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CASE REPORT
Coronary heart disease

Percutaneous coronary intervention in a patient with heparin resistance due to essential thrombocythaemia: a case report

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Background Coronary artery disease is uncommon in patients with essential thrombocythaemia (ET); therefore, no treatment strategies have been established.

Case summary A 68-year-old man visited our hospital with worsening effort angina complicated with ET. Coronary angiography (CAG) revealed moderate stenosis of the left main trunk and left anterior descending artery (LAD). We planned to perform percutaneous coronary intervention (PCI) only after the patient's platelet count had fallen below 600 000/μL. Platelet factor 4 levels were markedly elevated (355.0 ng/mL; the normal range is <20 ng/mL). We observed a *de novo* lesion in the proximal left circumflex artery and stenosis progression in the LAD at the time of the PCI, neither of which had been detected at the previous CAG. During the PCI procedure, argatroban was infused to maintain the activated clotting time (ACT) above 250 s. The PCI was performed successfully without any complications. Follow-up CAG showed no restenosis, and no bleeding complications were observed during the course.

Discussion In patients with ET, it may be useful to measure platelet factor 4 before PCI and to monitor ACT during the procedure. When heparin resistance is suspected based on blood coagulation tests, infusion of direct thrombin inhibitor during PCI may be considered, with anticoagulation monitoring by ACT.

Keywords Case report • Essential thrombocythaemia • Heparin resistance • Percutaneous coronary intervention

Learning points

- The strategies for coronary artery disease in patients with essential thrombocythaemia are not well established.
- Before performing percutaneous coronary intervention (PCI), platelet count was reduced to less than half of the original count; however, platelet factor 4 was positive which is associated with heparin resistance.
- When heparin resistance is suspected in ET patients with elevated platelet factor 4, the usage of a direct thrombin inhibitor can be considered during PCI.

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Introduction

Ischaemic stroke and ischaemic heart disease have marked effects on prognosis in patients with essential thrombocythaemia (ET).[1] The main purpose of ET treatment is to prevent vascular events; however, no strategies have been established to manage coronary artery disease in patients with ET due to the rare prevalence of ET itself. In the present report, we describe a case of worsening coronary artery disease during treatment for ET. The patient was successfully treated using coronary stenting, while argatroban was used to avoid the thrombotic complications of possible heparin resistance.

Timeline

Time	Event
Five years before visit	Diagnosis of essential thrombocythaemia (ET), treatment with hydroxyurea was started.
One month before visit	Treatment of ET had changed from hydroxyurea to anagrelide.
First presentation	Patients visited our hospital for premature ventricular contraction and shortness of breath on effort.
First admission	Coronary angiography (CAG) showed moderate stenosis on the left main trunk and left anterior descending artery (LAD). The value of instantaneous wave-free ratio of proximal LAD lesion was 0.88. Platelet factor 4 markedly increased (91.7 ng/mL).
Two weeks after from 1st admission	Treadmill test showed significant ST depression in V4–V6.
Seven months after 1st admission	Platelet count had fallen <600 000/μL using the combination of hydroxyurea and anagrelide.
Second admission	We observed a *de novo* lesion in the proximal left circumflex artery and stenosis progression in the LAD at the time of the percutaneous coronary intervention (PCI), neither of which had been detected at the previous CAG. During the procedure, argatroban was infused for activated clotting time control. Percutaneous coronary intervention was performed successfully without any complications.
Nine months after PCI	Follow-up CAG showed no restenosis or any bleeding complication was not observed during the course.

