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Predominant microvessel proliferation in coronary stent restenotic tissue in patients with diabetes: Insights from optical coherence tomography image analysis

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ABSTRACT

Background: Coronary optical coherence tomography (OCT) enables virtual depiction of histological findings of in-stent restenotic tissue. The aim of this study was to investigate the microvessel proliferation within in-stent restenotic tissue and the influence of diabetes mellitus (DM).

Methods: We examined 54 in-stent restenotic coronary artery lesions (stenotic area > 50%) from 50 consecutive patients including 28 with DM (56%) and 9 insulin-treated DM patients (18%); who underwent coronary time-domain OCT imaging with automatic pull back (1 mm/s, 20 frames/s). Microvessels were defined as low-signal cavities with a diameter of 50–150 microns and a trajectory parallel to the lumen recognized on 3 consecutive cross-sectional OCT image frames. The microvessel index was calculated as the number of frames with microvessel/total number of frames × 100. Patients were stratified into 3 groups: 1) without microvessels, 2) with a low (< median value) microvessel index, 3) with a high microvessel index.

Results: Microvessels were detected in 566 frames (3.1%) from 26 lesions (48%) in 24 patients (48%). A greater incidence of DM and higher serum glucose levels were observed in the high microvessel index group (DM: 42% vs 58% vs 83%, $p = 0.049$; serum glucose level: 118.2 ± 44.6 vs 122.6 ± 31.0 vs 172.8 ± 63.1 mg/dL, $p = 0.03$ between low and high microvessel index group, $p = 0.005$ between no microvessel and high microvessel index group).

Conclusions: Microvessel formation may be a unique pathophysiological factor of in-stent restenoses in patients with DM.

1. Introduction

In spite of the lower incidence of in-stent restenosis associated with drug-eluting stents (DES) compared with either conventional balloon angioplasty or bare-metal stents, this adverse event remains a major clinical problem in the DES era [1]. In particular, patients with diabetes mellitus (DM) have an increased risk of restenosis even after DES implantation [2]. In a large scale pivotal study, the rate of target lesion failure particularly among patients with DM did not reveal significant difference between the groups that received everolimus-eluting and paclitaxel-eluting stents, whereas the overall data showed that everolimus-eluting stents were superior [3]. Some drug-eluting technology may be particularly effective for diabetic coronary artery disease. It is possible that patients with DM have a unique restenosis pathophysiology [4,5] that should be explored for the development of future interventional strategies.

Currently, coronary optical coherence tomography (OCT) enables identification of subtle differences in coronary artery disease that may not be detected by conventional intravascular ultrasonography [6]. Previous investigations in humans have shown the utility of OCT for *in vivo* assessment of individual stent strut coverage and in-stent restenotic tissue [7–16]. OCT is especially useful for evaluating malapposition and insufficient neointimal coverage after DES implantation, which may lead to late stent thrombosis [17,18], a major concern in contemporary percutaneous coronary intervention (PCI) procedures.

Microvessel formation is a subtle change that can be detected by coronary OCT [19,20]. Microvessels often appear following vascular injury and promote neointimal hyperplasia [21]. Marked microvessel formation is observed and is considered a pivotal factor in patients with multiorgan complications of DM [22–24].

The aim of this study was to investigate the microvessel proliferation within in-stent restenotic tissue and the influence of DM.

2. Materials and Methods

We retrospectively examined 54 in-stent restenotic coronary artery lesions (stenotic area > 50%) obtained from 50 consecutive Japanese patients who underwent coronary OCT electively. The study was approved by our institutional ethics committee,

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and the necessity for informed consent was waived according to Japanese standard ethical policy established by the Ministry of Health, Labor and Welfare. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology. We do not have any disclosure regarding this investigation. The observers were blinded to the patient demographics during analysis of the quantitative images.

