ESC European Society of Cardiology

European Heart Journal - Case Reports (2023) **7**, 1–7
https://doi.org/10.1093/ehjcr/ytad005

**GRAND ROUND**
*Coronary intervention*

# Probable tirofiban-induced thrombotic microangiopathy after stent thrombosis: a case report

**Maria Mattioli [1]*, Giorgia Paoli[1], Benedetta Cambò [2], and Rosario Bonura [1]**

[1]Unità di Terapia Intensiva Coronarica (UTIC), Cardiology Unit, Parma University Hospital, Parma, Italy; and [2]Ematologia e CTMO, Parma University Hospital, Parma, Italy

*Received 9 May 2022; first decision 20 June 2022; accepted 4 January 2023; online publish-ahead-of-print 7 January 2023*

**Background** Glycoprotein (GP) IIb–IIIa inhibitors are antithrombotic drugs used in selected patients during and after percutaneous coronary interventions (PCIs), usually as a bail-out in the setting of no-reflow or thrombotic complications. A notorious life-threatening adverse effect of this drug class is immune-mediated drug-induced thrombocytopenia (DITP). Thrombotic microangiopathy (TMA) induced by GP IIb–IIIa inhibitors has never been reported.

**Case summary** A 72-year-old woman admitted for anterior myocardial infarction treated with primary PCI and stent implantation underwent a first tirofiban infusion as a bail-out strategy. After a new procedure for stent thrombosis, she received a second tirofiban infusion and developed sudden severe thrombocytopenia (platelet count <20 000/μL). Tirofiban was stopped but no observed increase in platelet count. Acute kidney injury due to renal ischaemia and left ventricular thrombosis followed. Unexpectedly, evidence for haemolysis and schistocytosis at peripheral blood smear prompted a diagnosis of TMA. Plasma exchange was immediately started with evidence for initial increase in platelet count, but the patient died due to sudden haemodynamic and respiratory deterioration.

**Discussion** Tirofiban is known to rarely cause immune-dependent DITP. However, it has never been associated with TMA. This case report not only describes the first case of probable tirofiban-induced TMA, but also highlights the importance of a systematic approach to severe thrombocytopenia, even in the setting of low platelet count from a known DITP-related drug. Treatment of TMA in the difficult context of recent myocardial infarction and stent thrombosis requires a complex interplay between cardiologist, haematologist, transfusionist, and nephrologist, carefully balancing thrombotic and haemorrhagic risk.

**Keywords** Thrombotic microangiopathy • Glycoprotein IIb–IIIa inhibitors • Tirofiban • Thrombocytopenia • Acute myocardial infarction • Stent thrombosis • Case report

**ESC Curriculum** 3.2 Acute coronary syndrome • 7.3 Critically ill cardiac patient • 7.4 Percutaneous cardiovascular post-procedure

* Correspondingauthor. Tel: +39 0521 702070, Email: mmattioli@ao.pr.it
Handling Editor: Ying Xuan Gue
Peer-reviewers: Christoph Clemens Kaufmann; Diego Araiza-Garaygordobil
Compliance Editor: Emmanouil Mantzouranis
Supplementary Material Editor: Lynsey Hewitson

## Learning points

- Maintaining a systematic approach to severe thrombocytopenia is important even in the setting of low platelet count from a known DITP-related drug, in order not to miss alternative diagnosis. A diagnosis of thrombotic microangiopathy can prompt life-saving measures and avoid detrimental platelet transfusion.
- Dealing with severe thrombocytopenia in the difficult context of recent stent thrombosis, left ventricular thrombus and renal ischaemia is extremely challenging and requires a complex interplay between cardiologist, haematologist, transfusionist, and nephrologist, carefully balancing thrombotic and haemorrhagic risk.
- Management of antithrombotic drugs in the setting of plasma exchange requires awareness of the mechanism of thrombocytopenia, careful consideration of antithrombotic agents pharmacokinetic, and coordination with transfusionists.