Case presentation

A 68-year-old man with ET visited our hospital for premature ventricular contractions (PVCs) and shortness of breath on effort. He had started taking anagrelide 1.5 mg daily, an inhibitor of megakaryocyte maturation and polyploidization, 1 month before his visit because his platelet count could not be controlled using hydroxyurea. He had normal physical findings with no clinical evidence of heart failure. He did not have any thrombotic or bleeding complications of ET. He underwent Holter monitoring, echocardiography, and coronary computed tomography (CT). Holter monitoring showed no sustained ventricular tachycardia, and the patient's PVC burden was <20%. It was suspected that the PVCs had been induced by the anagrelide, and his palpitations gradually resolved without any changes to his medication. However, his shortness of breath persisted. Echocardiography showed normal left ventricular ejection function (70%), with no evidence of valve disease. Coronary CT showed severe stenosis of the left anterior descending artery (LAD), prompting coronary angiography (CAG) that revealed moderate stenosis of the left main trunk (LMT) and LAD (*Figure 1A–D*, *Video 1*). The instantaneous wave-free ratio value of the proximal LAD lesion was 0.88. To estimate the efficacy of the heparin, we checked the activated clotting time (ACT), which was 144 s, even after 8000 units of unfractionated heparin had been delivered intravenously. Therefore, heparin resistance was suspected. We did not measure fractional flow reserve because the patient had active asthma, PVCs, and an inadequate prolongation of ACT. The patient's platelet factor 4, a protein in platelet α-granules released, was markedly increased (91.7 ng/mL; the normal range is <20 ng/mL), whereas he was negative for antithrombin (AT)-3 and heparin-induced thrombocytopenia platelet factor 4 antibody (HIT-Ab). Conventional anti-anginal therapy was implemented, but his shortness of breath persisted and a treadmill test showed significant ST depression in V4–V6. We planned to perform percutaneous coronary intervention (PCI) only after the patient's platelet count had fallen below 600 000/μL. Meanwhile, the patient was treated by a haematologist at our hospital using hydroxyurea and anagrelide. Seven months after the initial CAG date, the patient's platelet count was <600 000/μL. On the day before his PCI, his platelet factor 4 was 355.0 ng/mL, which was still markedly higher than the upper normal limit. We observed a *de novo* lesion in the proximal left circumflex artery (LCX) and stenosis progression in the LAD at the time of the PCI, neither of which had been detected at the previous CAG (*Figure 2A* and *B*). During the PCI procedure, argatroban was infused to maintain the ACT above 250 s. Specifically, 1 mg/kg of argatroban was injected intravenously, followed by infusion at 31 mL/h. The PCI was performed successfully without any complications. Synergy stents were implanted in the LMT-LCX (diameter: 3.5 mm, length 24 mm) and LAD (diameter: 3.0 mm, length 24 mm; *Figure 2C* and *D*, *Video 2*). After 9 months, follow-up CAG showed no restenosis, and no bleeding complications were observed during the course (*Figure 3A* and *B*, *Video 3*). The patient received dual antiplatelet therapy (aspirin and prasugrel) after stent implantation.

