CASE REPORT

Idiopathic catastrophic thrombosis with happy ending

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SUMMARY

A 59-year-old male patient suffered three life-threatening instant thromboses after an initial resuscitation due to an ST-segment elevation myocardial infarction of the anterior cardiac wall. With a high-risk profile for heparin-induced thrombocytopenia (HIT), he was placed on argatroban after the second reinfarction. Under this apparently appropriate treatment, a third reinfarction occurred, and the patient had to undergo high-risk cardiac bypass surgery. Later on, a deep vein thrombosis and an intracardiac thrombus formed. Despite a positive screening test for HIT and a single positive result in the heparin-induced platelet aggregation test, we are not convinced that HIT was the only underlying cause for this 'catastrophic thrombotic syndrome'. We speculate that a massive generation of thrombin, reflected in consistently high D dimers and the need of copious amounts of a direct thrombin inhibitor, triggered the set of events. With this case report, we want to raise awareness for cardiac complications in patients with complex clotting disorders and share our experience in the diagnostic and therapeutic management of such an unusual scenario.

BACKGROUND

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CASE PRESENTATION

The term 'catastrophic thrombotic syndrome'—first described by Kitchens as 'thrombotic storm' in 1998¹—summarises a cluster of different clotting disorders that have in common the rapid onset of multiple thromboembolic events in various vascular beds. The hypercoagulable state is often very difficult to interrupt, sometimes it seems even refractory to any treatment.¹ The combination of multiple potentially life-threatening thromboses and a difficult therapeutic management makes such patients a challenge. Here, we share our experience with one complex patient as a contribution to the development of a standardised treatment approach for such patients.

A 59-year-old Caucasian man complained about shortness of breath and feeling sick after a tennis match. Shortly after, his tennis partner found him unconscious in the changing rooms. Immediate cardiopulmonary resuscitation (CPR) was started on the scene including a single electric shock by an automated external defibrillator. On arrival of the emergency ambulance, the patient showed signs

of regaining consciousness. The initial three-lead ECG showed a complete left bundle-branch block of unknown age equivalent to an ST-segment elevation myocardial infarction (STEMI). The patient was brought into our facility for emergency coronary angiography.

Previous to this event, the patient had been well and healthy. He clearly denied any angina/chest pain before resuscitation and classified himself as in good physical shape. His cardiovascular risk profile consisted only of a short smoking period several decades ago and a positive family history for coronary artery disease (mother). With a normal body weight (body mass index 24.8 kg/m²), no regular medication and without a previous diagnosis of arterial hypertension, hypercholesterolaemia or diabetes mellitus, he had a low 10-year risk for heart disease or stroke as per the 2013 American College of Cardiology/American Heart Association atherosclerotic cardiovascular disease risk calculator.² His medical history only included a central venous thrombosis of the left eye approximately 10 years ago. Back then, the initial therapy with acetylsalicylic acid (ASA) and pentoxifylline was discontinued after a short period. No underlying clotting disorder had been identified.

The immediately performed coronary angiography showed severe coronary artery disease of all three major vessels. The occluded left anterior descending (LAD) artery was identified as culprit lesion and reopened by percutaneous transluminal coronary angioplasty (PTCA) and bifurcation stenting of the LAD artery and the ramus diagonalis 1 (RD1). In the same session, a high-grade stenosis of the left circumflex (LCX) artery was dilated (PTCA) and double stented. All implanted stents were drug-eluting stents. The status of the coronary tree preintervention and postintervention is depicted in figure 1A,B. The left ventricular function was severely impaired. Dual antiplatelet therapy with ASA (100 mg/day) and ticagrelor (180 mg/day) was started. Unfractionated heparin (UFH) had been given as a bolus prehospital (5000 international units, IU) and during intervention (7500 IU). With a normal platelet count in the initial blood results (see figure 2), a continuous infusion was started for thrombosis prophylaxis (450 IU/hour) after the procedure.

The patient recovered well. Only a minor lesion in the brain stem causing double vision was reported as neurological residue. The initially present atrial fibrillation had resolved after revascularisation into a stable sinus rhythm. With stable platelet counts, UFH was switched to low-molecular weight heparin (LMWH) in prophylactic dose (enoxaparin

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Figure 1 (A) The initial coronary angiography showed a complete occlusion of the left anterior descending (LAD) artery (filled arrow) and a high-grade stenosis of the left circumflex (LCX) artery (framed arrow). (B) Recanalisation was achieved by percutaneous transluminal coronary angioplasty (PTCA)/bifurcation stenting of LAD artery (filled arrow) and ramus diagonalis 1 (RD1) (dotted arrow) as well as PTCA/double stenting of LCX artery (framed arrow). (C) First instant thrombosis of LAD artery (filled arrow) and LCX artery (framed arrow). (D) Recanalisation of LAD artery (filled arrow) with thrombus aspiration, tirofiban and PTCA/stenting. RD1 (dotted arrow) remained occluded. Instant thrombosis of LCX artery (framed arrow) reopened with thrombus aspiration, tirofiban and PTCA. (E) Third instant thrombosis of LAD artery (filled arrow) leading to the final emergency coronary bypass surgery. CABG, coronary artery bypass graft.

