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LETTER TO THE EDITOR
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Rapid progression of atherosclerosis in a patient with acute coronary syndrome and ANCA-associated vasculitis: split or confluence?

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A 59-year-old female patient was admitted to our hospital on 9 March 2021, due to recurrent chest pain. She underwent percutaneous coronary intervention, with a focus on the proximal segment of the left anterior descending (LAD) artery, six months prior to admission. The patient had a long-term history of hyperlipidaemia and obstructive sleep apnoea syndrome (OSAS). She also had rheumatoid arthritis and ANCA-associated vasculitis that lasted for more than 10 years and a 9-year history of concomitant hypertension. She was on long-term oral leflunomide and intermittent oral prednisone. The patient underwent a computed tomography angiogram (CTA) six years ago (2015), which showed minor atherosclerotic plaque build-up in the LAD artery and the right coronary artery (RCA) (Figure 1). Three years later, a coronary CTA revealed tight stenosis of the proximal segment of the LAD. The patient did not present with classic symptoms, such as chest pain, nor have additional complaints, so further diagnostic testing or treatment was not provided.

The patient was hospitalized in October 2020 when she presented with severe chest pain, which led to a diagnosis of acute anterior myocardial infarction. Examination of blood lipids during hospitalization revealed that total cholesterol (TC) was 8.33 mmol/L; low-density lipoprotein cholesterol (LDL-C) was 3.28 mmol/L; and total triglycerides (TGs) was 5.64 mmol/L. A coronary angiogram (CAG) was performed and revealed diffuse stenosis in the proximal and middle segments of the LAD with approximately 90% stenosis in the most severely affected segment. Tubular, eccentric stenosis blocking 50%–60% of the lumen was also observed in the mid distal segment of the RCA. A Resolute™ Integrity stent measuring 2.75 × 30 mm (Medtronic, Inc. USA) was implanted into the proximal-middle segment of the LAD (Figure 2). Dual antiplatelet therapy with aspirin and clopidogrel was prescribed postoperatively, and atorvastatin in combination with acipimox was used for intensive lipid-lowering therapy. Outpatient re-examination of the patient's blood lipid parameters on 18 November 2020 revealed thar TC was 5.16 mmol/L; LDL-C was 2.67 mmol/L; and TG was 4.63 mmol/L. Acipimox was discontinued and replaced with statins combined with bezafibrate as part of the enhanced lipid-lowering therapy. The key therapeutic strategies at this point focused on lifestyle modification, intensive lipid reduction, and risk factor control. The patient did not experience any chest pain during this period.

On 15 March 15 2021, chest pain recurred while the patient performed chores at home, but was relieved at rest. The patient was then readmitted to our hospital on 19 March 2021. Her electrocardiogram showed clear ST-T dynamic changes coinciding with the onset of chest pain during hospitalization (Figure 3). Cardiac ultrasonography revealed a left atrial diameter of 44 mm, a left ventricular dia-

