·临床病理讨论·

Clinicopathological Conference (the 53rd case)

Application of optical coherence tomography in diagnosis of thrombosis secondary to in-stent plaque rupture after bare metal stent implantation in one case

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Case presentation

A 67 years old female patient, complaining of "paroxysmal chest pain for more than half month", was admitted to Second Affiliated Hospital of Harbin Medical University on April 14, 2010. Half month ago, the patient suffered paroxysmal precordial squeezing pain with unclear incentive. The pain radiated outwards the shoulders and lasted for 5 minutes, which was relieved by taking nitroglycerin. The patient had been treated with antiplatelet, anticoagulant and lipid-lowering, but the symptom still attacked intermittently. The patient was admitted to our hospital for further diagnosis and treatment.

Past medical history: The patient had a 7-year history of hypertension with the highest blood pressure at 200/120mmHg, and the systolic pressure and diastolic pressure were controlled within range from 120mmHg to 130mmHg and 90mmHg to 95 mmHg respectively by taking oral Nifedipine Controlled-Release Tablets. The patient also had a 7-year history of hyperlipidemia and took oral atorvastatin calcium tablets daily, but the plasma lipid level did not meet the target level. The patient has undergone percutaneous coronary intervention (PCI) twice. A bare-metal stent (BMS) was implanted in the middle of right coronary artery (RCA) seven years ago, and a drug-eluting stent (DES) in the distal portion of RCA six months ago. She denied a history of diabetes.

Physical examination: Body temperature was 36.7℃, pulse rate 62 beats/min, respiratory rate 18 times/min, and blood pressure 160/100 mmHg. The patient had clear consciousness. On chest auscultation, pulmonary sounds were clear and symmetrical, neither dry nor moist rale was heard. Her cardiac rhythm was regular at 62 beats/min. No pathological murmur was heard in each valve area. Physical examination revealed soft abdomen, no tenderness or rebound tenderness. Liver and spleen were not enlarged. The patient presented with no edema on lower limbs.

Examination after admission: The plasma lipid level test: TG5.43 mmol/L, TC3.97 mmol/L, HDL-C 1.45 mmol/L, LDL-C 3.92 mmol/L; fasting serum glucose 7.32 mmol/L; 2h postprandial plasma glucose 13.8mmol/L; glycosylated hemoglobin 6.9%; hs-CRP 11.3 mg/L; electrocardiogram showed ST-segment depression in leads Ⅱ, Ⅲ, avF.

Treatment: On the second day after admission, the patient successfully underwent coronary angiography (CAG) and PCI. The CAG showed 60% stenosis in the proximal of the left descending artery (LAD), 80% stenosis in the ostium of the first diagonal branch, 30% stenosis in the proximal of the left circumflex coronary artery (LCX), 80% stenosis in the BMS located in the middle of RCA, and no stenosis in the DES. Optical coherence tomography(OCT) revealed ruptured lipid-rich plaque and thrombosis inside BMS(Figure 1). One DES was successfully implanted in the BMS which was located in the middle of RCA, and then the symptom disappeared. The patient is currently in the follow-up with stable postoperative condition.

Clinicopathologic discussions

Dr. MENG Lingbo: This patient was admitted to our hospital due to “paroxysmal chest pain for more than half month”. Half month ago, the patient began to suffer chest pain for unknown cause, which was considered as unstable angina pectoris. The patient had undergone PCI twice, and had a history of hyperlipidemia. In addition, diabetes mellitus was diagnosed when the patient was hospitalized this time. So we considered the chest pain might be caused by plaque rupture and secondary thrombosis, restenosis in stent, thrombosis in stent, coronary spasm and so on. The patient had been treated with antiplatelet therapy, anticoagulant therapy and lipid-lowering therapy before she was admitted to our hospital, but the symptom was not obviously relieved. So CAG should be performed as early as possible to definite

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the causes, which could assist us to choose the correct management.

