A woman in her 60s with large thrombotic masses in the aorta

A woman in her 60s was admitted with acute pain and loss of strength in both legs. Clinical examination detected severe ischaemia in her lower limbs. CT angiography revealed massive thrombotic masses in the abdominal aorta, and an acute thrombectomy was performed. Further workup revealed an unusual cause of the thrombosis.

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A woman in her 60s, with known seropositive rheumatoid arthritis and three previous hospitalisations for acute pancreatitis, was admitted with abdominal pain. On admission, amylase was 1 611 U/l (< 120 U/l) and CT abdomen showed changes consistent with acute pancreatitis. She improved rapidly after intravenous fluid therapy, and was discharged after five days.

Thirteen days after her discharge, she was admitted to the Department of Neurology with suspected transitory ischaemic attack (TIA) after two days of episodes of dizziness and slurred speech. She also reported slight pain in the right flank that did not resemble the pain of pancreatitis. The neurological examination yielded negative findings. CT of the head and ultrasound of the carotids were normal.

Twelve years earlier, she had suffered a minor stroke, and had been using clopidogrel since then. Blood tests taken on admission revealed newly developed thrombocytopenia. Her thrombocytes had fallen from 315 · 10^9/l at the time of discharge 13 days earlier to 69 · 10^9/l (145–390 · 10^9/l). At the same time, she had a slightly prolonged activated partial thromboplastin time (APTT) of 50 seconds (< 42 sec), but a normal INR of 1.0 (≤ 1.1). She experienced no further episodes of dizziness or speech problems during her stay in hospital and was discharged after twenty four hours without the cause of the symptoms being found.

Acquired thrombocytopenia may be due to production failure or peripheral destruction/increased consumption. Production failure may be benign (due to medication, vitamin B_{12}/folate deficiency, cytostatics, radiation injury or infections) or malignant (haematological neoplasia or bone marrow metastases).

Peripheral destruction or increased consumption is either immunologically conditioned (e.g. immunological thrombocytopenia, heparin-induced thrombocytopenia and post-transfusion purpura) or non-immunologically conditioned (disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), HELLP syndrome (haemolysis, elevated liver enzyme levels in serum and thrombocytopenia), hypersplenism and infections). Pseudothrombocytopenia should also be excluded by looking for thrombocyte aggregates in a blood smear(1).

Only a few hours after discharge, she was re-admitted with acute pain and loss of strength in her lower limbs. Clinical examination revealed pale feet and lack of groin pulse bilaterally. Doppler examination of her lower limbs detected no measurable pressure. After a while the toes of her right foot developed a bluish colour, consistent with critical ischaemia. CT angiography of the abdomen/pelvis and lower limbs revealed massive thrombotic masses around the aortic bifurcation (Fig. 1).

She was transferred to the Vascular Surgery Section, and twelve hours after her admission an open thrombectomy of distal aorta, pelvic and femoral arteries was carried out successfully. It was observed that the thrombic masses appeared organised, and that there was remarkably little arteriosclerosis in the vascular walls. The vessels undergoing thrombectomy were flushed with abundant heparinised saline during the intervention, according to standard procedure.

Acute aortic thrombosis is a serious condition which is most often due to embolisation from a central source, usually the heart. Thrombosis with pronounced underlying arteriosclerosis is the second most common cause (2).

A saddle embolus in the aortic bifurcation without local wall changes aroused suspicion that the emboli had a central source or a systemic cause. Neither CT angiography of the thoracic aorta nor echocardiography detected any embolic source.

The patient was treated post-operatively with low-molecular heparin subcutaneously (dalteparin, Fragmin 5 000 IU × 2). Two days later her thrombocytes fell to 24 · 10^9/l. The

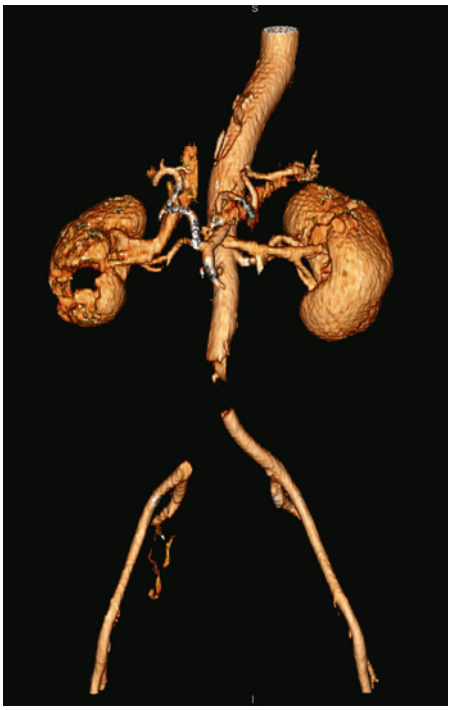

Figure 1 *Three-dimensional CT angiography shows lack of contrast filling in distal abdominal aorta and right common iliac artery, consistent with occluding thrombic masses. In addition a focal perfusion defect is seen caudally in the right kidney, which raises suspicion of infarction*

third post-operative day they fell further, to 15 · 10⁹/l. A haematologist was contacted to determine the cause of the thrombosis and thrombocytopenia.

The patient developed arterial thromboses and pronounced thrombocytopenia without a tendency to haemorrhage. Possible differential diagnoses are disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, catastrophic antiphospholipid syndrome, and heparin-induced thrombocytopenia (HIT). The haematologist ordered blood tests (Table 1, 4th column) and a blood smear (Fig. 2). In light of these results, thrombotic thrombocytopenic purpura was suspected of being the cause of the thrombocytopenia and the thromboses.

