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CASE REPORT
Coronary heart disease

Histopathological findings of late-phase restenosis after directional coronary atherectomy with drug-coated balloon angioplasty: a case report

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Background Drug-coated balloon angioplasty after directional coronary atherectomy (DCA) allows for a stentless strategy providing good short-term outcomes; however, late-phase restenosis and its mechanism remain unclear. Moreover, histopathological evaluation for late-phase restenosis post-drug-coated balloon angioplasty after DCA has never been reported.

Case summary We report the first case of late-phase restenosis post-drug-coated balloon angioplasty after DCA, wherein tissue analysis using intravascular coronary imaging and histopathology suggested neovascularization in newly developed neointimal proliferation. A 52-year-old man with a history of dyslipidaemia presented with exertional angina pectoris. He underwent percutaneous coronary intervention (PCI) with drug-coated balloon angioplasty after DCA for the proximal left anterior descending artery. Although coronary angiography after nine months revealed no restenosis, he experienced recurrent chest discomfort after 25 months. Coronary angiography confirmed late-phase restenosis, and intravascular ultrasound showed progressively developed neointima above the underlying residual plaque. Optical coherence tomography suggested developing neovascularization within the neointima. Stentless PCI with drug-coated balloon angioplasty after DCA was re-performed, and collected restenotic sample. The histopathological evaluation confirmed less-cellular neointimal proliferation with rich neovascularization and concomitant diffuse vascular endothelial growth factor (VEGF) expression.

Discussion Late-phase restenosis post-drug-coated balloon angioplasty after DCA comprised less-cellular neointima, suggesting inhibition of cell proliferation by drug-coated balloon efficacy. However, diffuse VEGF expression and concomitant rich neovascularization with haemorrhage and inflammation might indicate neointimal proliferation. Further large-scale investigations of the restenotic mechanism should be performed to avoid long-term target vascular failure after drug-coated balloon angioplasty post-DCA.

Keywords Case report • Directional coronary atherectomy • Drug-coated balloon • Late-phase restenosis • Neovascularization

ESC Curriculum 2.1 Imaging modalities • 3.1 Coronary artery disease • 8.6 Secondary prevention

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Learning points

- The restenotic tissue of late-phase restenosis post-DCA/DCB angioplasty was mainly composed of fibrous tissue with poor cellularity and neovascularization with localized inflammation and intraplaque haemorrhage.
- Neovascularization with the expression of vascular endothelial growth factor might be associated with neointimal proliferation in late-phase restenosis post-DCA/DCB.

Introduction

Percutaneous coronary intervention (PCI) with the latest thin-strut drug-eluting stents (DESs) can provide good cardiovascular outcomes; however, in-stent restenosis (ISR) remains an unresolved issue.[1] The mechanisms of ISR are based on several factors, including stent condition (stent under expansion and stent fracture), neointimal hyperplasia due to sensitive reactions to stent metal, polymer, and drugs or delayed healing, and development of neoatherosclerosis. Therefore, the evaluation of ISR aetiologies using intravascular imaging before intervention is recommended.[1–3] Recently, a novel strategy with stentless PCI (avoiding metal or polymer) using drug-coated balloon (DCB) angioplasty has been reported. Moreover, optimal plaque preparation before DCB angioplasty is recommended for achieving good cardiovascular outcomes.[4]

Directional coronary atherectomy (DCA) is a procedure for lesion preparation by reducing plaque volume in large vessels.[5] Although DCA monotherapy was insufficient due to the high frequency of target lesion revascularization required, DCA followed by DCB angioplasty (DCA/DCB) is reportedly effective owing to the drug efficacy of DCB.[6] However, long-term cardiovascular outcomes post-DCA/DCB remain unreported, and the histopathology of late-phase restenosis post-DCA/DCB has not been studied.

We herein report the first case of late-phase restenosis post-DCA/DCB, in which the restenosis mechanism was evaluated by intravascular coronary imaging and histopathology.