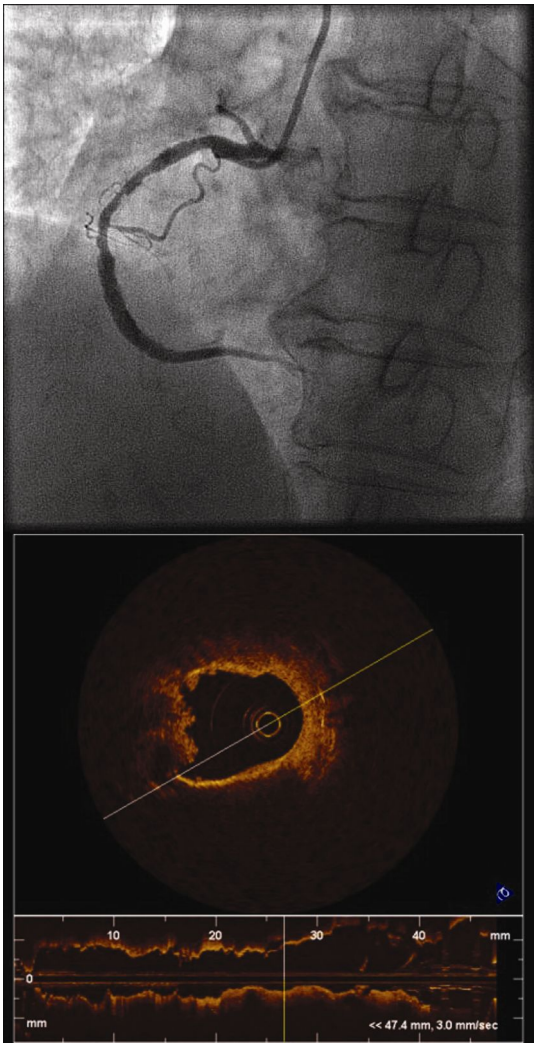

Figure 1 Ruptured lipid-rich plaque and thrombosis inside bare-metal stent revealed by optical coherence tomography

Dr. HAN Zhigang: The patient's CAG indicated 60% stenosis in the proximal of LAD, 80% stenosis in the ostium of the first diagonal branch, 30% stenosis in the proximal of LCX, 80% stenosis in the BMS which was located in the middle of RCA, and no stenosis in the DES which was located in the distal of RCA. Restenosis, which was considered as unstable lesion through the CAG image, was found in the stent located in the middle of RCA. Moreover, electrocardiogram showed ST-segment depression in leads Ⅱ, Ⅲ, avF. All of these were consistent with the clinical symptoms. But the resolution of CAG is not high enough to well reflect the characteristics of the culprit lesion. Moreover, the CAG image cannot identify the detailed characters of the lesion inside the stent. On the basis of clinical features and CAG images mentioned above, we considered there may be neointimal hyperplasia or thrombosis which induced the formation of restenosis in stent. So we need other instruments with higher resolution to identify the culprit lesion inside the stent.

Dr. YANG Shuang: To identify the features of the lesion in stent located in the middle of RCA and to choose the best treatment, we could use intravascular ultrasound (IVUS) or OCT to accomplish it. Both IVUS and OCT are intracoronary imaging techniques with high resolution, which can reveal the feature of the lesion. IVUS, the current clinical technology with the high resolution and penetrating power, has a maximum axial resolution of 100 μm. IVUS can be used to measure plaque burden and positive or negative vascular remodeling, assess the left main stem lesion and evaluate perivascular injury (hematoma or perforation). OCT is a non-contact, light-based imaging modality utilizing newly developed fiber-optic technologies. OCT has higher resolution and faster scanning speed than IVUS. Comparing with IVUS, OCT is superior in defining the plaque and thrombus, evaluating the immediate vascular response to stent implantation, and evaluating the character of neointimal. CAG findings showed in-stent restenosis in middle of RCA, which was considered as neointimal hyperplasia or thrombosis. Moreover, because the diameter of IVUS catheter is bigger, the lesion in the stent could be injured when IVUS catheter passes it. So we tended to prefer OCT for this patient. OCT image acquisition was performed using a commercially available system for intracoronary imaging and a 0.019-inch ImageWire. To acquire the accurate images, we should avoid to injury the lesion when the wire passes the lesion, and use the balloon to interrupt blood at the proximal of the stent.

Dr. HOU Jingbo: There was 80% stenosis in the stent located in middle of RCA, and OCT imaging showed ruptured lipid-rich plaque and thrombosis inside the stent. Although the patient had received antiplatelet therapy, anticoagulant therapy and lipid-lowing therapy, the symptom did not disappear. We decided to implant one stent (Cypher) in the BMS. OCT imaging showed complete stent apposition after procedure(Figure 2). The patient undergoing antithrombotic treatment after PCI should strictly control the level of blood pressure as well as blood glucose. To a large extent, the formation of in-stent restenosis is related to the poor lipid control, so we should apply intensive statin therapy to the patient. According to the ATP III guidelines, the target of low-density lipoprotein cholesterol (LDL-C) (< 700mg/L) is a therapeutic option for certain patients at very high risk. The lower the level of LDL-C is, the greater the potential gain in terms of disease treatment will be. Intensive statin therapy showed beneficial effects in patients treated with PCI or coronary artery bypass grafting

(CABG). Statins play an important role in delaying atherosclerosis, reducing adverse coronary events, and lowing cardiovascular mortality and morbidity in patients with CVD. When the high-risk patient has high triglycerides, fibrates drug can be taken into consideration for controlling the balance of diet and sugar. On the other hand, the atherosclerotic process may gradually progress because the patient has more risk factors. So it will be very important to have regular follow-up of this patient besides pharmacotherapy, so as to observe development of coronary lesion and adjust medication, and eventually all of this will be beneficial to avoid the occurrence of major adverse cardiac events.