The OCT system used in the study consisted of a computer, a display monitor, an interface unit (M3x Cardiology Imaging System, LightLab Imaging Inc.), and a 0.019-inch imaging wire (ImageWire, LightLab Imaging Inc.). Images were acquired during an automatic pull back at 1 mm/s and 20 frames/s. The patients were administered 100 IU/kg of heparin before the procedure. The OCT image system was introduced into the target coronary segment through a 6-Fr or 7-Fr guiding catheter. A dedicated occlusion balloon catheter (Helios, Avantec Vascular Corp., Sunnyvale, CA, USA) was inflated at 0.5–0.7 atm and positioned proximal to the target segment. During inflation, the distal vessel was filled with heparinized (10 IU/mL) Ringer's lactate solution to remove blood and assure optimal image quality.

Semiautomated measurements of stenotic areas were carried out on OCT images showing in-stent restenosis (stenotic area > 50%) [25]. The lumen contour was first delineated automatically. The stent strut position was then identified manually on the center of the stent strut as a bright "blooming" appearance [26] and the contour of the stent area was delineated by connecting the stent struts. In cases where the appearance of the stent strut was blunt or unclear, the stent contour was delineated using the closest frame with an identifiable strut. The inner stent strut was applied to the overlapped stenting region to determine the contour of the stent area. The contours of the lumen and the stent were delineated using cubic spline interpolation. Stenotic area was calculated by the formula: (stent area − lumen area)/stent area × 100 (%). Minimal lumen area and stenotic area were evaluated for each lesion. All the analyzed frames were divided into three subsegments: in-stent stenosis, in-stent non-stenosis, and stent edge (5 mm proximally and 5 mm distally). The presence of microvessels in these 3 subsegments was recorded. The stent edge region included 5 mm within the border of the in-stent region (10 mm in total). The border of the in-stent and stent edge regions was defined as the existence of a stent strut in one-half of the vessel's circumference.

Microvessels were defined as low-signal cavities with a diameter of 50–150 microns with a trajectory parallel to the lumen that were observed on 3 consecutive cross-sectional OCT images. Small side branches running perpendicular from the adventitia to the lumen were distinguished from microvessels by reviewing consecutive frames. Fig. 1 shows a representative case. A microvessel index was calculated using the following formula: number of frames with microvessels/total frame number. The assessment of microvessel distribution included only lesions with microvessels, with the microvessel index being calculated for each subsegment. Analysis was performed by 2 independent observers, while a third observer provided the final decision only when there was an inconsistency between the 2 observers.

Clinical demographics were reviewed and blood samples were obtained at the time of admission for cardiac catheterization and the OCT procedure. DM was diagnosed according to the guidelines of the Japanese Diabetes Society. However, HbA_1c was adjusted to the National Glycohemoglobin Standardization Program value by adding 0.4% to the value measured at our institution, on the basis of the Japanese Diabetes Society guidelines.

2.1. Statistical analysis

Continuous values were expressed as mean and standard deviation and compared using unpaired t-test and ANOVA test. Categorical variables were expressed as frequencies and comparisons performed according to Chi-square and Fisher's exact tests. Interobserver variability was determined using the kappa value. A p value of <0.05 was considered to be statistically significant, and all reported p values are 2-sided. Multiple logistic regression analysis was performed to identify independent predictors of microvessel proliferation. The statistical analyses were performed using JMP software (SAS Institute, Cary, NC, USA).