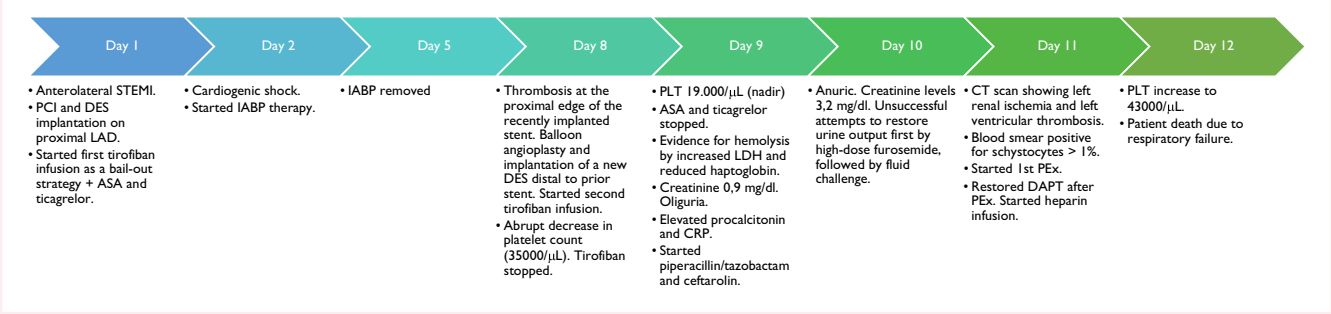
# Primary Specialties involved other than cardiology

Haematology, transfusion medicine.

# Introduction

Glycoprotein (GP) IIb–IIIa inhibitors are antithrombotic drugs used in selected patients during and after percutaneous coronary interventions (PCIs), usually as a bail-out in the setting of no-reflow or thrombotic complications.[1] Thrombocytopenia induced by GP IIb–IIIa inhibitors is a rare, although notorious life-threatening adverse effect. Immune-mediated mechanisms are generally advocated, such as antibodies production induced from conformational changes to GP IIb/IIIa binding site after binding to the GP IIb/IIIa receptor, but the actual pathophysiology is unclear.[2] Among different hypotheses, thrombotic microangiopathy has never been reported. We present the first case of a probable drug-induced thrombotic microangiopathy (DITMA) after tirofiban exposure in a critically ill patient.

# Timeline




ASA, acetylsalicylic acid; CRP, C-reactive protein; CT, computed tomography; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; IABP, intra-aortic balloon pump; LAD, left anterior descending artery; LDH, lactate dehydrogenase; PCI, percutaneous coronary intervention; PEx, plasma exchange; PLT, platelet count; STEMI, ST-elevation myocardial infarction.

# Case presentation

A 72-year-old woman was admitted at the ER for acute, severe chest pain started 90 min earlier. She had a history of hypertension under treatment with valsartan, smoking, and chronic bronchitis. Her physical examination showed normal heart sounds, tachyponea without signs of pulmonary or peripheral congestion, and no mucocutaneous or other obvious clinical sign of bleeding. Her blood pressure was 140/90 mmHg.

An electrocardiogram (ECG) showed ST-segment elevation myocardial infarction in anterolateral leads (*Figure 1*). She received 250 mg intravenous lysine acetylsalicylate according to local standard and soon underwent emergent coronary angiography showing proximal left anterior descending (LAD) artery occlusion. A drug-eluting stent (DES) was implanted with final angiographic evidence of slow-flow and only partial symptom relief and ST-segment elevation reduction on ECG despite good stent position on angiography (see Supplementary material online, *Video S1*, *Figure 2*). A 12-h tirofiban infusion was started as a bail-out strategy (0.04 μg/kg/min loading dose, followed by 0.01 μg/kg/min infusion) and ticagrelor loading dose (180 mg) was administered after the procedure due to concerns over drug absorption, the patient being nauseous before coronary intervention. The patient was eupnoeic soon after the procedure, with no clinical sign of congestion, bleeding, or thrombotic manifestations; her blood pressure decreased to 90/60 mmHg and pulse oxygen saturation was 96% room air. Transthoracic (TT) echocardiography showed moderately-to-severely reduced (35%) left ventricular ejection fraction (LVEF), with no intracardiac thrombus or clinically relevant valvular disease. The patient developed cardiogenic shock that resolved in a few days with supportive therapy by means of temporary intra-aortic balloon pump (IABP) therapy and vasopressors. Mechanical complications were excluded by TT echocardiography and CT scan. Despite uninterrupted dual antiplatelet therapy, on day 8, the patient experienced acute chest pain and *de novo* ST-segment elevation in anterolateral leads. A new emergent coronary angiography confirmed the suspected stent thrombosis at the proximal edge of the recently implanted DES (see Supplementary material online, *Video S2*). Balloon angioplasty was performed at the level of stent thrombosis, and a new DES was implanted distally due to persistent coronary slow-flow (see Supplementary material online, *Video S3*). A second tirofiban infusion was started. Chest pain resolved, and vital parameters were stable after the procedure, with no clinical sign of systemic hypoperfusion or procedural bleeding or thrombotic complication on physical examination. Due to her critical conditions, the patient received the transfusion of one unit of red blood cells on the same day for persistent but