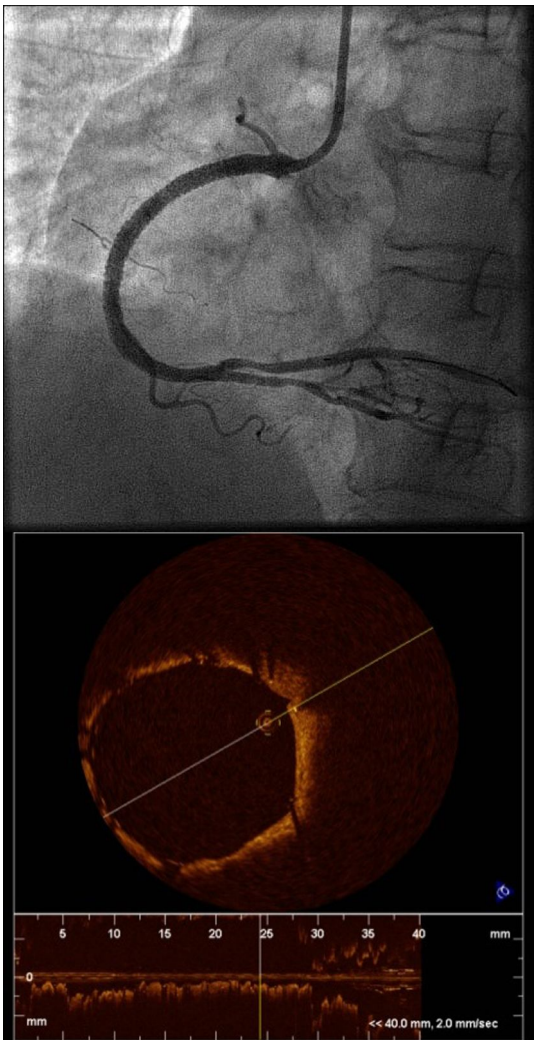

Figure 2 Optical coherence tomographic imaging shows complete stent apposition post procedure

Dr. YU Bo: OCT findings revealed lipid-laden atherosclerotic plaque formed inside BMS located in middle of RCA, and ruptured plaque with thrombosis. So we speculated that the clinical symptoms can be attributed to disruption of thin-cap fibroatheroma and secondary very late stent thrombosis. Finally, the patient presented unstable angina pectoris. Following the development of intracoronary imaging technology and the extension of follow-up time after PCI, the reports about in-stent lipid plaque are increasing. Atherosclerosis of the neointima within the stent was defined as peristrut foamy macrophage clusters with or without calcification, fibroatheromas, thin-cap fibroatheromas, and ruptures with thrombosis. In all cases, there was no communication of the lesion within the stent with the underlying native atherosclerotic plaque. Although the underlying processes responsible for the development of neoatherosclerosis after stent implantation have not yet been fully elucidated, it may be due to the inability to maintain a fully functional endothelialized luminal surface within the stented segment, and the deposition of lipid into neointimal which leads to the formation of plaque within the stent finally. In our previous study, we applied OCT imaging in 39 patients with 60 BMS who developed recurrent ischemia. Lesion that had features of lipid-rich plaque (LRP) was found in 20 stents in 16 patients, and one patient had ruptured plaque with thrombosis within the stent. Seven restenotic lesions with LRP were responsible for unstable angina symptoms. Moreover, we found that the development of LRP inside the BMS was after about 6 years of stenting. Nakazawa *et al* have reported that 197 BMS from 147 autopsy cases with implant duration >30 days were examined for the presence of neointimal atherosclerotic disease. The neoatherosclerosis inside the BMS was found in 31 lesions, and 10 lesions displayed vulnerable plaques, and the BMS duration with neoatherosclerosis exceeded six years. The results of above clinical observation and autopsy indicate that the BMS duration with lipid plaques usually exceeds six years. The plaque within the BMS can induce restenosis and late or very late stent thrombosis, which can lead to adverse outcomes, including unstable angina pectoris, myocardial infarction and sudden death. For this patient, she was implanted with a BMS 7 years ago and failed to efficiently control the lipid and blood glucose level; all above are high risk factors for the formation of in-stent plaque. In our hospital, the patient underwent OCT, and we eventually ensured that the culprit lesion which induced recent clinical syndroms was the neointimal hyperplasia and ruptured plaque with thrombosis.