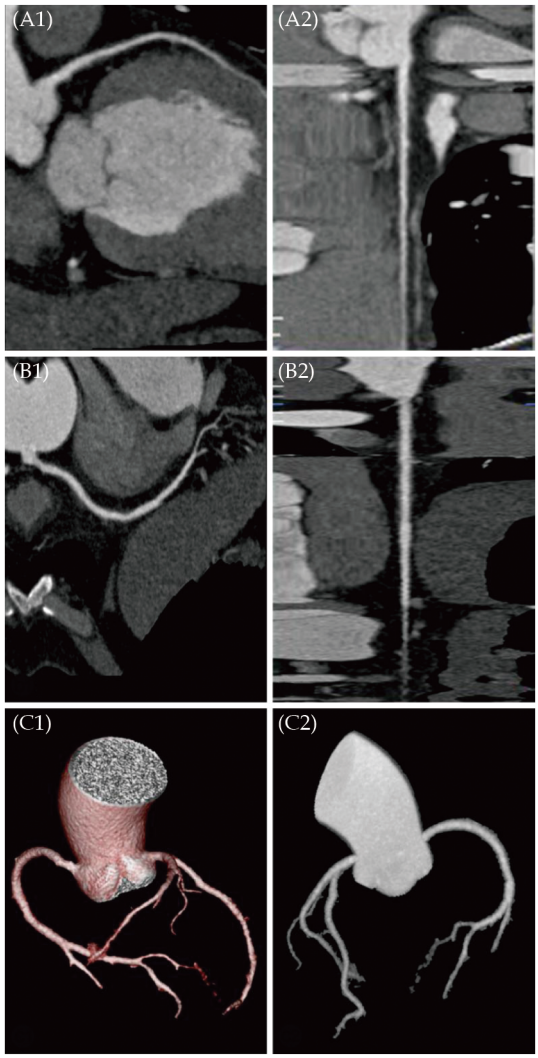

Figure 1 First CTA of the patient in March 2015. (A1 & A2): Mild plaque in the proximal segment of the LAD; (B1 & B2): mild plaque in the proximal segment of the RCA; and (C1 & C2): volume rendering of the coronary arteries. CTA: computed tomography angiogram; LAD: left anterior descending branch; RCA: right coronary artery.

meter of 59 mm, an ejection fraction of 52%, and decreased left ventricular diastolic function. Biochemical examination of blood lipids revealed that TC was 6.13 mmol/L; LDL-C was 2.53 mmol/L; and TG was 5.48 mmol/L (Figure 4). The patient was diagnosed with acute non-ST-segment elevation myocardial infarction with a troponin level of 0.031 μg/L. Compared with the CAG that was performed 4 months prior, the stent in the LAD was patent, while the RCA showed significant lesion progression with a 90% eccentric lesion in the proximal segment and a diffuse lesion of 50%-60% in the middle

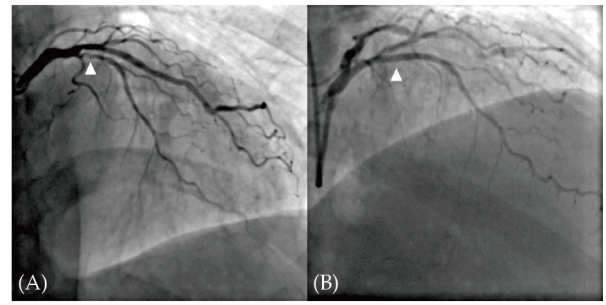

Figure 2 First CAG and PCI in the proximal segment of LAD. (A): CAG indicates 90% diffuse stenosis in the middle section of the LAD in October 2020; and (B): postoperative image of LAD PCI (a Resolute Integrity 2.75 × 30 mm stent was implanted (Medtronic, Inc. USA)). CAG: coronary angiogram; LAD: left anterior descending branch; PCI: percutaneous coronary intervention.

segment (Figure 5). PCI was then performed under the guidance of optical coherence tomography (OCT). However, during the procedure, the OCT catheter was unable to be withdrawn once it passed through the stenosed segment. Therefore, further OCT examination was performed after balloon predilatation using a 2.5 × 20 mm balloon (Ryujin, Terumo Corporation, Japan) at the proximal RCA lesion. This revealed a fibrous lipid plaque and thin-cap fibroatheroma (TCFA) in the middle and distal segments of the RCA (without balloon dilatation, it was located at the distal end of the lesion).

An organized thrombus, several cholesterol crystals, and macrophage infiltration were observed in this area, with a minimum lumen area of 2.61 mm^2, and the stenosis was approximately 77% (Figure 6). As per the "normal to normal" principle, two stents [Promus PREMIER™ 3.5 × 38 mm, Promus PREMIER™ 4.0 × 20 mm (Boston Scientific Corporation, USA)] were implanted at the proximal segment of the RCA. Postoperative OCT revealed that the minimum inner area of the stent was 7.18 mm^2, and the stent expansion rate was 67%, which was due to tissue prolapse and the presence of a thrombus within the stent. This, in turn, may have been caused by the rupture of the lipid-rich plaque at the site of the lesion due to the stent implantation itself (Figure 7). Tirofiban was injected into the coronary artery and continued intravenously.

Preoperatively, low levels of ANCA and anti-protease 3 antibody were detected; the complement 3 level was slightly higher (1.73 g/L), and the immun-