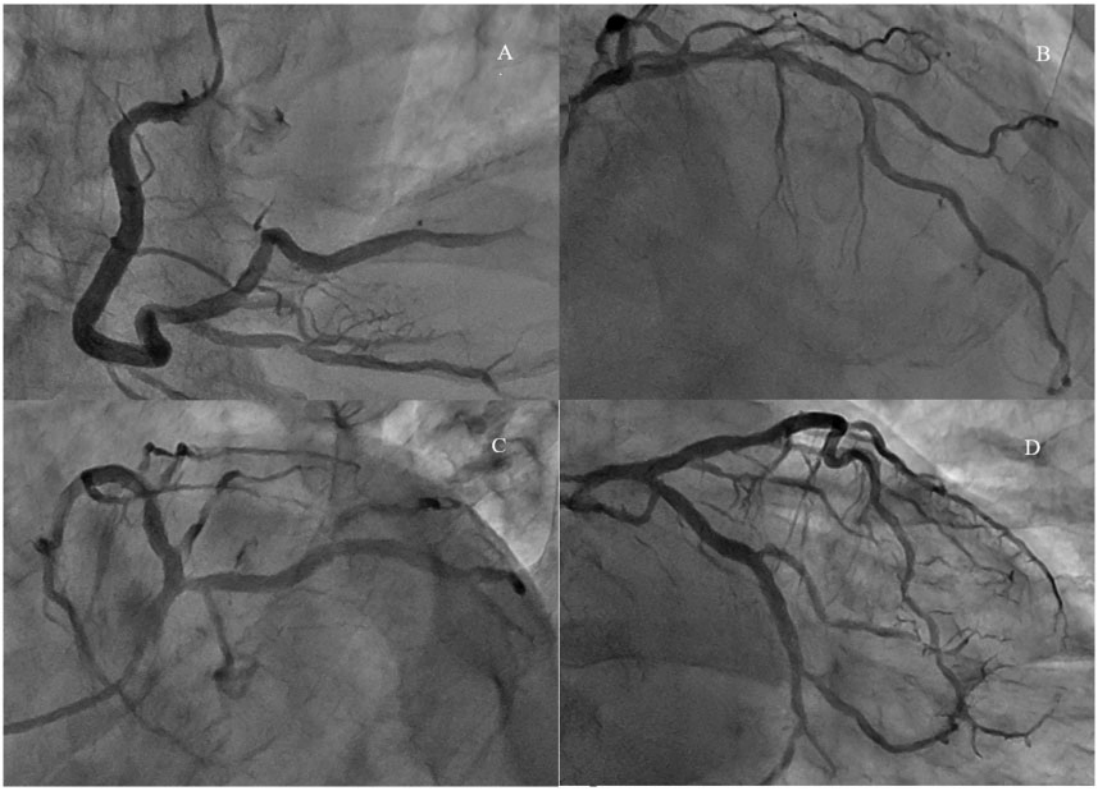
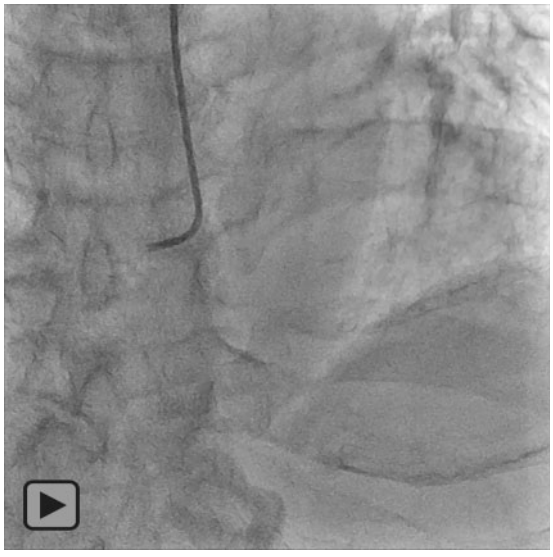
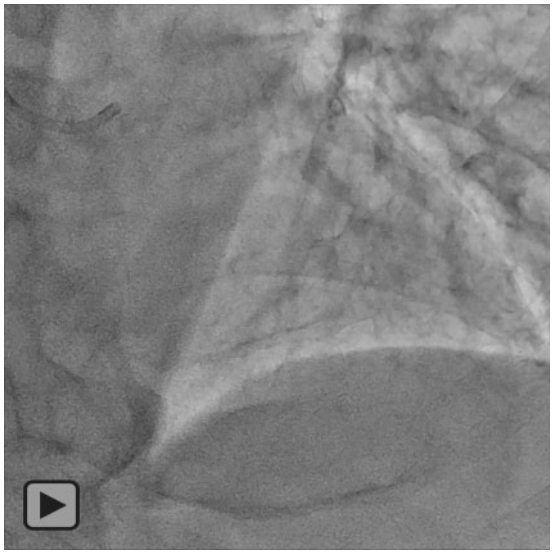


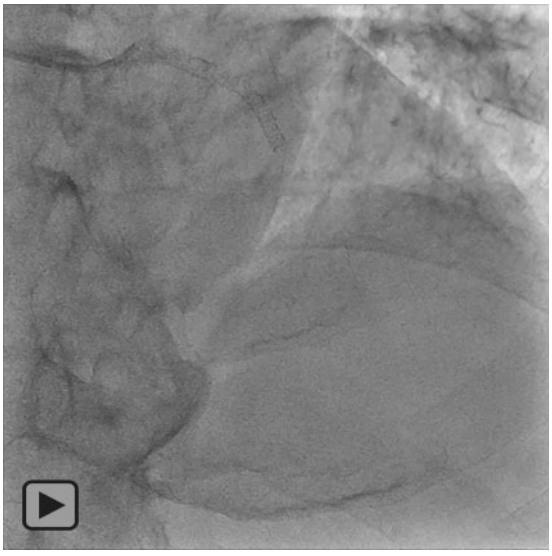
Figure 1 (*A*) The right coronary artery was intact. (*B–D*) Moderate stenosis is evident in the left main trunk and proximal segment of the left anterior descending artery.



Video 1 Initial coronary angiography.



Video 2 Percutaneous coronary intervention.



Video 3 Follow-up coronary angiography.