| | |
|---|---|
| Day 1 | Anterolateral ST-elevation myocardial infarction. Percutaneous coronary intervention and drug-eluting stent implantation on proximal descending anterior artery. Started first tirofiban infusion as a bail-out strategy, acetylsalicylic acid, and ticagrelor |
| Day 2 | Cardiogenic shock. Intra-aortic balloon-pump therapy |
| Day 5 | Intra-aortic balloon-pump removed |
| Day 8 | Thrombosis at the proximal edge of the recently implanted stent. Balloon angioplasty and implantation of a new drug-eluting stent distally. Started second tirofiban infusion<br>Abrupt decrease in platelet count (35 000/μL). Tirofiban stopped |
| Day 9 | Acetylsalicylic acid and ticagrelor stopped<br>Platelet count 19 000/μL (nadir)<br>Evidence for haemolysis by increased lactate dehydrogenase and reduced haptoglobin<br>Creatinine 0.9 mg/dL. Oliguria<br>Elevated procalcitonin and C-reactive protein. Started piperacillin/tazobactam and ceftarolin |
| Day 10 | Anuric. Creatinine levels 3.2 mg/dL. Unsuccessful attempts to restore urine output first by high-dose furosemide, then fluid challenge |
| Day 11 | Computed tomography scan showing left renal ischaemia and left ventricular thrombosis<br>Blood smear positive for schistocytes (>1%)<br>Started first plasma exchange<br>Restored dual anti-platelet therapy after plasma exchange. Started heparin infusion |
| Day 12 | Platelet count increase to 43 000/μL<br>Patient death due to respiratory failure |

stable moderate-to-severe anaemia (haemoglobin level prior to transfusion 8.4 g/dL).

A few hours later, the patient developed severe thrombocytopenia (platelet count 35 000/uL) (*Figure 3*). Tirofiban was immediately stopped. As platelet count fell below 30 000/uL (nadir 19 000/uL) dual antiplatelet therapy was discontinued. Pseudothrombocytopenia was excluded by performing platelet count with sodium citrate. Suspect heparin-induced thrombocytopenia was likewise excluded by negative test results for antiplatelet factor 4 (anti-PF4) antibodies. Also, the search for antiplatelet antibodies was negative. High platelet fluorescence intensity (31.1%, normal range 1.0–7.0%) and high reticulocyte count excluded bone marrow failure syndrome (see *Table 1* showing blood tests on day 9). No exposure to other drugs potentially associated with thrombocytopenia was identified. On the same day, a significant increase in white blood cell count, C-reactive protein, and procalcitonin prompted broad-spectrum antibiotic therapy (piperacillin/tazobactam + ceftarolin). Urine and blood cultures tested negative.

On day 9, the patient rapidly developed confusion, anuria, and creatinine abruptly increased within 24 h from 0.9 to 3.2 mg/dL. After consultation with a nephrologist, there was a first attempt with high-dose furosemide and a second attempt with fluid challenge, both unsuccessful in restoring urine output. After repeated consultation with a nephrologist, the need for a diagnosis for such a rapid increase in creatinine levels prompted a subsequent thoraco-abdominal contrast-enhanced CT scan that showed signs of cortical ischaemia of the left kidney (*Figure 4*) and apical left ventricular thrombosis (*Figure 5*).

Finding of schistocytes (>1%) on peripheral blood smear (*Figure 6*), together with signs of haemolysis (rapid increase of serum lactate dehydrogenase and reduced haptoglobin) and compatible coagulation parameters (normal prothrombin time, partial thromboplastin time, and fibrinogen, see *Table 1*) lead to suspect thrombotic thrombocytopenic purpura. Blood test for ADAMTS13 (A Disintegrin and Metalloproteinase with Thrombospondin motifs-13) activity was performed before starting any treatment and showed a mild reduction (53%, reference range 65–130%) without evidence of anti-ADAMTS13 antibodies (5 U/mL, reference range below 16 U/mL). Isovolaemic plasma exchange (PEx) was promptly arranged. After PEx, dual antiplatelet therapy was restored, and sodium heparin infusion (12 U/kg/h) was started. Ticagrelor was resumed with a loading dose 30 min before the end of PEx. At the end of PEx, 250 mg i.v. lysine acetylsalicylate was administered. An increase in platelet count was observed 8 h later (45 000/uL).