Timeline

Index PCI	The patient was diagnosed with effort angina pectoris of the proximal left anterior descending artery stenosis, where PCI with DCA followed by DCB angioplasty was performed.
Nine months later	Coronary angiogram (CAG) revealed no significant stenosis in the treated lesion.
25 months later -Second PCI	The patient had experienced worsening of exertional chest discomfort. CAG confirmed a newly developed focal restenosis, defined as late-phase restenosis post-DCA/DCB. PCI with DCA followed by DCB was re-performed in accordance with the patient's wishes.
One year after the second PCI	No further cardiovascular event was observed.

Case presentation

A 52-year-old non-smoking Japanese male patient with no history of chronic inflammatory disease or coronary risk factors, except dyslipidaemia, presented with exertional angina pectoris. The patient had taken aspirin (100 mg/day) and bisoprolol (5 mg/day) for one month prior to admission. Coronary angiography (CAG) showed significant stenosis in the proximal left anterior descending artery, where a PCI with DCA/DCB (SeQuent Please, paclitaxel-coated balloon, B. Braun, Melsungen, Germany) angioplasty had been performed as per patient preference (not to have a stent implanted) (Index PCI images: *Figure 1A–D*). A 3-month dual antiplatelet therapy (DAPT) with aspirin 100 mg/day and clopidogrel 75 mg/day, and subsequent aspirin monotherapy had been initiated after the index PCI as per Japanese guidelines.[7] The patient had also taken vonoprazan (10 mg/day) for chronic gastritis and rosuvastatin (10 mg/day, high-dose as per Japanese guidelines) for dyslipidaemia. As per institutional policy and patient agreement, a routine follow-up CAG, nine months after the index PCI, was performed to investigate the presence of DCA-related aneurysmal formation, which showed no restenosis (*Figure 1E–F*).

The patient experienced exertional chest discomfort 25 months after the index PCI, and presented to our emergency department because he was developing angina symptoms at rest. Physical examination showed no abnormalities, and he was haemodynamically stable (blood pressure: 116/72 mmHg; heart rate: 70 bpm). Cardiac examinations (electrocardiography and transthoracic echocardiography) revealed no abnormalities, but laboratory test results revealed slightly elevated troponin-T levels (0.094 ng/mL, normal range: ≤0.014 ng/mL) (*Table 1*). A semi-emergency CAG confirmed a newly developed focal restenosis, defined as late-phase restenosis post-DCA/DCB (*Figure 1G*, see Supplementary material online, Video 1). The restenotic lesion characteristics were investigated using intravascular ultrasound (IVUS) and optical coherence tomography (OCT). IVUS showed a low-echoic area above the underlying residual plaque, suggesting progressively developed neointima, compared with earlier serial IVUS images (*Figure 1H*, see Supplementary material online, Video 2). Subsequent OCT findings confirmed that the restenotic lesion comprised a clearly bordered, low-signal area, with several luminal structures extending from the tunica adventitia of the distally located plaque, suggestive of neointima with neovascularization (*Figure 2A*, see Supplementary material online, Video 3). After discussion with the patient, who still wished not to have a stent implanted, we decided to perform DCA followed by DCB angioplasty (with the same drug, owing to regional limitations), as before. Therefore, we re-performed DCA using Atherocut™ L (NIPRO, Osaka, Japan) and collected a sample from the restenotic lesion. Although angiographic findings at both the procedures were in line

