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Macrophage behaviour 72 hours after implantation of biodegradable polymer-based sirolimus-eluting stent in a case of ST elevation myocardial infarction

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SUMMARY

While the vascular healing process after drug-eluting stent implantation is not fully elucidated, it is generally accepted that macrophages play an important role in inflammation. It is also known that macrophages involved in the pathogenesis of atherosclerosis may stem from several origins, that is, monocyte-derived macrophages versus resident macrophages. However, little is known about the role of human macrophages on reperfusion of culprit coronary arteries in patients with atherosclerotic disease who have sustained acute coronary syndrome. In this present case report, we describe the presence of cluster of differentiation (CD) 163-positive macrophages in close proximity to the stent struts at the luminal site 72 hours after drug-eluting stent implantation in the culprit coronary lesion for ST elevation myocardial infarction by postmortem examination.

BACKGROUND

The healing process after coronary artery stent implantation is dependent on the resolution of the inflammatory reaction that drives atherogenesis. Macrophages are known to play an important role in the development of atherosclerotic lesions¹ with two macrophage phenotypes having been associated with different areas of the lesions: M1 (proinflammatory) macrophages that have been detected in the rupture-prone area of the intima, and M2 (anti-inflammatory) macrophages that have been localised in the adventitia underlying advanced plaques.^{2–5}

However, little is known about which type of macrophage is mobilised just after stent implantation on vulnerable plaques in a culprit coronary artery after ST elevation myocardial infarction (STEMI).⁶ Behaviour of human macrophages just after stent implantation in the infarct-related artery in STEMI patients is rarely investigated because the only definitive examination could occur postmortem. As such, we describe a postmortem case with the presence of cluster of differentiation (CD) 163-positive macrophages in close proximity to the stent struts 72 hours after drug-eluting stent implantation in the culprit coronary lesion for STEMI.

CASE PRESENTATION

The patient was a man in his 80s transferred to our hospital with chief complaint of chest pain. Interval of symptom onset to hospital arrival was 110 min. The patient reported a medical history of

hypertension which was controlled by medication. On initial examination, his systolic blood pressure was 70 mm Hg, heart rate was 60 beats per minute and pulse oximetric oxygen saturation was 94% on room air.

INVESTIGATIONS

A 12-lead ECG revealed sinus rhythm and ST-segment elevation in leads II, III, aVF and ST-segment depression in leads I, aVL, V2–V5. Transthoracic echocardiogram illustrated hypokinesia in the inferolateral wall and left ventricular ejection fraction of 40%. Initial coronary angiography showed total occlusion of the proximal left circumflex artery (LCX) (figure 1A).

TREATMENT

Primary percutaneous coronary intervention (PCI) to the proximal LCX was performed and a biodegradable polymer-based sirolimus-eluting stent (Orsiro 2.5×15 mm; Biotronik, Bülach, Switzerland) was implanted (figure 1B) in the culprit lesion. Although reperfusion therapy was successful with resultant thrombolysis in myocardial infarction flow grade 3 (door to balloon time was 81 min) (figure 1C), the patient's continued haemodynamic instability required both mechanical (intra-aortic balloon pumping and percutaneous cardiopulmonary support) and pharmacological circulatory support with catecholamines.

OUTCOME AND FOLLOW-UP

Unfortunately, the patient's blood pressure did not recover, and 72 hours after PCI, he passed away.

Postmortem examination was performed 3 hours 50 min after death. His autopsy revealed extensive lateral wall myocardial infarction with haemorrhage on macroscopic examination. The coronary arteries were extracted and the LCX (figure 1D) was incised to examine the stent (figure 1E). The dissected coronary artery with the stented segment was fixed with 5% formalin. After excision of the metal struts, the stented region (figure 2B), with reference segments (figure 2A,C) within 5 mm of both the proximal and distal ends, was processed for H&E staining or immunohistochemical staining. Immunohistochemical staining for CD68, CD80, CD163 and arginase 1 was performed.