The patient remained anuric and developed both clinical and radiological signs of pulmonary congestion (*Figure 5*), without signs of respiratory distress nor hypoxaemia upon oxygen therapy. There were frequent consultations with nephrologists and haemodiafiltration was planned the morning after PEx. However, during the night her respiratory and haemodynamic status rapidly deteriorated, with signs of hypoperfusion and acute respiratory failure (*Table 2*). The patient was rapidly transferred to the Nephrology unit for emergent haemodiafiltration. Non-invasive ventilation was started while waiting for intubation and mechanical ventilation, but the patient died due to sudden worsening of her respiratory and haemodynamic status.

## Discussion

Tirofiban is a parenterally administered platelet GP IIb–IIIa inhibitor mainly used in the context of periprocedural antithrombotic therapy of acute coronary syndromes. Recommendations for its use have been narrowed to selected cases (mainly thrombotic complications of PCI), due to an increase in bleeding events in clinical studies.[1] In our case, it was used as a bail-out strategy after primary angioplasty.

A rare but notorious, class-related complication of tirofiban infusion is sudden severe drug-induced thrombocytopenia (DITP).[2] In DITP, the drug induces the formation of antibodies that react with platelets, leading to a rapid decrease in platelet count (minutes to hours), often below 50 000/μL.

Thrombotic microangiopathies (TMAs) are rare conditions characterized by antibody- or complement-mediated activation of platelets and endothelium in the microcirculatory bed, leading to microangiopathic haemolytic anaemia, decrease in platelet count, and organ damage.[3] TMAs include, among others, thrombotic thrombocytopenic purpura (TTP, Moschowitz disease), and haemolytic uraemic syndrome. One of the diagnostic hallmarks of all TMAs is the presence of damaged red blood cells (named *schistocytes*) on peripheral blood smear. All TMAs are characterized by variably reduced activity of ADAMTS13, a protease that cleaves vonWillebrand factor multimers. These highly thrombogenic uncleaved multimers accumulate in the microcirculatory bed, thereby causing widespread thrombosis and organ damage. Marked reduced activity of ADAMTS13 is the hallmark of Moschowitz disease that is characterized by the presence of antibodies against ADAMTS13, with immune-mediated ADAMTS13 destruction as main mechanism leading to microangiopathy. Many causes of TMA are known, such as infections, malignancies, pregnancy-related (HELLP syndrome), malignant hypertension, organ transplants, haematopoietic stem cell transplant and related-complications (e.g. use of calcineurin inhibitors, Graft vs. Host disease).[4]

Sometimes, TMAs are triggered by drugs. Drug-induced thrombotic microangiopathies (DITMAs) are generally divided in immune-mediated

