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Recurrent stent thrombosis in two coronary territories within two months in a patient with atrial fibrillation on triple antithrombotic therapy: a case report and literature review

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ABSTRACT

Introduction: Stent thrombosis is a rare but serious complication of percutaneous coronary intervention (PCI), with high morbidity and mortality. Recurrence in several coronary territories in the same patient is exceptional and raises questions about predisposing factors and antithrombotic strategy, especially in patients with atrial fibrillation (AF) who require oral anticoagulation.

Case presentation: We report the case of a 69-year-old man with known coronary artery disease (right coronary artery stent in 2016), former smoker and cannabis user, with dyslipidaemia and paroxysmal AF on rivaroxaban. Eight weeks before admission, he had an inferobasal myocardial infarction due to thrombotic occlusion of the right coronary artery at the site of the old stent (very late stent thrombosis), complicated by an electrical storm and treated with stent-in-stent implantation. Ten days before admission, a drug-eluting stent was implanted in the mid left anterior descending artery (LAD). He was admitted for an extensive anterior ST-segment elevation myocardial infarction while on triple antithrombotic therapy (aspirin, clopidogrel, rivaroxaban), with no reported interruption. Coronary angiography showed thrombotic in-stent occlusion of the mid LAD (TIMI 0 flow), treated with balloon angioplasty and intracoronary tenecteplase, with final TIMI 2 flow. The course was complicated by left ventricular failure (ejection fraction falling from 51% to 25%) and right-sided pneumonia. Because of a suspected apical thrombus, rivaroxaban was replaced by acenocoumarol, and he was discharged on one month of triple antithrombotic therapy (aspirin, clopidogrel, acenocoumarol) and full heart failure therapy.

Conclusion: This case illustrates the multifactorial nature of stent thrombosis: maximal antithrombotic protection (triple therapy) does not eliminate the risk. Recurrent stent thrombosis despite well-conducted treatment should prompt intravascular imaging to identify mechanical causes, consideration of poor response to antiplatelet agents and thrombophilia, and adjustment of antithrombotic intensity.

KEYWORDS

stent thrombosis; acute coronary syndrome; atrial fibrillation; oral anticoagulants; triple antithrombotic therapy; percutaneous coronary intervention

MAIN ARTICLE

INTRODUCTION

Coronary angioplasty with stent implantation has become the standard treatment for acute coronary syndromes (ACS) [1]. Despite advances in new-generation drug-eluting stents and antiplatelet therapy, stent thrombosis remains "the Achilles' heel" of the technique [3,4]. It most often presents as ST-segment elevation myocardial infarction (STEMI) or sudden death. Mortality of myocardial infarction due to stent thrombosis can reach 45% despite emergency reperfusion [3].

According to the Academic Research Consortium (ARC), stent thrombosis is classified by level of certainty (definite, probable, possible) and by timing: early (0 to 30 days, including acute < 24 h and subacute forms), late (31 days to 1 year) and very late (beyond 1 year) [2,3]. Its predisposing factors relate to the patient, the stent and the procedure [3,6].

In patients with atrial fibrillation (AF) undergoing PCI, the need to combine oral anticoagulation with antiplatelet therapy requires a delicate balance between ischaemic and bleeding risk [1,13,15]. We report the case of a patient who had two stent thromboses in two different coronary territories within two months, the second occurring ten days after drug-eluting stent implantation while on triple antithrombotic therapy with aspirin, clopidogrel and rivaroxaban. This case is reported in accordance with the CARE guidelines.

CASE PRESENTATION

Patient information and history

A 69-year-old man, married with three children, presented with the following cardiovascular risk factors: age, male sex, chronic smoking with cannabis use (both stopped one month before admission) and dyslipidaemia treated with a statin. He had no family history of premature coronary artery disease and no diabetes.

He had known coronary artery disease since 2016, when he presented with a non-ST-segment elevation myocardial infarction (NSTEMI) due to single-vessel disease of the right coronary

artery (RCA), treated with a drug-eluting stent. He also had paroxysmal AF treated with a direct oral anticoagulant (rivaroxaban).

Eight weeks before admission (day -56), the patient had an inferobasal STEMI due to thrombotic occlusion of the proximal-to-mid RCA at the site of the old stent, i.e. very late stent thrombosis. This episode was complicated by haemodynamic instability due to an electrical storm requiring intensive care admission. Angioplasty with stent-in-stent implantation was performed, with good haemodynamic and rhythmic outcome.