Light microscopy of cross-sections of the artery, stained by H&E, revealed eccentric atherosclerotic plaques in reference segments (figure 2 A# C#) and stented segment (figure 2 B#). On higher



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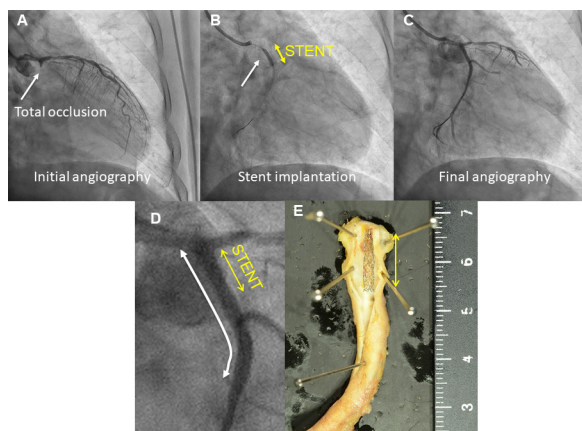


Figure 1 (A) The left coronary artery in initial coronary angiography in the RAO 30 and CAU 20 view. Total occlusion in the proximal circumflex artery is observed (white arrow). (B) RAO 24 and CAU 17 view, illustrating a balloon (yellow arrow) inflating stent in the occlusion lesion (white arrow). (C) Final angiography by RAO 24 and CAU 17 view, indicating TIMI flow grade 3 in the circumflex artery. (D) Magnification image of (C). White double-headed arrow represents the length of the extracted segment of the LCX. Yellow double-headed arrow represents the actual stent. (E) Autopsy specimen of the extracted segment of the LCX. Yellow double-headed arrow demonstrates the length of the implanted stent that is visible with the artery. CAU: caudal, LCX: left circumflex, RAO: right anterior oblique, TIMI: thrombolysis in myocardial infarction.

magnification, the stented segment appeared hypocellular, with scant inflammatory cells including lymphocytes or neutrophils observed around the stent struts (figure 2D,E). By immunohistochemical staining, CD80-positive cells were not observed in either the luminal site or the vessel wall, including around the stent struts and both the distal and proximal vessel ends. Both CD163-positive cells and arginase 1-positive cells were identified at the border of the vascular lumen (CD163 and arginase 1, figure 3A,C) and appeared to be in close proximity to the edge of each stent strut (* shows site of the stent strut, CD163 and arginase 1, figure 3B,D) in the culprit lesion. Moreover, both

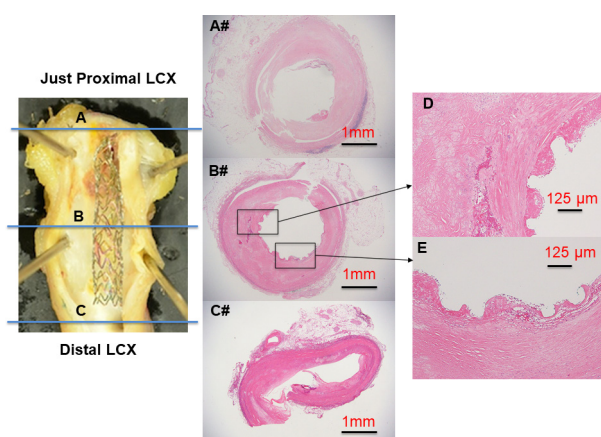


Figure 2 Left panel: The extracted proximal LCX segment with a stent. Blue lines A, B and C correspond to the sites of cross-sectioning of the artery. Middle panel: Cross-sectional images of the proximal LCX (A#), stented segment (B#) and distal LCX (C#) stained for H&E. Right panel: D, E represent high magnification H&E-stained images of the stented segment around the stent struts. LCX: left circumflex.