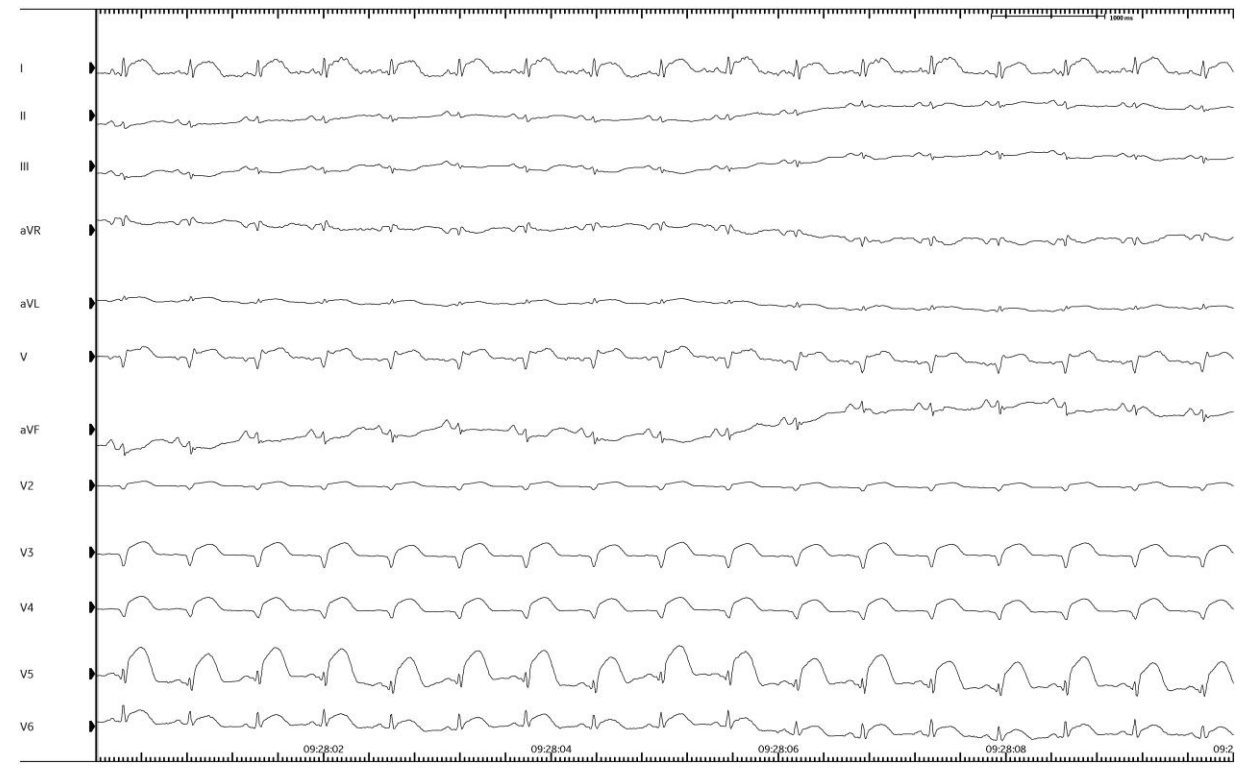



**Figure 1** Electrocardiogram showing ST-segment elevation myocardial infarction in anterolateral leads.

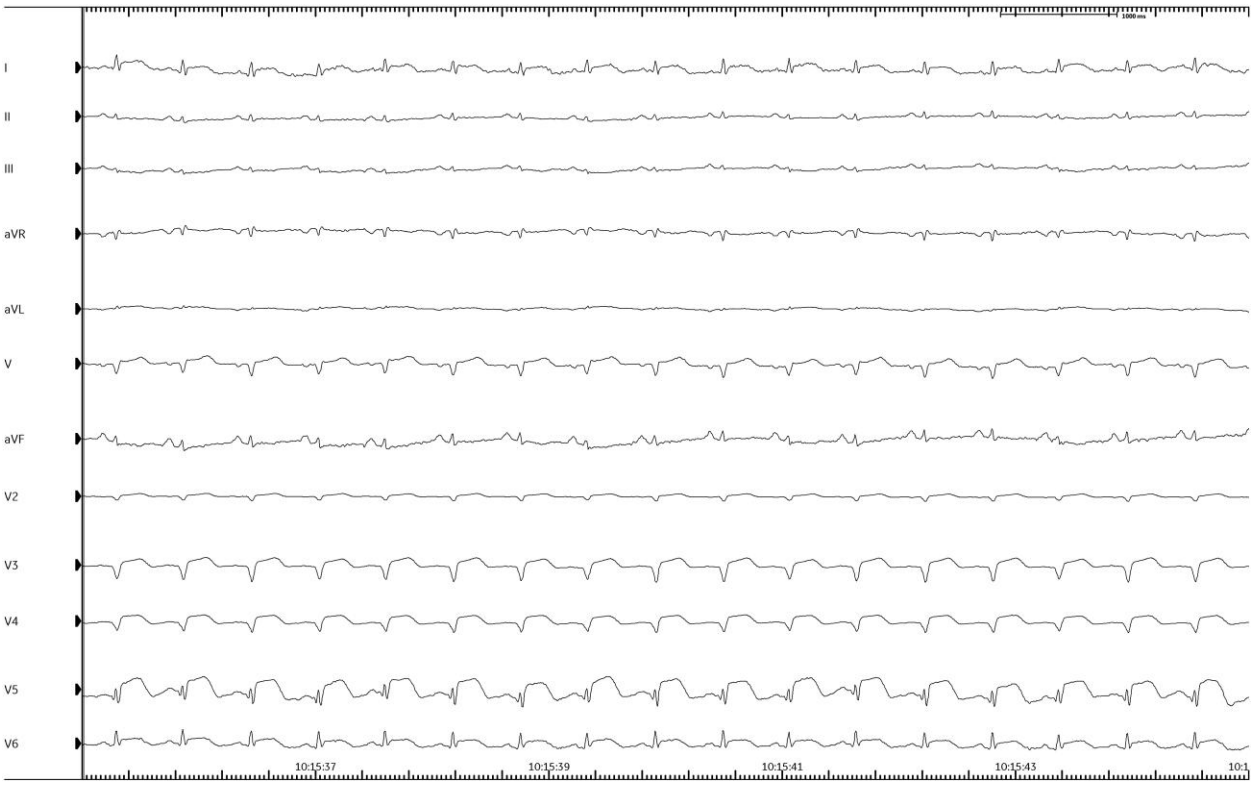



**Figure 2** Electrocardiogram after primary percutaneous coronary intervention showing partial ST-segment elevation reduction.

