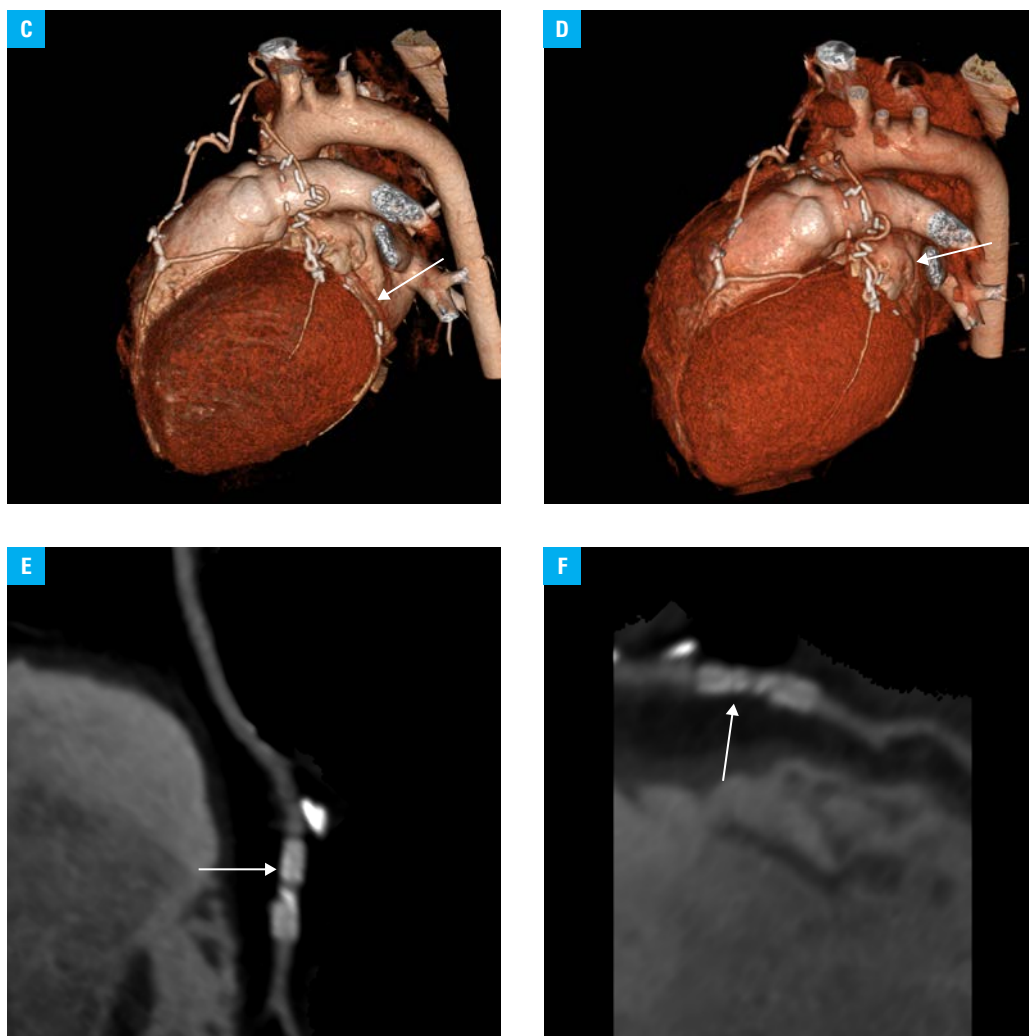
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FIGURE 1

C, D – computed tomography showing the occluded radial artery to the second marginal branch graft (arrows); **E** – computed tomography showing restenosis in a drug-eluting stent (DES) implanted into the right internal mammary artery to the LAD graft (arrow); **F** – computed tomography showing a DES implanted into the circumflex artery (arrow), with no signs of restenosis



marginal branch, and RA to the second marginal branch. Optimal medical therapy, which included dual antiplatelet therapy, β -blocker, and statin, was introduced and cessation of smoking was advised. The first episode of recurrent angina occurred in October 2011, and critical stenosis of the circumflex artery and the RIMA-LAD graft was treated by a drug-eluting stent (DES). During follow-up, dyspnea, fatigue, and stable angina were observed. Computed tomographic angiography was performed to confirm the progression of CAD. It revealed an occluded RA-MgII graft due to disseminated vasculopathic lesions (FIGURE 1C and 1D) and a restenosis in the DES implanted into the RIMA-LAD graft (FIGURE 1E and 1F). Despite smoking cessation and an intensified treatment with aspirin (75 mg/d orally), clopidogrel (75 mg/d orally), metoprolol (50 mg orally every morning, 25 mg orally every evening), and rosuvastatin (20 mg/d orally), the results of lipid-lowering therapy remained unsatisfactory (total cholesterol, 3.7 mmol/l; low-density lipoprotein cholesterol, 2.01 mmol/l; high-density lipoprotein cholesterol, 1.11 mmol/l; and triglycerides, 2.34 mmol/l).

The patient was tested for hereditary and acquired hypercoagulable disorders, with negative results. Moreover, lipoprotein metabolism

disorders were excluded with hyperlipidemia gene testing and statin myopathy variants.

Familial hypercholesterolemia, which results from a heterozygous pathogenic variant in one of the several genes (APOB, LDLR, and PCSK9), is a relatively common disorder with a prevalence of 1:200 to 1:250 in the general population.⁴ The panel targeted protein-coding exons and exon-intron gene boundaries, including mutations located outside these coding regions. All analyzed nucleotides were covered with a median depth of 585x. The test was suitable for identifying single nucleotide variants and insertions and deletions; however, it did not identify large copy-number variations due to limitations of the next-generation sequencing technique. Large deletions or duplications represent up to 10% of the pathogenic variants in the *LDLR* gene,⁵ which could explain the negative result. Therefore, we suspect that the patient's disease was most likely caused by CNVs or genetic mutations not yet associated with the phenotype. Nevertheless, the patient remains symptomatic and the etiology of persistent CAD progression remains unknown.

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