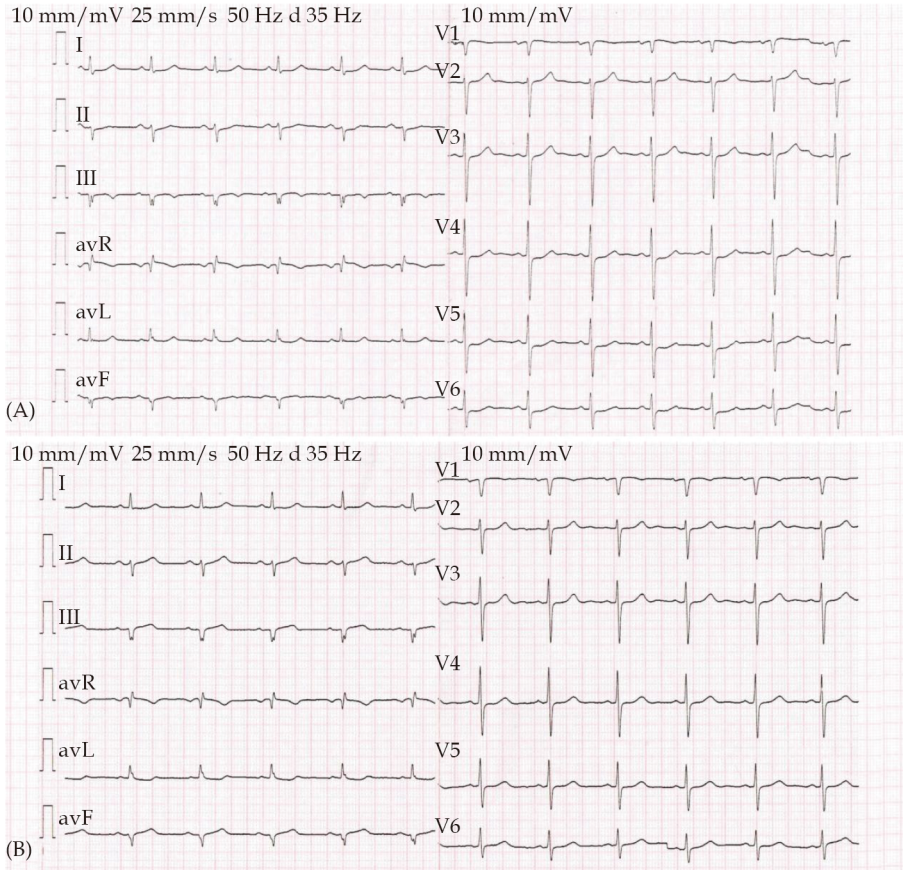

Figure 3 ECG changes in the patient. (A): ECG at admission in March 2021; and (B): ECG during the onset of chest pain during hospitalization (dynamic change compared with admission). ECG: electrocardiogram.

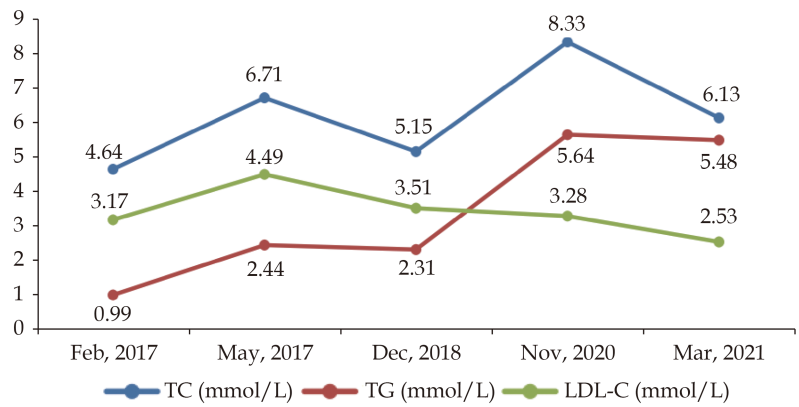

Figure 4 Changes in blood lipid levels in the patient. LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride.

oglobulin G level was slightly lower (7.38 g/L) than normal. Antinuclear antibody titers, rheumatoid factor levels, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were normal. Postoperative imaging of the thrombus showed an arachidonic acid inhibition rate of 94.9% and adenosine diphosphate (ADP) inhibition rate of 82.6%. Dual antiplatelet therapy with aspirin and clopidogrel was continued postoperatively, and ezetimibe combined with bezafibrate was used as part of the enhanced lipid-regulation therapy. No adverse cardiovascular or cerebrovascular events have been ob-

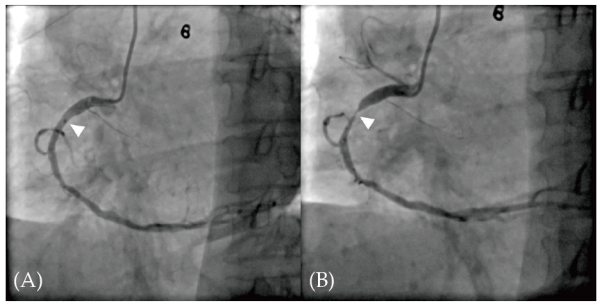

Figure 5 Second CAG in RCA. (A): Proximal RCA plaques in October 2020; and (B): CAG re-examination in March 2021 showed tubular, eccentric stenosis of 90% of the proximal segment of the RCA. CAG: coronary angiogram; RCA: right coronary artery.