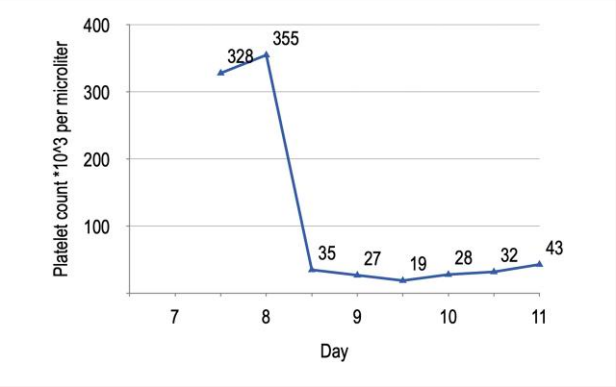



**Figure 3** Graphical representation of platelet levels before and after stent thrombosis and the second tirofiban infusion on day 8.

**Table 1 Main laboratory tests at admission and at day 9**

| Parameter, unit measure | Value | | Reference range |
|---|---|---|---|
| | At admission | Day 9 | |
| WBC count (*$10^3$/μL) | 13.19 | 17.39 | 4.00–10.00 |
| RBC count (*$10^6$/μL) | 4.58 | 3.29 | 4.00–5.20 |
| Hb (g/dL) | 14.3 | 9.9 | 12.0–16.0 |
| Ht (%) | 43.9 | 31.9 | 36.0–46.0 |
| Mean cellular volume (fL) | 95.9 | 95.5 | 80.0–95.0 |
| Platelet count (*$10^3$/μL) | 457 | 27 | 150–400 |
| Immature platelet fraction (%) | – | 31.1 | 1.0–7.0 |
| Schystocytes (%) | – | 2.60 | <1.00 |
| Platelet count, sodium citrate (*$10^3$/μL) | – | 24 000 | 150–400 |
| Folic acid (ng/mL) | – | 2.9 | 3.1–19.9 |
| Vitamin B12 (pg/mL) | – | 108 | 180–914 |
| LDH (U/L) | 526 | 1597 | <248 |
| Total bilirubin (mg/dL) | 0.4 | 1.0 | 0.1–1.1 |
| Procalcitonin (ng/mL) | 0.35 | 9.9 | <0.50 |
| CRP (mg/L) | 77.2 | 79.4 | <5.0 |
| Prothrombin time ratio | 0.85 | 1.25 | 0.86–1.20 |
| Activated partial thromboplastin time (s) | 33.4 | 48.4 | – |
| Activated partial thromboplastin time ratio | 1.06 | 1.53 | 0.82–1.20 |
| Fibrinogen (mg/dL) | 400 | 336 | 150–400 |
| Haptoglobin (mg/dL) | – | 12.3 | 20–150 |

**Table 2 Blood gas analysis on day 11 before and after respiratory deterioration**

| Parameter, unit measure | Value | |
|---|---|---|
| | Before | After |
| pH | 7.37 | 7.24 |
| $pCO_2$, mmHg | 43.4 | 45.5 |
| $pO_2$, mmHg | 78.0 | 66.1 |
| $sO_2$, % | 95.7 | 88.6 |
| $HCO_3^-$, mmol/L | 24.3 | 18.0 |
| Lactate, mmol/L | 1.0 | 5.9 |
| $pO_2/FO_2$, mmHg | 372 | 315 |
| Potassium, mmol/L | 4.0 | 5.6 |