Ten days before admission (day -10), staged angioplasty of the mid left anterior descending artery (LAD) was performed with implantation of a drug-eluting stent. Since then, the patient had been on triple antithrombotic therapy: aspirin 75 mg/day, clopidogrel 75 mg/day and rivaroxaban.

Current presentation

On the day of admission (day 0), the patient developed typical ischaemic chest pain at rest at 4 p.m., similar to his previous coronary events. He presented to the emergency department of another hospital four hours after pain onset. The qualifying electrocardiogram (ECG) showed extensive anterior ST-segment elevation with inferior reciprocal changes. There was no dyspnoea, palpitations, syncope or sign of infection. The patient reported no interruption of his treatment, in particular of aspirin, clopidogrel and rivaroxaban.

Emergency coronary angiography and PCI

Emergency coronary angiography showed thrombotic in-stent occlusion of the mid LAD, extending proximal to the stent, with TIMI 0 flow. Recanalisation was achieved with balloon dilatation combined with intracoronary tenecteplase (Metalyse®), with final TIMI 2 flow. The procedure report does not mention intravascular imaging (IVUS or OCT). Dual antiplatelet therapy with therapeutic-dose enoxaparin was prescribed, and repeat angiography was recommended. The patient was then transferred to our cardiac intensive care unit.

Clinical examination on admission

The patient was conscious and oriented, without respiratory distress (respiratory rate 16 breaths/min, SpO₂ 95% on room air), with residual pain rated 3–4/10 (compared with 8/10 initially). Blood pressure was 147/72 mmHg and heart rate 80 bpm. Heart sounds were regular, without murmur. Peripheral pulses were present and symmetrical. Lung auscultation revealed

no crackles. There was no sign of deep vein thrombosis, and the rest of the examination was unremarkable.

Investigations

Electrocardiograms. The admission ECG showed regular sinus rhythm at 65 bpm, left axis deviation, PR interval 160 ms, narrow QRS complexes, inferior and anterior Q waves, and extensive anterior ST-segment elevation with inferior reciprocal changes. The ECG recorded immediately after PCI (Figure 1) showed transient QRS widening (140 ms) with an axis of 145° and persistent ST-segment elevation from V2 to V6. Eight hours later (Figure 2), the rhythm was sinus at 108 bpm, QRS complexes were narrow (82 ms), the axis was -34° , with QS waves from V1 to V4 and persistent ST-segment elevation, maximal in V3–V4. On day 14 (Figure 3), the ECG showed sinus rhythm at 61 bpm, anterior necrosis sequelae (QS waves from V1 to V3), negative T waves in the anterior leads and a QTc of 498 ms.

Transthoracic echocardiography (TTE). TTE performed on admission (day 0) showed a non-dilated left ventricle (LV), akinesia of the apical inferior and septal segments, hypokinesia of the inferior wall and the mid inferoseptal segment, and a preserved LV ejection fraction (LVEF) of 51% (biplane Simpson). An apical thrombus was suspected in the akinetic segments. Follow-up TTE on day 8 showed a non-dilated LV with a thinned septum and akinesia of the apex and adjacent segments, of the inferior, inferoseptal and inferolateral walls, and of the mid segment of the anterior wall. LVEF had dropped to 25% (biplane Simpson). The mitral inflow pattern was restrictive ($E/A = 2.9$) and there was mild mitral regurgitation. The probability of pulmonary hypertension was intermediate (peak tricuspid regurgitation velocity 2.9 m/s), right ventricular function was preserved, and there was no pericardial effusion. No LV thrombus was seen; the initially suspected apical image corresponded to a false tendon.

Chest X-ray (Figure 4) showed a bilateral alveolar-interstitial pattern and right-sided consolidation.

Laboratory tests. The main results are summarised in Table 1. They notably showed elevated troponin, CRP of 7 mg/L, normal renal function and LDL cholesterol of 0.60 g/L on statin therapy.

Table 1. Main laboratory results.