40 mg/day) at day 4. Five days after the initial event, the patient was transferred from the intensive care unit to a regular medical ward.

On day 7, the patient suffered a reinfarction with ventricular fibrillation due to a stent thrombosis of LAD and LCX arteries, requiring CPR for 18 min before return of spontaneous circulation was resumed. Recanalisation of both arteries was achieved by thrombus aspiration, administration of 7500 IU UFH plus tirofiban and re-PTCA, followed by implantation of 5 drug-eluting stents in total. RD1 remained occluded despite maximal efforts. In order to minimise any neurological damage from the circulation failure, the patient was cooled afterwards. UFH was restarted targeting an activated partial thromboplastin time (aPTT) of 40–50 s. After rewarming, the patient regained consciousness without significant neurological deficits.

On day 11, the second re-reinfarction occurred, again due to instant thromboses of both LAD and LCX arteries. Both vessels were reopened by the same measures as 4 days before (figure 1C,D).

At this point, heparin-induced thrombocytopenia (HIT) was suspected for the first time. With an intermediate risk in the 4T score³ (see table 1, 4 out of 8 points) despite an overall normal to slightly raised platelet count, UFH was discontinued, and anticoagulation with argatroban was started (initial dose 1.5 µg/kg/min, targeting again an aPTT of 40 s). Simultaneously, the laboratory

diagnostic algorithm for HIT was started. While the screening assays (particle gel immunoassay (PaGIA) and ELISA) came back positive, the first heparin-induced platelet aggregation (HIPA) test came back negative on day 17.

Furthermore, an expanded coagulation panel was sent. The summary of relevant results is shown in table 2. Up to this point, the functional assays for ASA and ticagrelor had shown appropriate platelet inhibition.

On day 18 after admission—being on active treatment with argatroban—the patient suffered a fourth myocardial infarction, again an instant thrombosis of LAD artery (figure 1E). The decision was made to proceed with a surgical approach. Despite a positive immunological and functional assay for HIT at this point (the first and only positive HIPA being reported immediately before the procedure on day 19), the quadruple coronary bypass surgery went without further thrombotic complications on an UFH/iloprost regimen.⁴ Argatroban was restarted after the procedure as soon as the bleeding risk seemed tolerable.

The patient recovered well from the surgery. Postoperatively, the platelet count dropped to the nadir of 193/µL (figure 2). Over the course of the next days, platelet numbers recovered. More and more argatroban was needed to achieve the targeted aPTT (above 60 s), up to 19 µg/kg/min was required, which is almost 10-fold the standard dose. While the IgG antibodies against platelet factor 4 (PF4)/heparin complexes were still detectable by immunological assays, the heparin-induced platelet activation assay remained negative in several subsequent samples.

Seven days after the surgery, the patient complained about swelling of his right arm. A deep vein thrombosis (DVT) of the axillary to brachial vein was identified by ultrasound. Furthermore, a thrombus was seen in the apical left cavity of the heart by routine echocardiography. The aPTT goal was raised to 70 s.

Fortunately, no further thrombotic events occurred under intensified anticoagulation. Further work-up did not show any cancer or chronic inflammatory processes (see table 2), only a focal calcification in the left thyroid (calibre 4 mm) with slightly enlarged adjacent lymph nodes and a borderline elevated cancer antigen 125 were identified.

Four weeks after the initial STEMI, a vitamin K antagonist was started (phenprocoumon, targeting an international normalised ratio of 2–3). The triple therapy (ASA, ticagrelor and phenprocoumon) was continued for 12 months, during which the patient did not suffer any bleeding complications. After 12 months, ticagrelor was discontinued. Owing to the persisting intracardiac thrombus and in the absence of any bleeding complications, phenprocoumon was maintained. Despite a significant reduced left ventricular function, the patient reports a good quality of life.

DISCUSSION

The central question in this case was whether the chain of thrombotic events was triggered by an HIT or a different cause.