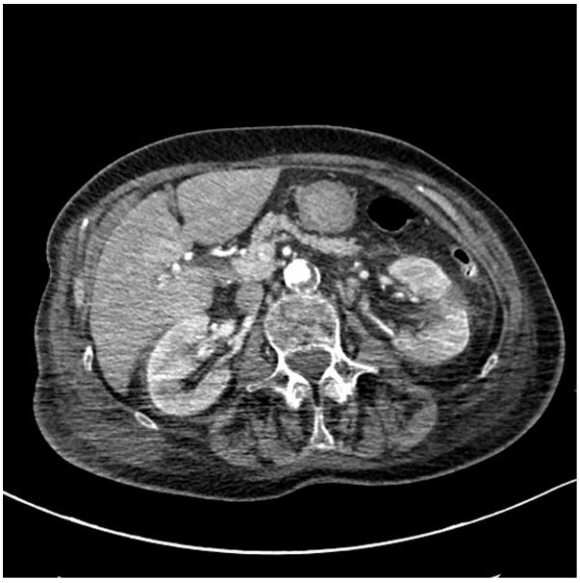


**Figure 4** Computed tomography scan demonstrating left cortical kidney ischaemia.

syndromes (antibody-mediated, non-dose-related) and non-immune-mediated syndromes (usually dose-related).[5]

In our patient, there was a drop in platelet count a few hours after her second exposure to tirofiban, with a very low nadir (19 000/μL), suggesting antibody-mediated mechanism. However, in contrast with other reported cases, platelet count did not recover upon tirofiban discontinuation. Moreover, the patient had thrombotic manifestations (renal ischaemia). One possible explanation could be the self-sustaining mechanism of TMA, with peripheral platelet destruction despite a hyper-productive bone marrow (as indicated by high immature platelet fraction). This is supported by the observation of an increase in platelet count only after the first plasma exchange. Another possible explanation is the reduced drug washout caused by acute kidney injury.

Tirofiban has never been associated with DITMA.[5–8] In this case, a strong relationship between tirofiban infusion and TMA is suggested by several clinical elements but establishing definite causal relationship in a critically ill patient is challenging. Our patient was septic, and TMA can occur in the context of infection. However, there are elements that make this hypothesis unlikely, namely: (1) the sudden drop in platelet count, suggesting an immune-mediated mechanism; (2) the sharp temporal relationship with the second tirofiban infusion, suggesting prior sensitization; (3) and the absence of coagulation abnormalities typical of disseminated intravascular coagulation. IABP was an

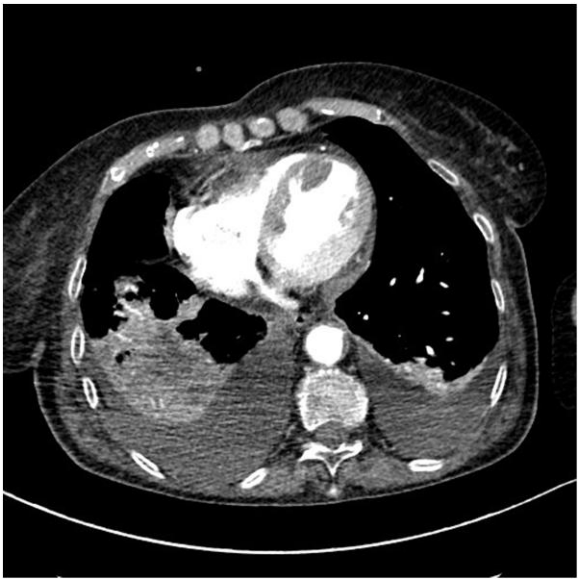


**Figure 5** Computed tomography scan showing apical left ventricular thrombosis.

unlikely cause of thrombocytopenia as it was stopped a few days before onset of TMA. Also, unfractionated heparin was administered during percutaneous coronary angioplasty as per guidelines, but timing of platelet count fall and absence of anti-PF4 antibodies pointed against heparin-induced thrombocytopenia. Thrombocytopenia as a post-transfusion reaction was deemed highly unlikely as it is exceedingly rare and usually delayed (5–10 days). No test for drug-dependent antibodies was performed because of the already known link between GP IIb–IIIa inhibitors and thrombocytopenia. We did not measure complement activation and did not perform autoimmune tests to exclude vasculitis or antiphospholipid syndrome, but the patient's clinical history was uneventful, making the hypothesis of a pre-existing systemic disease unlikely.