Parameter	Day 1	Day 12
Haemoglobin (g/dL)	12.4	—
White blood cells (/mm³)	10,200	—
Platelets (/mm³)	253,000	—
Sodium / potassium (mmol/L)	136 / 4.1	138 / 4.5
Bicarbonate (mmol/L)	—	26
Urea (g/L)	0.30	0.74
Creatinine (mg/L)	8.6	10.4
CRP (mg/L)	7	—
Troponin	28.8	—
Total cholesterol / LDL / TG (g/L)	1.15 / 0.60 / 0.40	—
Prothrombin time (%) / INR (on acenocoumarol)	—	66 / 2.36

Diagnosis

The final diagnosis was extensive anterior STEMI due to definite (ARC criteria), early (subacute, day 10) stent thrombosis of the mid LAD. The event occurred eight weeks after very late stent thrombosis of the RCA. It was complicated by left ventricular failure and right-sided pneumonia.

Management and outcome

From an ischaemic and rhythmic standpoint, the patient had no recurrent angina and no new ECG changes during hospitalisation. Haemodynamically, an episode of left ventricular failure was treated with diuretics. The outcome was favourable, with no signs of congestion at discharge (BP 90/61 mmHg, HR 73 bpm, SpO₂ 97%, no crackles). Right-sided pneumonia was treated with amoxicillin–clavulanic acid for seven days, with good clinical and biological response.

Antithrombotic therapy was modified: because of the suspected apical thrombus on admission TTE, rivaroxaban was replaced by a vitamin K antagonist (acenocoumarol, INR 2.36 on day 12). Triple antithrombotic therapy (aspirin 75 mg + clopidogrel 75 mg + acenocoumarol) was

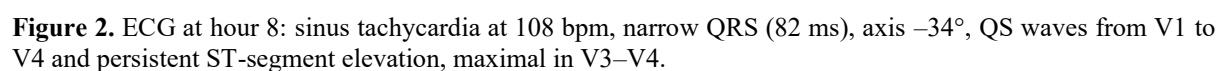
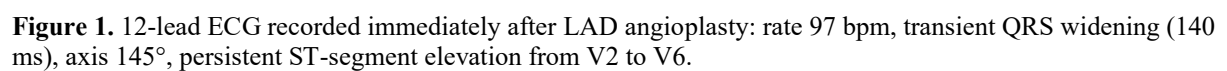
prescribed for one month, followed by dual therapy (clopidogrel + acenocoumarol). Discharge treatment also included:

- lansoprazole 30 mg/day (gastric protection);
- rosuvastatin 20 mg/day;
- ramipril 1.25 mg/day, bisoprolol 5 mg/day, spironolactone ½ tablet of 10 mg/day, dapagliflozin 10 mg/day and ivabradine 5 mg/day;
- furosemide 1 tablet in the morning and ½ tablet at 2 p.m., with potassium supplementation.

The patient remained abstinent from tobacco and cannabis. He is followed up in the ischaemic heart disease outpatient clinic.

Table 2. Timeline of events (day 0 = day of admission).

Time	Event
2016	NSTEMI – single-vessel RCA disease – drug-eluting stent
Day –56	Inferobasal STEMI – thrombotic occlusion of the RCA at the old stent (very late stent thrombosis) – electrical storm – stent-in-stent implantation
Day –30	Smoking and cannabis cessation
Day –10	Staged PCI of the mid LAD – drug-eluting stent; treatment: aspirin + clopidogrel + rivaroxaban
Day 0	Extensive anterior STEMI (4 h) – in-stent thrombosis of the LAD (TIMI 0) – balloon + intracoronary tenecteplase – TIMI 2
Day 0	TTE: LVEF 51%, suspected apical thrombus → rivaroxaban replaced by acenocoumarol
Days 1–7	Left ventricular failure (diuretics); right-sided pneumonia (amoxicillin–clavulanic acid, 7 days)
Day 8	TTE: LVEF 25%, no LV thrombus (false tendon)
Days 12–14	INR 2.36 on acenocoumarol; ECG: anterior sequelae, QTc 498 ms; discharge on one month of triple therapy