(Translator: YANG Shuang)

应用光学相干断层成像发现金属裸支架内新生斑块破裂伴继发血栓 1 例

1 病例摘要

患者女，67 岁，主诉“阵发性胸痛半月余”，于 2010 年 4 月 14 日入院。患者于半月前无明确诱因出现心前区压榨性疼痛，伴肩背放射痛，持续约 5 min，含服“硝酸甘油片”可缓解，就诊于当地医院，给予抗血小板、抗凝、降脂及对症治疗，患者上述症状仍间断发作，遂来我院就诊。

既往史：高血压病史 7 年，血压最高达 200/120 mmHg，平日口服“拜新同”控制血压，血压水平控制在 120～130/90～95 mmHg 之间；高血脂病史 7 年，平日口服“立普妥”控制血脂水平，血脂未达标；两次 PCI 术治疗史：患者 7 年前右冠状动脉中段植入金属裸支架 1 枚，半年前右冠状动脉远段植入药物支架 1 枚。否认糖尿病病史。

查体：体温 36.7℃，脉搏 62 次/min，呼吸 18 次/min，血压 160/100 mmHg。神志清，双肺呼吸音清，未闻及干、湿啰音，心率 62 次/min，心律齐，各瓣膜听诊区未闻及病理性杂音。腹软，无压痛、反跳痛，肝脾未触及。双下肢不肿。

入院后进行各项检查。（1）血脂：总胆固醇 5.43 mmol/L，甘油三酯 3.97mmol/L，高密度脂蛋白胆固醇 1.45 mmol/L，低密度脂蛋白胆固醇 3.92 mmol/L；（2）空腹血糖 7.32 mmol/L；（3）餐后 2 小时血糖 13.8 mmol/L；（4）糖化血红蛋白 6.9%；（5）超敏 C-反应蛋白 11.3 mg/L；（6）心电图显示Ⅱ、Ⅲ、avF 导联 ST 段压低。

患者于入院第 2 天时，进行冠状动脉造影及支架植入术。手术过程顺利，冠脉造影提示：前降支近中段斑块浸润，狭窄达 60%，第一对角支开口狭窄 80%，回旋支斑块浸润，近中段狭窄达 30%，右冠状动脉弥漫性斑块浸润，中段支架内狭窄 80%，远段支架血流通畅。进行光学相干断层成像(OCT)检查，发现右冠中段支架内斑块破裂，血栓浸润。于患者中段支架内植入药物支架 1 枚，患者术后病情平稳，目前正处于随访中。

2 临床病理讨论

孟令波主治医师：本例患者因“阵发性心前区疼痛半月”入院。患者半月前无明确诱因出现胸疼症状，考虑为不稳定性心绞痛。患者既往有 PCI 手术史，平日血脂控制不佳，且本次入院发现糖尿病，推测引起患者出现本次症状的原因可能为（1）原有斑块破裂，血栓形成；（2）支架内再狭窄；（3）支架内血栓形成；（4）冠脉痉挛等。患者于当地医院进行了严格的抗血小板、抗凝、降脂等治疗，症状缓解不明显。目前，该患者应及早进行冠状动脉造影，以明确病因，选择正确的治疗手段。

韩志刚副主任医师：本例患者冠状动脉造影结果显示前降支近中段斑块浸润，狭窄达 60%，第一对角支狭窄达 80%；回旋支斑块浸润；右冠中段支架内狭窄达 80%，右冠远段支架血流通畅。患者右冠中段支架发生再狭窄，且支架内疑似不稳定病变，发作时心电图显示下壁缺血，与患者不稳定性心绞痛症状相吻合。由于冠状动脉造影的分辨率及清晰度较差，不能很好的体现出罪犯病变的特征，因此造影结果无法分辨支架内病变的性质。猜测可能存在支架内新生内膜过度增生或血栓形成。为明确病因，选择最佳治疗的策略，应选择分辨率更高的检测手段，以明确支架内病变的性质。