3. Results

Table 1 shows the demographics of the patients. The study cohort had a higher incidence of males (90%), hemodialysis (26%), and smoking history (64%). DM was diagnosed in 28 patients (56%). Of these, 9 (18%) were treated with insulin and 15 (30%) with oral hypoglycemic agents. Average (mean ± standard deviation) HbA_1c level was 6.0% ± 1.1% in the entire study cohort and 6.6% ± 1.0% in patients with DM. High HbA_1c levels were observed predominantly in patients with insulin-treated DM (Diet, 6.5% ± 0.6% vs. oral agents, 6.1% ± 0.7% vs. insulin, 7.6% ± 1.1%; p = 0.0007 oral agents vs insulin). Table 2 summarizes the demographics of the lesions. Lesions were relatively frequent in the left circumflex coronary artery (n = 11; 20%). Seventeen (31%) lesions developed restenosis 12 months after PCI, although no significant stenosis was observed in mid-term follow-up angiograms. A total of 17,981 OCT image frames were evaluated. Microvessels were detected in 566 frames (3.1%) from 26 lesions (48%) in 24 patients (48%). Interobserver variability (kappa values) for adjudication of microvessel was 0.88 for restenotic tissue structure. Table 1 shows the differences in patient demographics between groups with and without microvessels. non-insulin–treated DM showed a significant relationship with microvessels (non-DM, 29% vs non-insulin treated DM, 58% vs insulin treated DM, 13%; p = 0.02). Serum glucose level was higher in the patients with microvessels (118.2 ± 44.6 mg/dL vs 147.7 ± 55.0 mg/dL, p = 0.04). There was no significant difference in HbA1c between the two groups. Presence of microvessels was approximately 2-fold higher (61% vs 32%, p = 0.04) with a 27% increase of HbA1c level (6.6 ± 1.0% vs 5.2 ± 0.4%, p < 0.001) in DM patients. Among all categorical variables related to the patient demographics (male, age ≧65 years, hemodialysis, DM, hypertension, dyslipidemia, smoking, body mass index ≧25 kg/m^2), DM was independently associated with the presence of microvessels (Table 3). Patients with non-insulin treated DM showed the greatest presence of microvessels according to lesion level (non-DM, 1.40% ± 0.90% vs DM with diet and/or oral agents, 5.23% ± 0.96% vs insulin treated DM , 2.33% ± 1.46%; p = 0.014 diet and/or oral agents vs insulin). Table 2 shows the differences in lesion demographics between groups with and without microvessels. There was no significant difference in OCT measurement data between the 2 groups. There were no significant differences in the prevalence of microvessels in the lesions of the groups with drug-eluting vs bare

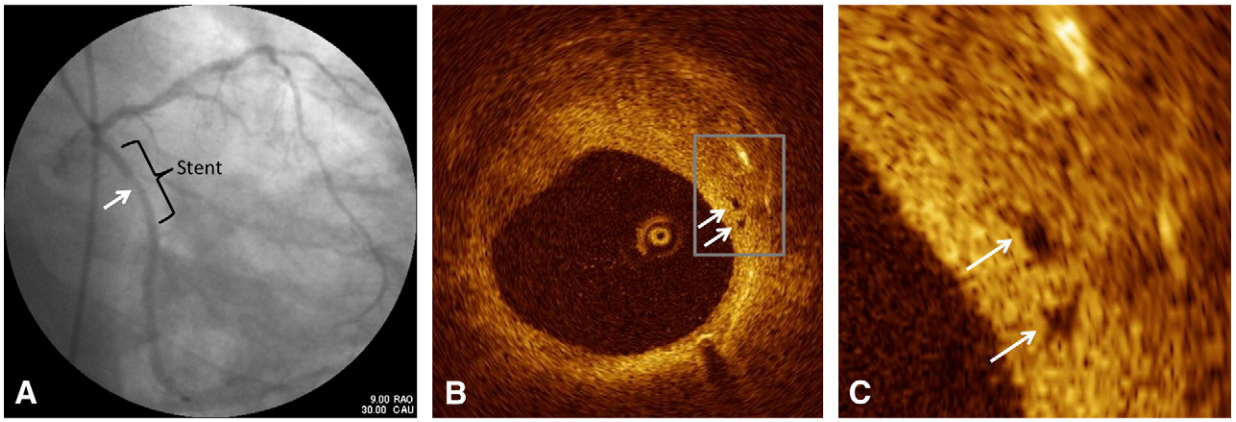

Fig. 1. Representative case. A 54-year-old man underwent DES implantation (3.0 × 18-mm sirolimus-eluting stent) in the proximal left circumflex coronary artery for stable coronary ischemia. He had diabetes mellitus and routinely underwent hemodialysis for diabetic nephropathy. He complained of angina pectoris 4 years later, and late in-stent restenosis (discrete) was observed (A, white arrow). The optical coherence tomography images showed microvessels in 22 of 23 frames, with a stenotic area over 50% (B and C, white arrow).