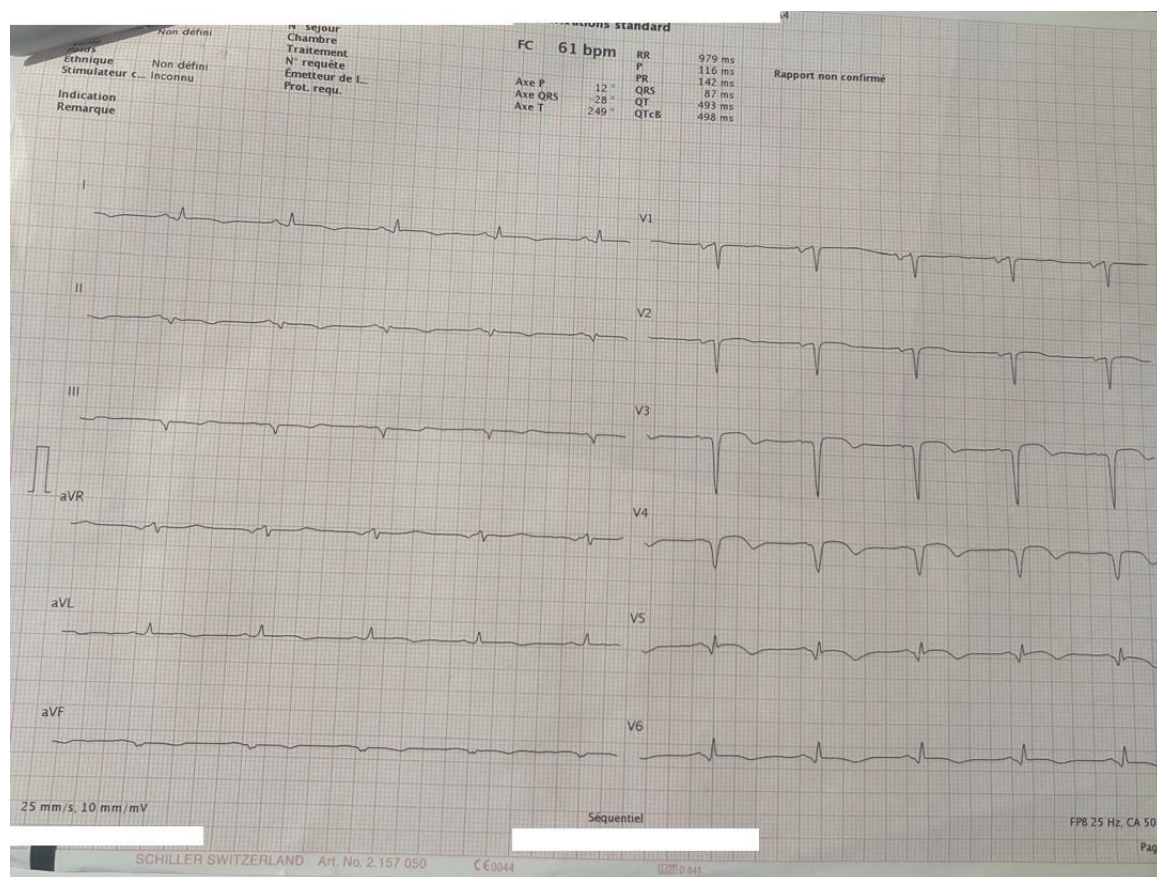


Figure 3. ECG on day 14: sinus rhythm at 61 bpm, anterior necrosis sequelae (QS waves from V1 to V3), negative T waves in the anterior leads and QTc prolongation (498 ms).

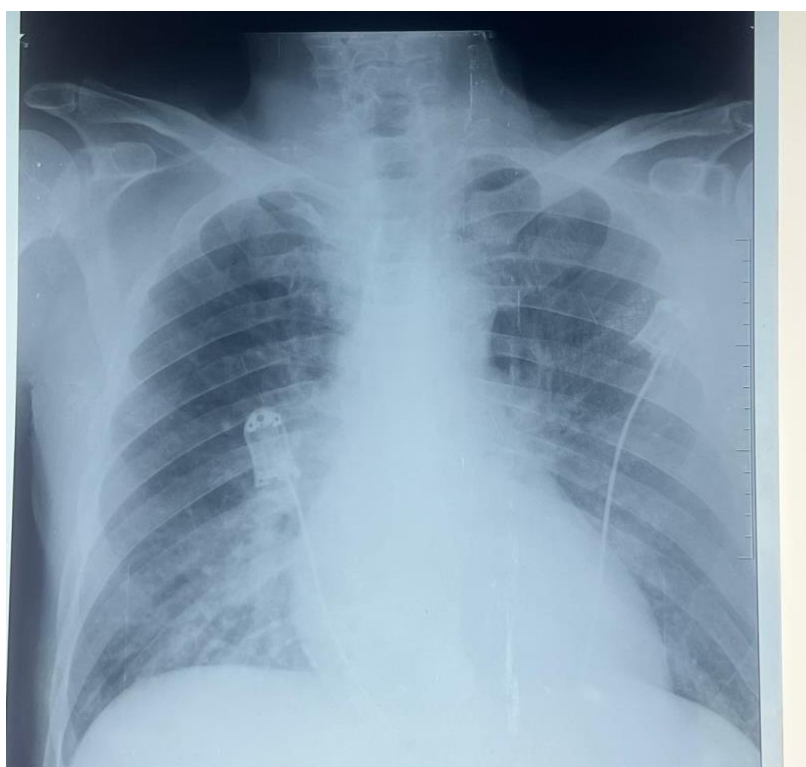


Figure 4. Bedside frontal chest X-ray: bilateral alveolar-interstitial pattern and right-sided consolidation.

