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EDITORIAL COMMENT

Neoatherosclerosis

Detection and Clinical Consequences*

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It is well known that vulnerable plaque is characterized by a thin cap with underlying soft atheromatous material that may rupture causing acute myocardial infarction. What is less well known is how to identify vulnerable plaque and how it should be treated to reduce major adverse cardiac events. The color yellow, observed at the time of atherectomy, autopsy, with near-infrared spectroscopy, or with angioscopy, has been associated with extensive atheroma that may be more likely to cause cardiac events. Moreover, angioscopy is helpful in visualizing soft, ulcerated plaques as well as distinguishing between red and white thrombus.

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In this issue of *JACC: Cardiovascular Interventions*, angioscopy was used to determine in-stent neoatherosclerosis after drug-eluting stents (DES). In a series of 360 patients with angioscopy 1 year after DES, Ueda et al. (1) found that the presence of yellow plaque was predictive of major adverse cardiac events at long-term follow-up. Yellow "neoatherosclerosis" was independently predictive of late events (hazard ratio: 5.38), along with small stent size and absence of statin (only 74% of patients were on a statin at 1 year). Unexpectedly, neointimal coverage and presence of thrombus were not predictive of late events. One may think of yellow atheroma as a vulnerable plaque, especially when associated with more thrombus as in this study; however, it was not associated with risk of unstable angina or myocardial infarction. Target lesion revascularization was largely responsible for the increased cardiac event rate. Although neoatherosclerosis has been implicated in late restenosis in other studies, these investigators did not report baseline atheromatous burden at the time of stenting, or minimal lumen diameter at 1 year (both are strong predictors of restenosis). Thus, one does not know whether the yellow color was due to "neo" or pre-existing atherosclerosis, and how much of the restenosis was due to neointimal proliferation already present at 1 year.

What is the difference between neoatherosclerosis and progression of existing disease? How can we detect it? Can we prevent it? Why does it matter? The term *neoatherosclerosis* was coined from imaging, atherectomy, and autopsy studies performed after DES. As opposed to natural atherosclerosis, which may take several decades to develop, autopsy and directional atherectomy specimens obtained from inside DES indicate that additional cholesterol deposition may occur within a few months, and neoatherosclerosis may be present in the majority of lesions with DES restenosis (2,3). We were not surprised by this, knowing that denuded endothelium in the presence of high circulating cholesterol was used as a mechanism to rapidly induce atherosclerosis in animals. What is surprising is that early neoatherosclerosis does not occur with bare-metal stents (BMS); smooth muscle cell proliferation is the primary mechanism of BMS restenosis. Serial angiographic and ultrasound studies have shown that BMS have early neointimal thickening, but after 1 year, there may be improvement in lumen size. Unfortunately, BMS may have late (>4 years) development of neoatherosclerosis contributing to late stent failure (4). Conversely, DES have less restenosis within the first several months but later have more loss of lumen area and late target vessel revascularization (TVR). This "late catch-up," attributed to neoatherosclerosis, was originally thought to be due to inflammation from

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early DES polymers. However, neoatherosclerosis has also been observed in second-generation stents with thinner struts and different polymers.

When we first heard about neoatherosclerosis, we were not concerned. After all, it remains indisputable that DES have sustained benefit at reducing TVR, and second-generation DES may actually have lower rates of stent thrombosis (ST) than BMS. Although neoatherosclerosis has been implicated in both late restenosis and late ST, these events occur far more frequently with paclitaxel- compared with sirolimus-eluting stents, despite TAXUS stents having *less* neoatherosclerosis (3). The mechanism of late ST is multifactorial, and it remains uncertain whether neoatherosclerosis contributes to late ST. There may be more compelling evidence of its contribution to late progression of disease requiring TVR (5–7). Moreover, when TVR is performed in the setting of neoatherosclerosis, the risk of periprocedural myocardial infarction may be increased (8).

Thus, detection of neoatherosclerosis may be useful to stratify lesions that may have higher complication rates with percutaneous coronary interventions. It appears that optical coherence tomography is most commonly used to detect neoatherosclerosis, consisting of signal-poor regions with diffuse borders, which may also have thin caps, neointimal rupture, and thrombi. One study found that 68% of DES with restenosis had neoatherosclerosis by optical coherence tomography (8). This study also found that near-infrared spectroscopy was able to detect smaller pools of lipid within the stented vessel. Although intravascular ultrasound virtual histology may be helpful with imaging de novo vulnerable plaques, its ability to accurately analyze in-stent tissue may be limited as a result of stent artifact.

It remains uncertain whether and how one can prevent neoatherosclerosis of DES. Use of drug-eluting balloons or bioabsorbable scaffolds will likely have a different healing response to injury, thus may not result in neoatherosclerosis. The use of high-dose statins before percutaneous coronary interventions has been shown to reduce periprocedural myocardial infarction and renal failure, but no clear reduction in restenosis of BMS (possibly due to lack of early neoatherosclerosis in BMS). Interestingly, the potential role of statins is raised by studies showing regression of non-stented disease with high-dose statins (9). Moreover, progression of disease in non-target lesion areas (presumably due to natural atherosclerosis) has been associated with in-stent neoatherosclerosis (6). Anti-inflammatory medications such as prednisone, celecoxib, and colchicine have shown some effect in small randomized trials of BMS. Likewise, small trials, mostly in BMS patients, have suggested that medications such as cilostazol, pioglitazone, or rosiglitazone may reduce restenosis. Whether these medications may affect neoatherosclerosis of DES is unknown.

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