In HIT, the immune system forms antibodies (mostly IgG types) against the complex of PF4 and heparin. The resulting immune complexes crosslink platelet Fcγ2a receptors, which lead to massive platelet activation in thrombin generation. Intravascular consumption of platelets leads to thrombocytopenia. While the formation of PF4/heparin antibodies is quite common in patients receiving heparin, only a minority of them is developing thrombocytopenia or thrombosis. Breakthrough of HIT depends on characteristics of the antibodies, with high-affinity antibodies being more clinically relevant than low-affinity antibodies⁵ and characteristics of platelets and the clotting system of the patient.

Figure 2 Timetable of important laboratory findings. CABG, coronary artery bypass graft; HIPA, heparin-induced platelet aggregation; LMWH, low-molecular weight heparin; STEMI, ST-segment elevation myocardial infarction; UFH, unfractionated heparin.

In general, the formation of IgG antibodies needs at least 5 days. Typically, thrombocytopenia and thrombosis manifest in HIT between days 5 and 10 after the start of heparin

with patients receiving UFH having 10 times risk for HIT than patients receiving LMWH.

The diagnosis of an HIT is based on various clinical and laboratory findings. The current diagnostic algorithm consists of an HIT likelihood score (4T score, see [table 1](#)) and subsequent laboratory testing.⁶ Immunoassays (such as PaGia and ELISA) detect antibodies that bind to PF4/heparin complexes. These antigen tests are highly sensitive and well suited to rule out HIT. However, they are not very specific for clinically relevant antibodies and have therefore a low positive predictive value. Functional assays such as the HIPA test had a much higher predictive value for clinical HIT, but still not each patient with a positive functional test will develop HIT.

The reported patient received UFH from day 1. As HIT typically occurs between days 5 and 10, the first myocardial infarct might have been caused by HIT, but without the preceding decrease in the platelet count, this was rather unlikely. The decrease in the platelet count of 35% between days 8 and 9 might be considered as a symptom for HIT, but before the second reinfarction, the platelet counts increase again, making HIT extremely unlikely. In addition, the second reinfarction occurred at day 11 which is already beyond the typical time period of HIT. Nevertheless, as a precaution, heparin was stopped at this point, and argatroban was started. The immediately initiated immunoassay came back positive, whereas the functional assay remained negative, which also in hindsight strongly argues against HIT being the reason for the two myocardial reinfarctions. Repetitive testing showed a positive HIPA test (reconfirmed with a repository sample). However, again the platelet count rose before the third infarct, probably

Table 1 4T score for heparin-induced thrombocytopenia

thrombocytopenia	Points	Our case
Platelet count falls >50% and platelet nadir >20/ μ L	2	
Platelet count falls 30%–50% and platelet nadir 10–19/ μ L	1	X
Platelet count falls <30% and platelet nadir <10/ μ L	0	
Timing of platelet count fall		
Clear onset between days 5 and 10	2	X
Platelet falls $\leq$ 1 day (prior heparin exposure within 30 days)		
Consistent with days 5–10 fall (but not clear)	1	
Onset after day 10		
Falls $\leq$ 1 day (prior heparin exposure 31–100 days ago)		
Platelet count falls <4 days without recent heparin exposure	0	
Thrombosis or other sequela		
New thrombosis	2	X
Skin necrosis		
Acute systemic reaction postintravenous heparin bolus		
Progressive or recurrent thrombosis	1	
Non-necrotising skin lesion		
Suspected thrombosis (but not proven)		
None	0	
Other causes for thrombocytopenia		
None apparent	2	
Possible	1	X
Definite	0	

Table 2 Work-up of potentially prothrombotic conditions

	Results	Comment
Genetics	Negative	
Factor V Leiden/APC resistance	Negative	
Prothrombin G20210A mutation	Negative	
Antiphospholipid syndrome	Negative	
Lupus anticoagulant	Negative	
Anticardiolipin antibodies	Negative	
β_2 glycoprotein antibodies (IgG/IgM)	Negative	
Thrombotic thrombocytopenic purpura	No evidence	
thrombocytopenia	No	
Purpura/bruising	No	
Haemolytic anaemia	No	
Schistocytes	Negative	
Disseminated intravascular coagulation	No evidence	
Baseline PT/aPTT	Normal	
Bleeding complications	No	
AT3 deficiency	AT3 level >120%	Normal
Protein C deficiency	Protein C activity >100%	Normal
	Free protein S activity 90.6%	Normal
Protein S deficiency		Normal
Factor II	110.7%	Normal
		Elevated, most likely as a sign of acute phase reaction
Factor VIII	241%	Elevated, most likely as a sign of acute phase reaction
vWF antigen	478.9%	
Investigation for occult malignancy	Negative	
CT chest/abdomen	No tumour identified	
OGD	Inconspicuous	
Hydrocolon MRI	No tumour identified	
Tumour markers	CA-125 48.5 U/mL	Slightly elevated, no clinical relevance
ENT review	Inconspicuous	
Urology review	Inconspicuous	
Sonography of the thyroid gland	Focal calcification in the left lobe	Not suspicious for active malignant process
Rheumatology screen	Negative	