Discussion

The importance of increased platelet count is unclear in patients with both angina pectoris and ET, but a reduction in platelet count reduces the frequency of thrombosis.[2] Cortelazzo *et al.*[3] suggested that the duration of platelet count <600 000/μL was inversely correlated with the rate of thrombotic events in patients with ET. In the present case, the patient's ET was refractory to pharmacological treatment and his symptoms of cardiac ischaemia were aggravated. Therefore, we implemented hydroxyurea and anagrelide combination therapy and waited until his platelet count was below 600 000/μL. Only then did we treat the coronary artery. Some reports have suggested that thrombi of the coronary artery are associated with ET, and that ET may carry a risk of sub-acute stent thrombosis.[4,5] Regarding treatment options for revascularization, patient preferred PCI and were only treated after providing informed consent. Cardiac surgery in patients with ET carries a high risk of perioperative thrombotic complications.[6]

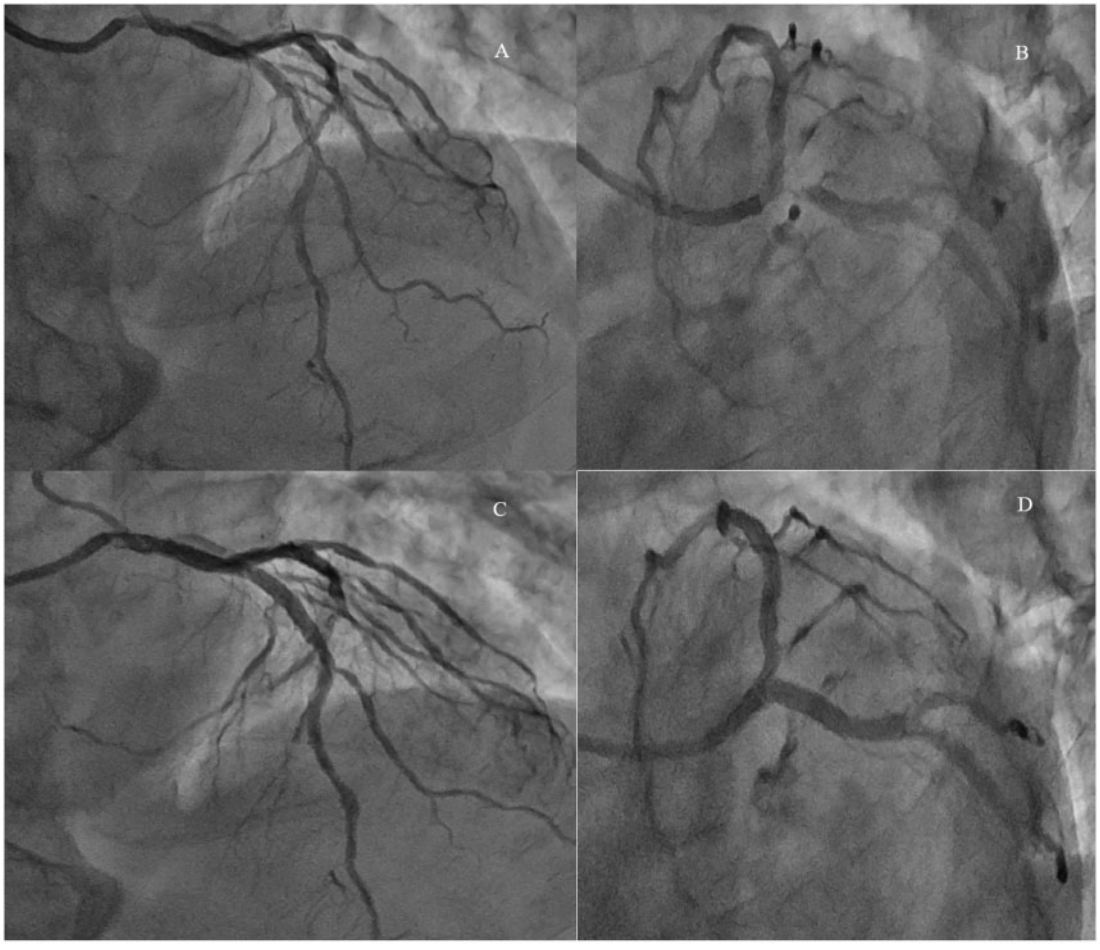


Figure 2 (*A* and *B*) A *de novo* lesion in the proximal left circumflex artery and stenosis progression in the left anterior descending artery at the time of the percutaneous coronary intervention. (*C* and *D*) Final angiography showed a good result in both lesions after implantation of synergy stents (diameter: 3.0 mm, length: 24 mm in the left anterior descending artery; diameter: 3.5 mm, length 24 mm in the left circumflex artery).