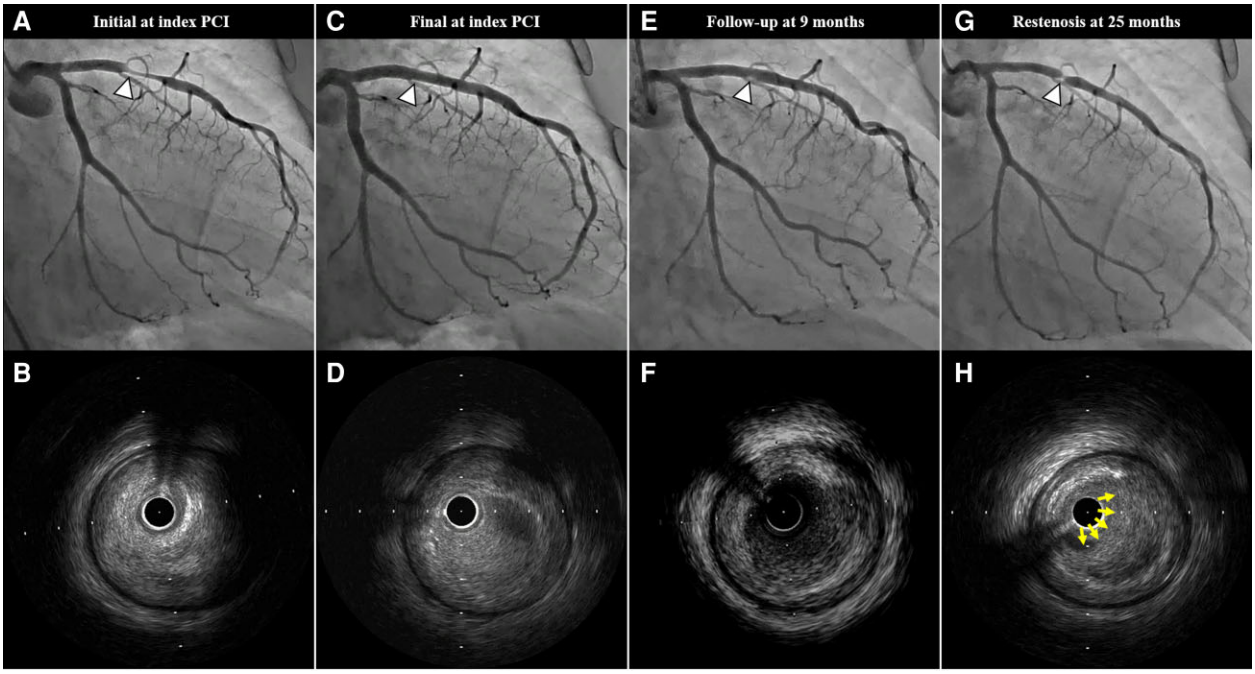

Figure 1 Serial coronary angiogram and intravascular ultrasound images. Coronary angiogram and intravascular ultrasonogram (*A*, *B*) at pre-index percutaneous coronary intervention, (*C*, *D*) at post-index percutaneous coronary intervention, (*E*, *F*) at 9-month follow-up, and (*G*, *H*) at late-phase restenosis (25 months). Arrowhead indicates the restenosis site. Yellow arrows indicate neointima above the underlying residual plaque.

with the recommendations for DCB angioplasty (residual diameter stenosis <30%, without major coronary dissection), the residual plaque volume at the second PCI was decreased to a residual percentage plaque area of 38% (minimum lumen area of 11.4 mm^2), less than that of 48% (minimum lumen area of 9.0 mm^2) at the index PCI (*Figure 2B*).[8] Histopathological findings revealed that the neointima was mainly composed of fibrous tissue with poor cellularity, with CD34-positive capillaries and surrounding intense CD68-positive cell and glycophorin-A staining (*Figure 3*). These findings suggest that neovascularization with inflammation and intraplaque haemorrhage may be associated with neointimal proliferation post-DCA/DCB. After the second PCI, prasugrel 3.75 mg/day (Japanese recommended dose) was initiated in addition to aspirin, as a component of DAPT, and 3-month DAPT was administered as per Japanese guidelines.[7] The rosuvastatin dosage was increased to 20 mg/day (highest dose as per Japanese guidelines) to strictly control dyslipidaemia and suppress local atherosclerotic inflammation. We also investigated apolipoproteins and glycaemic disorders as potential coronary artery disease risks. A 75 g oral glucose tolerance test and continuous glucose monitoring system revealed impaired glucose tolerance (*Table 1*, see Supplementary material online, *Figure S1*). Additional nutritional and exercise therapy were initiated to improve the glycaemic status. The patient was discharged from the hospital two days after the second PCI. No further cardiovascular event was observed for 1 year after the procedure.