DISCUSSION

This case is remarkable for two stent thromboses in two distinct coronary territories within two months. The second occurred early, ten days after drug-eluting stent implantation, in a patient on triple antithrombotic therapy who reported no treatment interruption. It allows discussion of the classification of the event, its predisposing factors, antithrombotic strategy in patients with AF, and the management of recurrent stent thrombosis.

Classification and incidence

According to ARC criteria, the LAD event is a **definite** stent thrombosis, angiographically confirmed, and **early** (subacute, between 24 hours and 30 days) [2,3]. The RCA event eight weeks earlier, on a stent implanted in 2016, is a **very late** stent thrombosis (beyond one year). The incidence of stent thrombosis is approximately 0.5% during the first month on dual antiplatelet therapy, and between 0.8% and 5.8% at one year depending on patient and lesion characteristics [3]. In the Tunisian series by Ben Ayed et al. of 76 ostial LAD angioplasties, the 12-month stent thrombosis rate was 5.2% [5]. In the series by Malki et al. from Rabat, thromboses were very late in 50% of cases, late in 16% and subacute in 33% [4]. Two thromboses with different timing in the same patient remain exceptional. This suggests a combination of local mechanisms (specific to each stent) and a prothrombotic background or insufficient antithrombotic protection.

Predisposing factors in our patient

Factors predisposing to stent thrombosis are traditionally divided into three categories: patient-related, stent-related and procedure-related (Table 3) [3,6].

Patient-related factors. Our patient had several recognised factors: age, the ACS setting, which increases the risk of thrombosis [3], and left ventricular dysfunction. Ben Ayed et al. identified impaired LVEF as an independent predictor of stent thrombosis ($p < 0.01$) [5], and Iakovou et al. had previously reported low LVEF as a predictor of thrombosis after drug-eluting stent implantation [11]. Smoking and cannabis use, stopped only one month before the event, may have contributed to a prothrombotic state and endothelial dysfunction; cannabis is also a recognised trigger of myocardial infarction [17]. Conversely, the patient was not diabetic, whereas diabetes is a major factor in the literature: in the EVASTENT study, the one-year thrombosis rate rose from 0.8% in non-diabetic single-vessel patients to 4.3% in diabetic

multivessel patients [3]. In the series by Malki et al., 66% of patients were diabetic, and interruption of antiplatelet therapy (clopidogrel or aspirin) was found in two of six cases [4]. Our patient therefore differs by the absence of these two classic factors: thrombosis occurred on well-adhered triple therapy, without diabetes.

Stent- and procedure-related factors. Early thrombosis is most often related to a mechanical problem: underexpansion, malapposition, edge dissection or incomplete lesion coverage [3,6]. Drug-eluting stents delay strut re-endothelialisation: this usually occurs within the first three months with bare-metal stents, but may take up to one year with drug-eluting stents [3,7]. Treatment of restenosis, multiple or overlapping stents in the same vessel and superimposed metal layers (stent-in-stent, as performed in the RCA) are also recognised factors [3,6]. Apart from intravascular imaging, no examination can assess the quality of stent deployment or the state of the neo-endothelium [3]. The absence of intravascular imaging during our patient's management does not allow a mechanical cause to be ruled out. European guidelines nevertheless recommend intravascular imaging to detect mechanical causes of stent failure [18]. The value of OCT in this setting is illustrated by the case reported by Thouvenot: acute thrombosis occurring fifteen minutes after bifurcation angioplasty was treated with thrombectomy and OCT-guided stent optimisation, without a new stent [10].