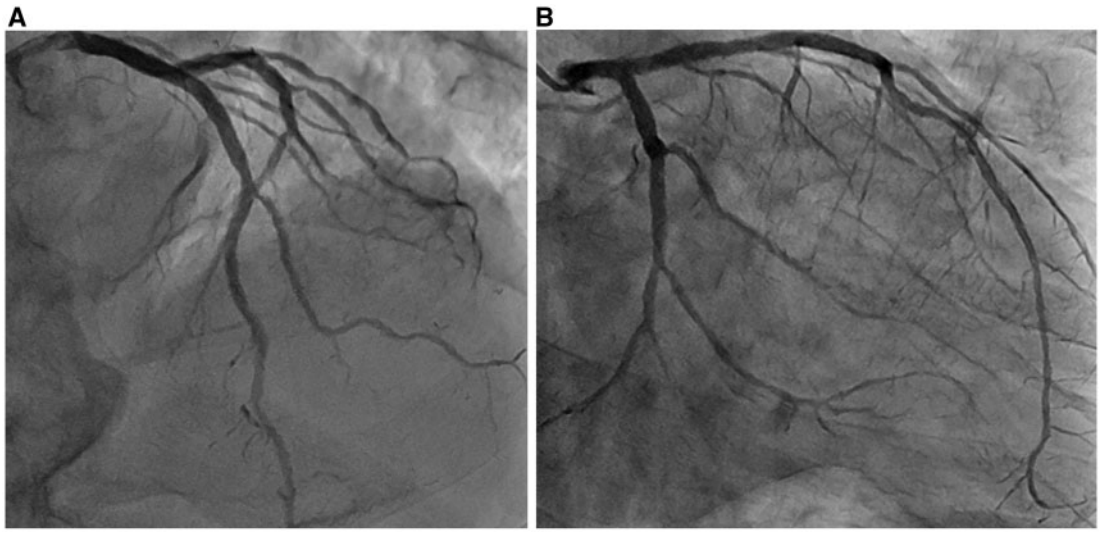


Figure 3 (*A* and *B*) Follow-up angiography showed no restenosis.

Platelet factor 4 increases in most patients with ET, as in the present case; it may be one of the mechanisms of heparin resistance.[7–9] Platelet factor 4 prevents low-density lipoprotein (LDL) degradation through its receptor and might lead to the generation of oxidized LDL.[10] In addition, it can promote the binding of oxidized LDL to macrophages and endothelial cells,[11] and high level of platelet factor 4 may cause HIT.[12] However, one study reported that reduced heparin activity was not associated with platelet factor 4 levels.[13] It follows that both platelet factor 4 and ACT monitoring may be important to evaluate heparin resistance and predict HIT before PCI in patients with ET. When HIT is suspected, a direct thrombin inhibitor is one treatment option.[14] Some studies showed that heparin is bound to and neutralized by platelet factor 4.[9,15] In contrast, direct thrombin inhibitors do not bind to plasma proteins such as platelet factor 4.[9] Although there are no randomized controlled trials of argatroban usage in PCI in patients with ET, argatroban was associated with lower risk of new thrombosis and morality in patients with HIT.[16] In the present case, we speculated that the patient may have had heparin resistance, and PCI was successfully performed using argatroban. Therefore, in patients with ET, it may be useful to measure platelet factor 4 before PCI and to monitor ACT during the procedure. When heparin resistance is suspected due to insufficient prolongation of ACT, additional heparin infusion can be considered in patients with ET who do not have elevated platelet factor 4, while infusion of a direct thrombin inhibitor during PCI can be considered in patients with ET who have elevated platelet factor 4. The duration and regimen of antiplatelet therapy after stent implantation are not well established in patients with ET. To reduce the risk of stent thrombosis, we chose to continue dual antiplatelet therapy in the present study.

Conclusion

In patients with ET, it may be useful to measure platelet factor 4 before PCI and to monitor ACT during the procedure. When heparin resistance is suspected due to insufficient prolongation of ACT in patients with ET who have elevated platelet factor 4, infusion of a direct thrombin inhibitor during PCI can be considered.

Lead author biography

Dr Toshitaka Okabe is an interventional cardiologist. He received his MD and PhD degrees from Showa University. He worked as a staff at Division of Cardiology, Showa University Northern Yokohama Hospital, Japan from 2010. His scientific interest is heart failure and PCI.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

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