Discussion

DCA prevents the slow flow phenomenon and side-branch occlusion, owing to plaque shift and carina shift, by reducing vulnerable plaque volume; however, DCA monotherapy reportedly has poor cardiovascular outcomes with frequent restenosis.[5] This is mainly caused by cell proliferation within the fibrous tissue, as observed in bare-metal stent implantation.[9,10] Recently, DCB angioplasty has been increasingly performed for various situations, such as ISR, de novo small vessel disease, and acute myocardial infarction.[4] Several studies show that DCA/DCB angioplasty could be an effective strategy to achieve stentless PCI because DCA/DCB offers the combination of plaque debulking and suppression of neointimal proliferation, thereby leading to good short-term outcomes.[6] Further investigation comparing the efficacy of DCB angioplasty and PCI with DES implantation in large vessels is warranted; long-term outcomes after DCA/DCB angioplasty are also yet to be investigated. To the best of our knowledge, late-phase restenosis after DCA/DCB angioplasty has not been formerly reported. This report is the pioneer to demonstrate a unique case of late-phase restenosis post-DCA/DCB, precisely evaluated based on intracoronary imaging and histopathological findings. Here, restenosis was caused by less-cellular neointimal proliferation with neovascularization from underlying residual plaque, leading to local inflammation, expressed as macrophage accumulation and intraplaque haemorrhage.

The potential causes of early restenosis post-DCA/DCB include inappropriate delivery of anti-proliferative drugs to target vessel walls because of lumen ovality post-DCA and geographical miss. However, the present restenosis occurred not in the early phase but in the late phase, and the neointimal tissue consisted of less-cellular fibrous tissue; suggesting the efficacy of paclitaxel (the component of DCB drug). Moreover, the neointimal tissue consisted of rich neovascularization. Vasa vasorum and neovascularization

Table 1 Laboratory results at the time of late-phase restenosis

Variables	Results	Normal reference range
Creatinine, (mg/dL)	0.81	0.53–1.02
eGFR, (mL/min/1.73 m^2)	77.8	>60
Troponin-T, (ng/mL)	0.094	<0.014
Total cholesterol, (mg/dL)	150	125–220
LDL-cholesterol, (mg/dL)	73	<100
HDL-cholesterol, (mg/dL)	56	>40
Triglyceride, (mg/dL)	85	45–150
Apolipoproteins		
Apolipoprotein-A1, (mg/dL)	139	119–155
Apolipoprotein-A2, (mg/dL)	31.3	25.9–35.7
Apolipoprotein-B, (mg/dL)	65	73–109
Apolipoprotein-E, (mg/dL)	2.1	2.7–4.3
RLP-cholesterol, (mg/dL)	3.3	<7.5
EPA/AA ratio	0.28	0.11–0.5
EPA, (μg/mL)	51	17–68
AA, (μg/mL)	179	113–166
HbA1c (%)	6.0	<6.5
75-g OGTT		
Fasting blood glucose, (mg/dL)	99	70–110
0.5-h blood glucose, (mg/dL)	188	—
1-h blood glucose, (mg/dL)	232	—
2-h blood glucose, (mg/dL)	160	—
Fasting IRI, (μU/mL)	3.4	2.1–19
0.5-h IRI, (μU/mL)	18.3	—
1-h IRI, (μU/mL)	42.1	—
2-h IRI, (μU/mL)	57.2	—

75-g OGTT = 75-g oral glucose tolerance test; AA = arachidonic acid; eGFR = estimated glomerular filtration rate; EPA = eicosapentaenoic acid; HbA1c = glycated haemoglobin; IRI = immunoreactive insulin; RLP = remnant like particle; — = there are no reference data.