Pharmacological factors. Variability in biological response to clopidogrel is well established: up to 37% of patients may be considered "poor responders" depending on the measurement method, and an insufficient response correlates with thrombotic events [3,19]. Drug interactions have been described, notably with omeprazole [3,20]; our patient received lansoprazole, whose interaction is less well documented. No platelet function test or CYP2C19 genotyping was performed, which is a limitation of our report, as in the series by Malki et al. [4]. Finally, thrombosis occurred on well-adhered triple antithrombotic therapy (aspirin, clopidogrel, rivaroxaban), i.e. the most intensive protection possible. This makes insufficient pharmacological protection unlikely, except in the case of poor response to clopidogrel. It therefore points towards a local mechanical cause or a prothrombotic background. This point is discussed below.

Table 3. Factors predisposing to stent thrombosis [3,6] and their presence in our patient.

Category	Factors described in the literature	Our patient
Patient	Age, ACS, diabetes, renal failure, LV dysfunction, inflammatory syndrome, poor adherence, antiplatelet interruption, poor antiplatelet response, thrombophilia	Age 69, ACS, impaired LVEF, recently stopped tobacco/cannabis; no diabetes; no renal failure; no reported interruption; clopidogrel response and thrombophilia not assessed
Stent	Drug-eluting stent (delayed re-endothelialisation), length, small diameter, complex lesions, polymer	Recent drug-eluting stent in the LAD; old stent (2016) then stent-in-stent in the RCA
Procedure	Underexpansion, malapposition, residual dissection, overlapping stents, stent-in-stent, direct stenting	Stent-in-stent in the RCA; no intravascular imaging; mechanism not documented
Treatment	Early interruption or de-escalation of antiplatelet therapy, poor clopidogrel response, drug interactions	Triple therapy with aspirin + clopidogrel + rivaroxaban without interruption; clopidogrel response not assessed; PPI (lansoprazole)

Antithrombotic strategy in patients with AF undergoing PCI

In patients with AF requiring PCI, the randomised trials PIONEER AF-PCI, AUGUSTUS, REDUAL PCI and ENTRUST-AF PCI showed that dual therapy combining a direct oral anticoagulant with a P2Y₁₂ inhibitor (most often clopidogrel) significantly reduces bleeding compared with triple therapy including aspirin [12–14]. However, the meta-analysis by Gargiulo et al. showed a significant increase in the risk of stent thrombosis with dual therapy compared with triple therapy, at the cost of a marked reduction in bleeding [12]. This excess risk is concentrated in the first weeks after PCI, when antiplatelet protection is most needed. In our patient, given a recent stent thrombosis in the RCA, the team logically opted for triple therapy, the most protective strategy from an ischaemic standpoint. The occurrence of early thrombosis on day 10 despite this triple therapy is therefore all the more remarkable. It shows

that intensifying antithrombotic therapy does not compensate for a possible mechanical stent defect or biological resistance to clopidogrel.

European guidelines therefore recommend, by default, a short course of triple therapy (up to one week), but allow it to be extended to one month in patients at high thrombotic risk: ACS, complex procedure, history of stent thrombosis [1,15]. Clopidogrel remains the P2Y₁₂ inhibitor of choice in combination with an anticoagulant; prasugrel is not recommended in this setting [1,15]. In our patient, at particularly high thrombotic risk (two stent thromboses, recurrent ACS, LV dysfunction), a new one-month course of triple therapy was chosen in line with these guidelines, at the cost of a high bleeding risk requiring gastric protection and close INR monitoring. As thrombosis occurred on clopidogrel, poor response to this drug should be suspected. A platelet reactivity test or CYP2C19 genotyping could justify replacing clopidogrel with ticagrelor in combination with the anticoagulant, at the cost of a higher bleeding risk [1,15].

The choice of anticoagulant also deserves discussion. Direct oral anticoagulants are preferred over vitamin K antagonists (VKA) in AF associated with PCI because they cause less bleeding [13,15]. In our patient, rivaroxaban was replaced by acenocoumarol because of the suspected apical thrombus on admission TTE, in the setting of extensive anterior infarction with apical akinesia. VKAs remain the best-documented option for LV thrombus, although direct oral anticoagulants are an increasingly used alternative [1]. This choice is also supported by the occurrence of two stent thromboses on rivaroxaban and by the hypothesis of thrombophilia, which has not yet been excluded. In antiphospholipid syndrome in particular, direct oral anticoagulants are contraindicated and VKAs remain the reference [6].