APC, activated protein C; aPTT, activated partial thromboplastin time; AT3, antithrombin 3; CA-125, cancer antigen 125; ENT, ear, nose, and throat; OGD, oesophagogastroduodenoscopy; PT, prothrombin time; vWF, von Willebrand factor.

because of intensified thrombin inhibition by increased doses of argatroban. Despite this aggressive treatment, DVT and then intracardial thrombus occurred. Table 3 summarises pros and cons for HIT in our patient.

Since HIT is very unlikely, we consider the positive HIPA test after the third reinfarction to be an epiphenomenon. Nevertheless, since the positive HIPA test result was available immediately before the operation and the complex cardiac surgical intervention should be performed with heparin, iloprost was added during surgery as precaution.

In summary, our patient provides a good example under which circumstances HIT should be ruled out or considered

Table 3 Pros/cons for HIT

Pros	Cons
Intermediate 4T score	HIPA test negative at the time of the first two reinfarctions
Positive PF4/heparin antibody test	Platelet count did not drop before or very close after the thrombotic complications
	The second and third reinfarctions occurred beyond the typical time window for HIT

HIPA, heparin-induced platelet aggregation; HIT, heparin-induced thrombocytopenia; PF4, platelet factor 4.

extremely unlikely. Since there was no evidence of other causes of catastrophic thrombotic syndromes such as catastrophic antiphospholipid syndrome, atypical thrombotic thrombocytopenic purpura or cancer-associated thrombosis, we are certain that another unidentified strong prothrombotic state ('idiopathic' catastrophic thrombotic syndrome)⁷ was the cause for the extreme clinical presentation of our patient. Except for increased factor VIII levels which could be explained by acute phase reaction, we have not identified any further thrombophilic factor. Therefore, the patient may have developed another antibody interfering with the clotting system.

We are nevertheless convinced that it was the right decision to switch anticoagulation to argatroban, as there was a considerable degree of uncertainty, and we did not want to worsen even very unlikely HIT. This case shows that in exceptional situations, very high doses of argatroban (up to 19 µg/kg/min in our patient) might be needed to control thrombin generation. A potential explanation could be the massive elevation of factor VIII, which was previously suggested as mechanism in a similar case of argatroban resistance.⁸ We strongly recommend training staff in the handling of rarely used anticoagulants on a regular basis.

The clinical recovery once PTT was sufficiently elevated underlines the central role of anticoagulation for treatment of idiopathic catastrophic thrombotic syndrome. We have not initiated additional therapies such as plasmapheresis and/or immunomodulatory agents as indicated in catastrophic antiphospholipid syndrome or atypical thrombotic thrombocytopenic purpura.⁷ If HIT could have been ruled out, UFH would also have been an appropriate anticoagulant in this condition. However, if initial PTT is extended, anti-Xa activities should be determined to ensure appropriate heparin dosing.

If thrombotic events progress despite an appropriate elevation of PTT under anticoagulation, further increase in dosing or switching to an alternative anticoagulant (eg, argatroban) might be considered. Addition of a platelet inhibitor might be another option. However, our patient already had dual antiplatelet therapy, indicating the limited efficiency of platelet inhibition in this condition.

Retrospectively, it might have been the right decision to perform a bypass surgery at an earlier timepoint. However, we initially feared the further activation of the coagulation system on the extracorporeal bypass machine and therefore proceeded with an interventional approach.

Finally, there is the question about switching to an oral drug and duration of anticoagulation. In case of catastrophic thrombotic events, switching to a vitamin K antagonist might be preferred by some doctors at least in the first months since in contrast to direct oral anticoagulants, anticoagulant therapy can be monitored. Even if a provoking event can be identified, one may consider an extended or indefinite anticoagulation.

Patient's perspective

- More than 2 years after hospital treatment, I have fully recovered and do sports on a regular basis (eg, intensive skiing). It took several months to balance the body and mind and restore confidence in my physical condition. However, although symptoms of heart failure are absent, and physical strength is almost as good as before the incident, I have avoided tennis so far, the situation leading to my initial heart attack. I have continued previous political activities in the town council. Anticoagulation with phenprocoumon is well-accepted and tolerated without any complications.

Learning points

- How to rule out heparin-induced thrombocytopenia (HIT).
 ► How to deal with conflicting testing results for HIT.
 ► How to use rarely needed anticoagulants.

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