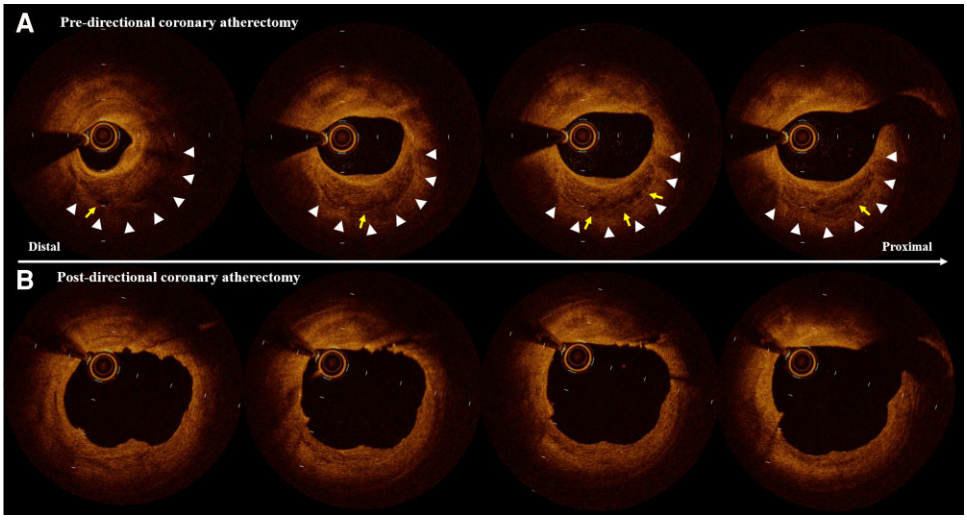

Figure 2 Optical coherence tomography. Optimal coherence tomography of (*A*) pre- directional coronary atherectomy, and (*B*) post-directional coronary atherectomy. Low-signal area and luminal structures suggest neointima (arrowheads) with neovascularization (yellow arrows).