Treatment of stent thrombosis

Stent thrombosis most often presents as STEMI and requires emergency reperfusion by primary PCI [1]. In the case of a large thrombus burden, selective thrombus aspiration, glycoprotein IIb/IIIa inhibitors or, more rarely, intracoronary fibrinolysis can be used as bail-out. Intracoronary tenecteplase, used in our patient, is off-label and supported by limited data. The suboptimal final TIMI 2 flow and persistent ST-segment elevation probably reflect microvascular damage (no-reflow) and partly explain the deterioration in LVEF.

Correcting the underlying mechanism is essential: high-pressure post-dilatation with a non-compliant balloon in the case of underexpansion, and implantation of an additional stent in the case of edge dissection or uncovered lesion [3,8]. As in in-stent restenosis, whose main

mechanism is excessive neointimal hyperplasia [7], the choice between stent-in-stent and drug-coated balloon depends on lesion characteristics. The drug-coated balloon avoids adding a new metal layer and allows a shorter duration of antiplatelet therapy [8,9]. In the study by Atlas et al. (180 patients treated for in-stent restenosis), the drug-coated balloon was associated with less recurrent restenosis at 12 months (12% vs 18%) and a lower target lesion revascularisation rate (10% vs 16%), whereas stent-in-stent remained preferable in diabetic patients and long lesions [9]. In the series by Malki et al., half of the patients were treated with PCI, one with coronary artery bypass grafting and two medically [4].

Aetiological work-up of recurrent stent thrombosis

Recurrent stent thrombosis, in two different territories and under antithrombotic treatment, should prompt a search for an underlying prothrombotic state. Sabri reported several cases of in-stent thrombosis associated with antiphospholipid syndrome (APS) [6]. In this setting, it is recommended to favour VKA anticoagulation (target INR 2.5–3.5), avoid direct oral anticoagulants, prolong heparin therapy and consider coronary artery bypass grafting rather than complex PCI [6]. Although this work-up is mainly proposed in young patients, testing (lupus anticoagulant, anticardiolipin and anti- β 2-glycoprotein I antibodies) seems justified in our patient given the recurrent and multifocal nature of the thromboses. This work-up was not performed, which is a limitation of our report; it could be offered during follow-up. A platelet function test could also guide the choice of P2Y₁₂ inhibitor [3].

Prognosis and secondary prevention

The patient's prognosis is worsened by severe left ventricular dysfunction (LVEF 25%). This justifies full therapy for heart failure with reduced ejection fraction (angiotensin-converting enzyme inhibitor, beta-blocker, mineralocorticoid receptor antagonist, SGLT2 inhibitor), reassessment of LVEF at follow-up and, if LVEF remains $\leq 35\%$, consideration of an implantable cardioverter-defibrillator, particularly as the patient has already had an electrical storm. QTc prolongation (498 ms) on day 14 requires monitoring and caution with QT-prolonging drugs. LDL cholesterol of 0.60 g/L remains above the 0.55 g/L target recommended for very-high-risk patients. A target below 0.40 g/L may even be considered in patients with a second vascular event within two years [16]. Lipid-lowering therapy should therefore be intensified (maximal-dose rosuvastatin, ezetimibe, or even a PCSK9 inhibitor). Finally, continued abstinence from tobacco and cannabis and cardiac rehabilitation are integral parts of secondary prevention.

CONCLUSION

Stent thrombosis remains a serious complication of coronary angioplasty, with a multifactorial mechanism. This case of recurrent thrombosis in two territories within two months, one occurring on day 10 on well-adhered triple antithrombotic therapy, shows that intensifying antithrombotic therapy is not always sufficient to prevent this complication in the early post-PCI phase. In recurrent stent thrombosis, a mechanical cause should be sought by intravascular imaging, along with poor response to antiplatelet agents and thrombophilia, and the intensity and duration of antithrombotic therapy should be adapted to the individual risk profile.

KEY POINTS

- Stent thrombosis is classified by ARC criteria as early (≤ 30 days), late (31 days–1 year) and very late (> 1 year).
- Predisposing factors relate to the patient, the stent, the procedure and antithrombotic therapy.
- In patients with AF undergoing PCI, dual therapy with a direct oral anticoagulant plus clopidogrel reduces bleeding but slightly increases the risk of stent thrombosis. Triple therapy for up to one month is justified in patients at high thrombotic risk, but it does not eliminate this risk.
- Recurrent stent thrombosis should prompt intravascular imaging (IVUS/OCT) and consideration of platelet function testing and a thrombophilia work-up, including APS.

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