杨爽副主任医师：为明确该患者右侧冠状动脉中段支架内病变的性质，采取最佳的治疗手段，我们可选择血管内超声（IVUS）或 OCT 来完成。IVUS 与 OCT 均可进行血管内成像，且分辨率较高，可以有效的观察病变的特征，二者各有其优缺点。IVUS 是利用高频超声波在血管内呈现高分辨率的影像，其分辨率可达 100μm，穿透力强，多用于评价斑块负荷，左主干分叉病变的指导，血管壁正性或负性重构的改变，血管周围损伤（血肿、穿孔）。OCT 是一种利用近红外光为光源的高分辨率的血管内成像手段。其分辨率较 IVUS 高，可达 10μm，且扫描速度较 IVUS 快，现已成为冠状动脉介入治疗的重要手段。由于 OCT 分辨率高及其成像特点，其不仅对斑块及血栓性质的判断、支架植入即刻的情况，而且对支架新生内膜的检测等方面均较 IVUS 有较大优势。本例患者右冠中段支架再狭窄，猜测可能有支架内新生内膜过度增生或血栓形成，选择 OCT 评价支架内病变的特征更为适合。且支架内狭窄程

度达 80%，IVUS 成像导丝较粗，通过支架内病变时病变部位可能因手术操作受到影响。在应用 OCT 对病变部位进行检测时导丝应小心通过病变部位，OCT 球囊应于支架近端进行阻断，避免对病变部位造成损伤，从而得到清晰、可靠的图像。

侯静波主任医师：该患者右冠状动脉中段支架内狭窄达 80%，并且经 OCT 证实支架内斑块破裂伴血栓形成。虽经积极的抗血小板、抗凝、降脂等治疗，症状缓解不明显，建议对支架内病变行 PCI 术。此次选择植入 Cypher 支架，术后再次行 OCT 检测，结果显示：支架贴壁良好。此患者术后在抗栓治疗同时应严格控制血糖、血脂。由于平日患者血脂控制不佳，导致 BMS 内斑块形成，此次 PCI 术后应采取强化他汀治疗。根据美国 ATP-Ⅲ指南，极高危患者应将低密度脂蛋白胆固醇治疗目标定为 700mg/L，低密度脂蛋白胆固醇水平越低收益越大。无论是 PCI 还是冠心病外科搭桥手术的患者，强化他汀治疗均能显示其潜在的治疗效益。他汀类药物在延缓动脉粥样硬化、减少冠状动脉不良事件、降低冠心病患者致残率等方面都具有十分重要的作用。此患者甘油三酯水平较高，也可考虑在控制饮食和血糖的同时选择加用贝特类药物。此患者危险因素较多，动脉粥样硬化程度逐渐进展，在药物控制的同时，应定期随访以了解冠状动脉的情况，随时调整用药，避免临床事件的发生。

于波主任医师：本例患者 OCT 检测结果显示右侧冠状动脉中段支架内新生动脉粥样硬化斑块形成，斑块破裂，血栓形成。推测此患者由于右侧冠状动脉中段支架内出现薄纤维帽的脂质斑块，斑块自发破裂后导致支架内超晚期血栓形成，最终引起临床症状，表现为不稳定性心绞痛。随着检测手段的不断进步及支架植入后随访时间的延长，支架内新生斑块形成的报道也越来越多。支架内新生斑块被定义为支架小梁周围有泡沫样变的巨噬细胞，伴或不伴有钙化、纤维粥样斑块、薄纤维帽风险斑块、破裂血栓形成，并且支架内与支架覆盖的动脉粥样硬化病变不相连。其形成原因尚未完全阐明，可能是由于支架植入导致内皮功能不全，失去对内膜的保护功能，使大量的脂质沉积于新生内膜，最终导致支架内斑块的形成。我们之前应用 OCT 对 39 名患者 60 枚 BMS 进行了临床观察，结果在 16 名患者 20 枚 BMS 中发现脂质斑块，1 名患者出现支架内斑块破裂伴血栓形成，其支架植入时间均大于 6 年，16 名患者中有 7 名患者表现为不稳定性心绞痛症状。Nakazawa 等对 143 例植入 BMS 30 后死亡的患者进行尸检，在总共 197 枚 BMS 中，有 31 枚 BMS 内出现了新生的动脉粥样硬化斑块，其中 10 枚 BMS 内表现为易损斑块，其支架植入时间均大于 6 年。上述临床观察及尸检结果表明，BMS 内斑块多于支架植入 6 年后发生，其可导致支架再狭窄，若发生斑块破裂，可引起支架内晚期或超晚期血栓形成，从而导致不稳定心绞痛、心肌梗死、猝死等心血管不良事件的发生。本例患者 7 年前植入 BMS，平日血脂控制不佳，糖尿病未及时发现、控制，均是 BMS 内斑块形成的危险因素。此患者通过 OCT 检查证实原 BMS 支架内膜过度增殖、斑块破裂伴血栓形成，应采取积极的方法治疗此罪犯病变。

（参加讨论医师：孟令波，韩志刚，杨 爽，侯静波，于 波）

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