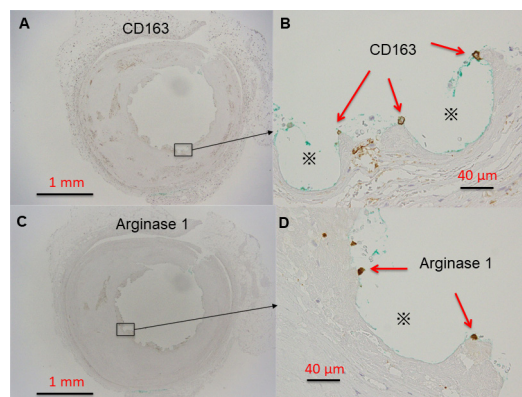


Figure 3 (A, B): CD163 stain, (C,D): arginase 1 stain of the culprit lesion after stent implantation. Black square frames in A and C are magnified in B and D. Note that both CD163-positive cells and arginase 1-positive cells (red arrows) are next to the stent struts (* shows site of the stent strut). CD: cluster of differentiation.

CD163-positive cells and arginase 1-positive cells were detected in the adventitia of the stented segment of the coronary artery.

DISCUSSION

To the best of our knowledge, this is the first report of both CD163-positive macrophages and arginase 1-positive macrophages detected close to the stent struts in the context of STEMI in humans. It has been reported that M2 macrophages play a reparative role.⁴ Indeed, the present images suggest that vascular injury repair by M2 macrophages may start 3 days after sirolimus-eluting stent implantation for STEMI.

M2 macrophages were also detected in the adventitia of the stented segment of the culprit coronary artery, which is consistent with a former report.⁵ There were almost no M2 macrophages either in the subintimal area or the intima 3 days after stent implantation. This leads us to deduce that the M2 macrophages in close proximity to the stent struts only at luminal site might not have migrated from the adventitia to the luminal site within 3 days, but may have originated from circulating monocytes.

However, the role of M2 macrophages in atherosclerosis progression remains controversial. Recent reports indicate that CD163 macrophages are associated with plaque progression⁷ and that CD163-expressing macrophages have a protective role during the progression of atherosclerosis.⁸ Moreover, the role of CD163 macrophages in adventitia has not been fully elucidated; therefore, further studies are warranted to understand the role of CD163 in culprit coronary artery in patients with STEMI.

Of note, scant number of inflammatory cells were detected in the stented segment of the culprit coronary artery and in both the proximal and distal segments of the artery shortly after STEMI, although, the culprit arterial wall was expected to be filled with abundant inflammatory cells.⁹ Taking into account that plaque morphology and cellular composition of coronary atherosclerosis leading to thrombosis is a heterogeneous process, and coronary erosion has less macrophages than plaque rupture, the formation of thrombosis is probably due to superficial erosion in the present case.⁹ Therefore, accumulation of pathological data including inflammatory cells will elucidate the mechanisms of coronary atherothrombosis at the very onset of STEMI.

CONCLUSION

CD163-positive macrophages and arginase 1-positive macrophages were detected in close proximity to drug-eluting stent

Learning points

- ▶ Acute coronary syndrome is a leading cause of death, provoked by acute coronary thrombosis, where inflammation has been reported as its main processes.
- ▶ Macrophages play an important role in inflammation, but behaviour of human macrophages just after coronary thrombosis and stent implantation in the infarct-related artery (IRA) is not fully elucidated.
- ▶ Present ST elevation myocardial infarction (STEMI) case shows that CD163-positive macrophages are neighbouring on stent struts 72 hours after stent implantation in IRA, indicating CD163-positive macrophages were recruited for healing process after stent implantation in IRA in patient with STEMI.
- ▶ The present results give us an opportunity to clarify a part of the process of healing vasculature after stent implantation in human coronary atherothrombosis.

struts deployed 3 days prior in the culprit coronary artery in patient with STEMI, giving us an opportunity to clarify a part of the process of healing vasculature after stent implantation in atherothrombosis.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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