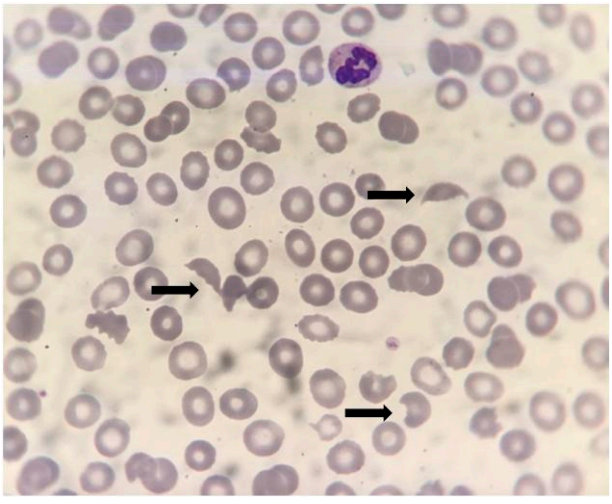


**Figure 6** Schistocytes at peripheral blood smear.

Further observations are needed to establish a causal association between tirofiban and DITMA.

In conclusion, even in the setting of low platelet count from a known DITP-related drug, a systematic approach to severe thrombocytopenia is of paramount importance. DITMA is a rapid-developing disease, with high mortality rates, that requires emergent measures. Excluding TMA in severe thrombocytopenia by performing peripheral blood smear and evaluation of haemolysis screening test (LDH, bilirubin, haptoglobin) can prompt life-saving measures and avoid detrimental platelet transfusion, sometimes routinely used in the context of GP IIb–IIIa inhibitors-induced thrombocytopenia. Platelet transfusion is contraindicated in thrombotic microangiopathies due to the risk of triggering life-threatening thrombotic events.

Dealing with severe thrombocytopenia in a patient with recent stent thrombosis and left ventricular thrombus was extremely challenging. Management of antithrombotic drugs in the setting of PEx has required awareness of the mechanism of thrombocytopenia (sustained low platelet count despite high turnover), careful consideration of antithrombotic agents pharmacokinetic, and coordination with transfusionists. At the time of writing, no guideline is available on the management of antithrombotic drugs in patients requiring PEx. In our case, we decided to restore ticagrelor treatment by loading dose 30 min before the end of PEx, while lysine acetylsalicylate and sodium heparin infusion were started as soon as PEx was finished. Intravenous administration of ASA was preferred over oral route to maximize bioavailability due to more predictable and faster pharmacokinetic. We did not observe thrombotic or major haemorrhagic events in the following hours, but the follow-up time was extremely short and no conclusion on the management of antithrombotic therapy in this complex setting can be drawn.

## Lead author biography

Maria Mattioli is a consultant cardiologist at Parma University Hospital, in Parma, Italy. She completed her medical education in Parma, with experiences in France and United States. Her interest for platelets started as an intern and research assistant in the laboratory of Human Anatomy Department of Parma University. Her areas of research are secondary cardiovascular prevention, platelets, and thrombosis. Her main clinical interest is acute cardiac care. Currently, she is attending a master's degree in intensive cardiac care.

## Supplementary material

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

**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 of the case report including images and associated text has been obtained from the relatives of the patient in line with COPE guidance.

**Conflict of interest:** None declared.

**Funding:** None declared.

## References


1. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, *et al.* 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2019;**40**:87–165.
2. Merlini PA, Rossi M, Menozzi A, Buratti S, Brennan DM, Moliterno DJ, *et al.* Thrombocytopenia caused by abciximab or tirofiban and its association with clinical outcome in patients undergoing coronary stenting. *Circulation* 2004;**109**:2203–2206.
3. George JN, Nester CM. Syndromes of thrombotic microangiopathy. *N Engl J Med* 2014; **371**:654–666.
4. Saha M, McDaniel JK, Zheng XL. Thrombotic thrombocytopenic purpura: pathogenesis, diagnosis and potential novel therapeutics. *J Thromb Haemost* 2017;**15**:1889–1900.
5. Al-Nouri ZL, Reese JA, Terrell DR, Vesely SK, George JN. Drug-induced thrombotic microangiopathy: a systematic review of published reports. *Blood* 2015;**125**: 616–618.
6. Reese JA, Bougie DW, Curtis BR, Terrell DR, Vesely SK, Aster RH, *et al.* Drug-induced thrombotic microangiopathy: experience of the Oklahoma Registry and the BloodCenter of Wisconsin. *Am J Hematol* 2015;**90**:406–410.
7. Saleem R, Reese JA, George JN. Drug-induced thrombotic microangiopathy: an updated systematic review, 2014–2018. *Am J Hematol* 2018;**93**:E241–e243.
8. Platelets on the Web. Drug Induced Thrombotic Microangiopathy. https://ouhsc.edu/platelets/DITMA.htm (06 April 2022).