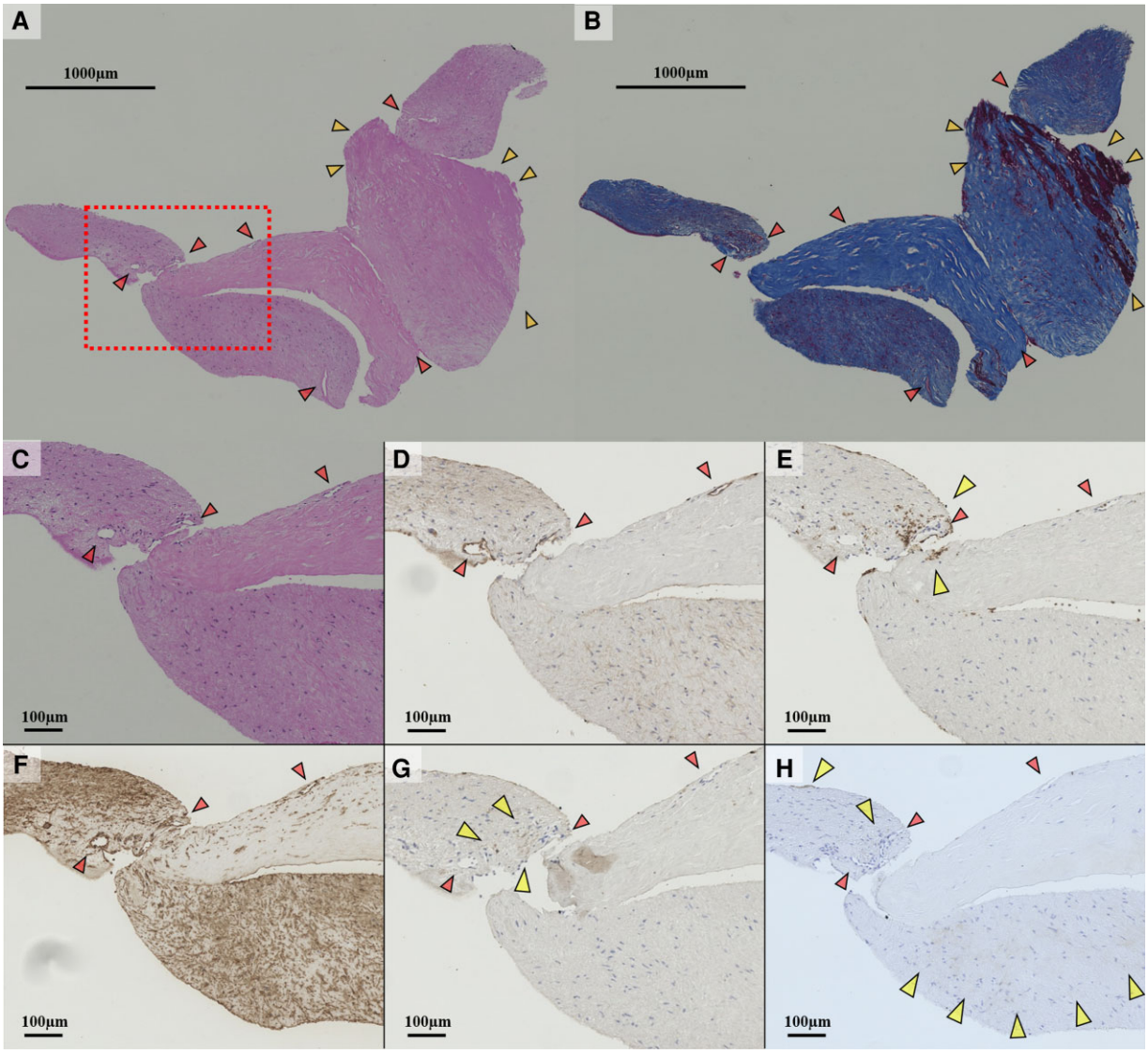

Figure 3 Histopathological findings. Histopathological findings of neointimal tissue obtained during directional coronary atherectomy: (*A*) haematoxylin-eosin staining and (*B*) Masson's trichrome staining showed that the restenotic tissue was mainly composed of fibrous tissue with poor cellularity and contained several neovascularizations (red arrowheads) and an organized thrombus (yellow arrowheads). High-power magnification images (red dotted box in *Figure 3A*) of (*C*) haematoxylin-eosin staining, (*D*) immunostaining for CD34, (*E*) glycophorin-A staining (yellow arrowheads suggesting haemorrhage), (*F*) alpha-smooth muscle actin staining, (*G*) immunostaining for CD68 (yellow arrowheads suggesting local inflammation), and (*H*) vascular endothelial growth factor staining (yellow arrowheads). Red arrowheads indicate neointimal neovascularization.

are strongly associated with inflammation and intraplaque haemorrhage, and play a pivotal role in atherosclerosis progression.[11] Neovascularization has a potential correlation with the development of neoatherosclerosis, as observed in late-phase restenosis post-DES implantation, and even in late-phase restenosis post-scaffold absorption.[12,13] Moreover, in this case, vascular endothelial growth factor (VEGF) was diffusely expressed in the neointimal tissue (*Figure 3H*). VEGFs are closely associated with angiogenesis (neovascularization) in coronary artery disease, which have several beneficial and harmful effects on atherosclerosis: although VEGFs in the heart are known to be protective for cardiomyocytes against ischaemia by promoting neovascularization, VEGFs in plaques prevent the repair of an endothelial lesion that can induce atherogenesis and promote monocyte adhesion, trans-endothelial migration, and activation, thus leading to vulnerable atherosclerosis.[14] A recent report using animal models showed that attenuation of neovascularization by targeting VEGF receptor resulted in reduced neoatherosclerosis.[15] Based on our histopathological findings of rich neovascularization and its relationship with neoatherosclerosis, we speculate that conventional managements including DCB angioplasty might be insufficient to suppress such neointimal proliferation, leading to long-term adverse events. Further investigations are warranted to study whether local suppressive therapy for excessive VEGF expression can reduce neovascularization and improve cardiovascular outcomes post-PCI.

Lead author biography

Hiroyuki Yamamoto received an MD at Kobe University, Japan, in 2010 and completed a PhD in the Kobe University Graduate School of Medicine, Japan, in 2019. He specializes in coronary artery disease, percutaneous coronary intervention with directional coronary atherectomy and rotational/orbital atherectomy procedures, and transcatheter intervention for structural heart diseases, including mitral regurgitation, atrial septal defects, and patent foramen ovale.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

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Slide sets: A fully edited slide set detailing these cases and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission of the case report including images and associated text has been obtained from the patient in line with the COPE guidelines.

Conflict of interest: None declared.

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Ethical information: This study was approved by the appropriate ethics review board of our institution (IRB approval number: R02-28) and conducted in accordance with the Helsinki Declaration.

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