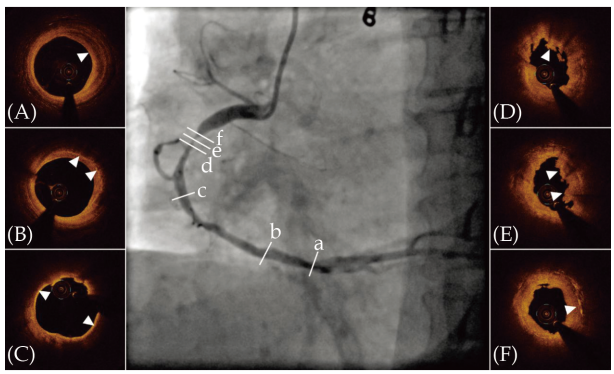

Figure 6 OCT results of RCA (before stenting). (A): Organized thrombosis; (B): macrophages; (C): TCFA; (D): dissection and thrombosis; (E): organized thrombosis; and (F): cholesterol crystals. OCT: optical coherence tomography; RCA: right coronary artery; TCFA: thin-cap fibroatheroma.

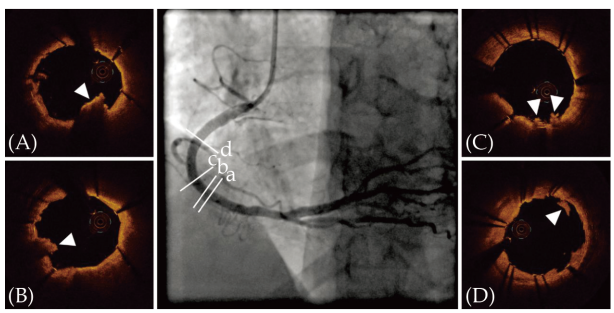

Figure 7 OCT results of RCA (after stenting). (A): Stent thrombosis; (B): tissue prolapse; (C): tissue prolapse; (D): stent thrombosis. OCT: optical coherence tomography; RCA: right coronary artery.

served in the patient after the therapies were administered.

The patient mentioned in this report had ANCA-associated vasculitis and acute coronary syndrome (ACS). Studies have shown that anti-neutrophil cytoplasmic antibody (ANCA) promotes cytokine release from neutrophils, prompting the release of oxygen free radicals and lytic enzymes, which leads to the lysis and destruction of vascular endothelial cells.[1] In addition, activated neutrophils can also induce the expression of protease 3 and myeloperoxidase on the cell surface while inducing more neutrophils to form an extracellular trap to adhere to and destroy vascular endothelial cells. The destruction and loss of function of endothelial cells are initiating factors of atherosclerosis; therefore, patients with ANCA-related vasculitis often have atherosclerosis.[2] Patients with ANCA-associated vasculitis have a 65% increased cardiovascular risk compared with the general population.[3–5] Museedi, *et al*.[6] found that patients with ACS and ANCA-associated vasculitis may present with ST-segment elevation myocardial infarction due to spontaneous coronary dissection; however, they did not provide intracoronary imaging evidence. Our OCT findings showed that, in addition to the severe stenosis induced by the rapid progression of a fibro-lipid plaque in the coronary artery wall, several cholesterol crystals, an organized thrombus, a TCFA, and macrophage infiltration were also present. Cholesterol crystals can activate the nucleotide binding oligomerization domain-like receptor (NLR) family, pyrin domain containing three inflammasomes, and the inflammatory cascade of interleukin-CRP. Inflammatory factors could play an important role in the rapid progression of coronary plaques from a microscopic point of view.[7] Although ANCA-associated vasculitis mainly targets the small vessels, it remains at its core, an immune-mediated disease that can very well affect the wall of the coronary artery. Moreover, OCT also revealed that there were some vulnerable plaque features along with TCFA in the coronary artery, and small dissections could be observed in the lesion. Although the role of balloon dilation itself in affecting the lesion cannot be excluded, it may also be that under the action of systemic inflammation, specifically of the intravascular kind, the plaques from mild to moderate stenotic lesions become unstable. This might have led to thrombus formation following thin fibrous cap rupture or erosion; then, organization of this thrombus probably caused worsening of the pre-existing stenosis. Although several risk factors of coronary artery dis-

ease, such as hypertension, dyslipidaemia and OSAS, were present in the patient and satisfactory lipid control was not achieved via treatment, local atherosclerotic luminal stenosis was not worsened in the beginning. The thrombotic event probably occurred due to the presence of vulnerable plaques. This suggests that inflammatory factors may play a critical role in "triggering" local coronary events.

Inflammatory regulators have been reported to influence atherosclerotic plaque generation, progression, and plaque rupture or erosion. Their main roles include: (1) influencing atheroprogression in the critically stable phase of the disease; (2) inciting plaque destabilization and thereby precipitating ACS; and (3) responding to cardiomyocyte death in myocardial infarction.[7] Recurrent cardiovascular events are triggered by multiple biological factors, meaning that various treatments are possible. Studies have reported that decreasing levels of high-sensitivity CRP (hs-CRP) by blocking interleukin-1β significantly reduces cardiovascular events in patients with coronary heart disease. [8] It has recently been shown in patients with coronary heart disease at high risk of residual inflammation (hs-CRP ≥ 2 mg/dL) that long-term oral administration of colchicine further reduces adverse cardiovascular and cerebrovascular events in patients with recent acute myocardial infarction and stable coronary heart disease. [9,10] Although indicators such as CRP and ESR were not high in the case presented here, the anti-inflammatory effect of leflunomide is not absolute, and leflunomide itself can have a procoagulant effect. Keeping patient safety as a priority, the lipid-regulation regimen was changed to ezetimibe with bezafibrate, and blood lipids were closely monitored. If necessary, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors can be given to enhance blood lipid control, and additional anti-inflammatory treatments may also be considered.

ANCA-associated vasculitis is closely related to the progression of coronary atherosclerosis. Some of the coronary artery stenosis seen in the case discussed was caused by the reduction of lumen area due to organized thrombosis formation, rather than in the increase of plaque volume. Inflammatory factors may play a critical role in “triggering” the process of local coronary events, and treatment protocols in such patients with cadiovascular diseases need to be revised.

FUNDINGS

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ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Clinical Investigation, Langfang People's Hospital. Informed consent from the patients/participants or patients/participants legal guardian/next of kin was obtained in this study.

CONFLICTS OF INTEREST

None

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REFERENCES

[1] Schreiber A, Kettritz R. The neutrophil in antineutrophil cytoplasmic autoantibody-associated vasculitis. *J Leukoc Biol* 2013; 94: 623–631.

[2] Tang S, Zhang JB. [Current progress in the immunopathogenesis of ANCA-associated systemic vasculitis]. *Immunological Journal* 2013; 29: 628 –631. [Article in Chinese].

[3] Eline H, Penne EL, Voskuyl AE, *et al*. Cardiovascular events in anti-neutrophil cytoplasmic antibody–associated vasculitis: a meta-analysis of observational studies. *Rheumatology (Oxford)* 2018; 57: 555–562.

[4] Kang A, Antonelou M, Tanna A, *et al*. High incidence of arteria and venous thrombosis in ANCA-associated vasculitis. *J Rheumatol* 2019; 46: 285–293.

[5] Berti A, Matteson EL, Crowson CS, *et al*. Risk of cardiovascular disease and venous thromboembolism among patientswith incidentanca-associated vasculitis: a 20 year population-based cohort study. *Mayo Clin Proc* 2018; 93: 597–606.

[6] Museedi AS, Nashawi M, Ghali A, *et al*. ST Elevation myocardial infarction as presenting feature of C-ANCA vasculitis: a case of a diagnostic dilemma. *Eur J Case Rep Intern Med* 2020; 7: 001658.
[7] Lawler PR, Bhatt DL, Godoy LC, *et al*. Targeting cardiovascular inflammation: next steps in clinical translation. *Eur Heart J* 2021; 42: 113–131.
[8] Ridker PM, Macfadyen JG, Everett BM, *et al*. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. *Lancet* 2018; 391: 319–328.
[9] Tardif JC, Kouz S, Waters DD, *et al*. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med* 2019; 381: 2497–2505.
[10] Nidorf SM, Fiolet A, Mosterd A, *et al*. Colchicine in patients with chronic coronary disease. *N Engl J Med* 2020; 383: 1838–1847.

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