In rare cases, clopidogrel may cause thrombotic thrombocytopenic purpura, and it was therefore terminated (3). Thrombocytopenia, schistocytes, high lactate dehydrogenase, increased reticulocytes, negative direct antiglobulin test and normal coagulation tests could be consistent with thrombotic thrombocytopenic purpura. In this condition, however, the thrombi are most commonly in the microcirculatory system, not in the major arteries. The haptoglobin level is also lowered and the bilirubin level usually elevated (4).

With disseminated intravascular coagulation, increased coagulation and fibrinolysis are seen, with both thrombosis and bleeding tendency. As a rule, APTT and INR are high, and the fibrinogen level is low, but there is wide variation. Disseminated intravascular coagulation is always associated with some other severe underlying disease, such as sepsis. However, her clinical condition gave no reason to suspect sepsis, and she had no tendency to haemorrhage.

Catastrophic antiphospholipid syndrome may be seen secondarily to other autoimmune disease, and may cause both thrombocytopenia and arterial thromboses. The condition usually results in prolonged APTT in the presence of lupus anticoagulant and slight or no thrombocytopenia. One in three have schistocytes in their blood (5). Given the patient's normal lupus anticoagulant, cardiolipin antibodies and anti-β2-glycoprotein I antibodies, the diagnosis was less likely.

Heparin-induced thrombocytopenia was also considered as a possible differential diagnosis. This is an immunological complication with thrombocytopenia due to antibody-mediated platelet activation and an increased tendency to thrombosis. The condition most frequently occurs 5–14 days after the start of exposure to unfractionated (UFH) or low-molecular weight heparin (LMH) (6).

Heparin-induced thrombocytopenia was considered improbable because, according to the medication charts, heparin had not been administered during the first two hospitalisations. Because the possibility of this condition could not be entirely eliminated, dalteparin was replaced by fondaparinux (Arixtra). Fondaparinux is a synthetic, selective inhibitor of activated factor X (Xa), which has been used in trials to treat heparin-induced thrombocytopenia (7).

Thrombotic thrombocytopenic purpura was regarded as the most likely diagnosis. The therapy is plasma replacement. This treatment commenced two days later, but the thrombocyte count began to rise before this nonetheless (Fig. 3).

Table 1 Results of blood tests

	First admission, acute pancreatitis, discharge day	Second admission, TIA? 13 days later	Third admission, next day with severe ischaemia	Fourth post-operative day	Reference range
B-Haemoglobin (g/100 ml)	13.0	13.2	12.6	8.7	11.7–15.3
B-Leukocytes, 10^9/l	5.7	11.4	16.3	10.4	3.50–10.0
B-Thrombocytes, 10^9/l	315	69	77	21	145–390
B-Reticulocytes (· 10^9/l)		124	115	184	30–100
P-Creatinine (µmol/l)	67	77	67	67	45–90
P-LD (U/l)	–	–	–	631	105–205
P-Haptoglobin (g/l)	–	–	–	1.43	0.50–2.10
P-APTT (sec)	–	50	52	41	< 42
P-INR	–	1.0	1.1	1.1	≤ 1.1
P-Fibrinogen (g/l)	–	–	–	4.5	2.0–4.5
B-Direct antiglobulin test	–	–	–	Negative	Negative
P-Bilirubin, total (U/l)	8	–	20	10	< 25

During plasma replacement, there were problems with coagulation in the dialysis filter, and after two days it was therefore decided to replace fondaparinux with heparin. At the same time, dalteparin was re-introduced as thrombosis medication. During the next few days, the thrombocytes fell despite plasma replacement. The nephrologist and haematologist then agreed that heparin-induced thrombocytopenia must be suspected after all.

The plasma replacement was terminated, and dalteparin replaced with fondaparinux. An ID-PaGIA Heparin/PF4 antibody test from Bio-Rad was also ordered. This was strongly positive, and confirmed that the patient had IgG antibodies to heparin platelet factor 4.

But the most important question remained unanswered: Had she been given heparin during her first two hospitalisations?

According to her medication charts, she had not received either low-molecular or unfractionated heparin. However she had received fluid intravenously during her stays. In the procedure for emplacement, dressing and monitoring of peripheral venous catheters, our hospital recommended flushing with heparin 100 IU/ml if the catheter was not in continuous use. The patient had therefore received small doses of unfractionated heparin several times a day.

Several articles have been published about patients who have developed heparin-induced thrombocytopenia after not receiving any heparin other than that administered through flushing of central venous catheters (8, 9) or intraarterial catheters (10).

When the diagnosis heparin-induced thrombocytopenia was confirmed, dalteparin was terminated and anticoagulation treatment continued with fondaparinux. Heparin allergy was noted in the electronic patient records under critical information, but not on the medication chart. A serious adverse event report was sent to the Regional Medicines Information Centre (RELIS), which later confirmed the causal relationship between heparin/dalteparin and the diagnosis.

The patient was discharged with warfarin therapy and good circulation in both legs. At a check-up eight weeks later, her general condition was good and she had a normal ankle-arm index.

Discussion

In heparin-induced thrombocytopenia, autoantibodies are formed which bind to complexes of platelet factor 4 (PF4) bound to heparin. Immune complexes containing IgG antibodies and PF4-heparin complexes bind to Fc receptors on the surface of the platelets. This leads to increased release of plate-

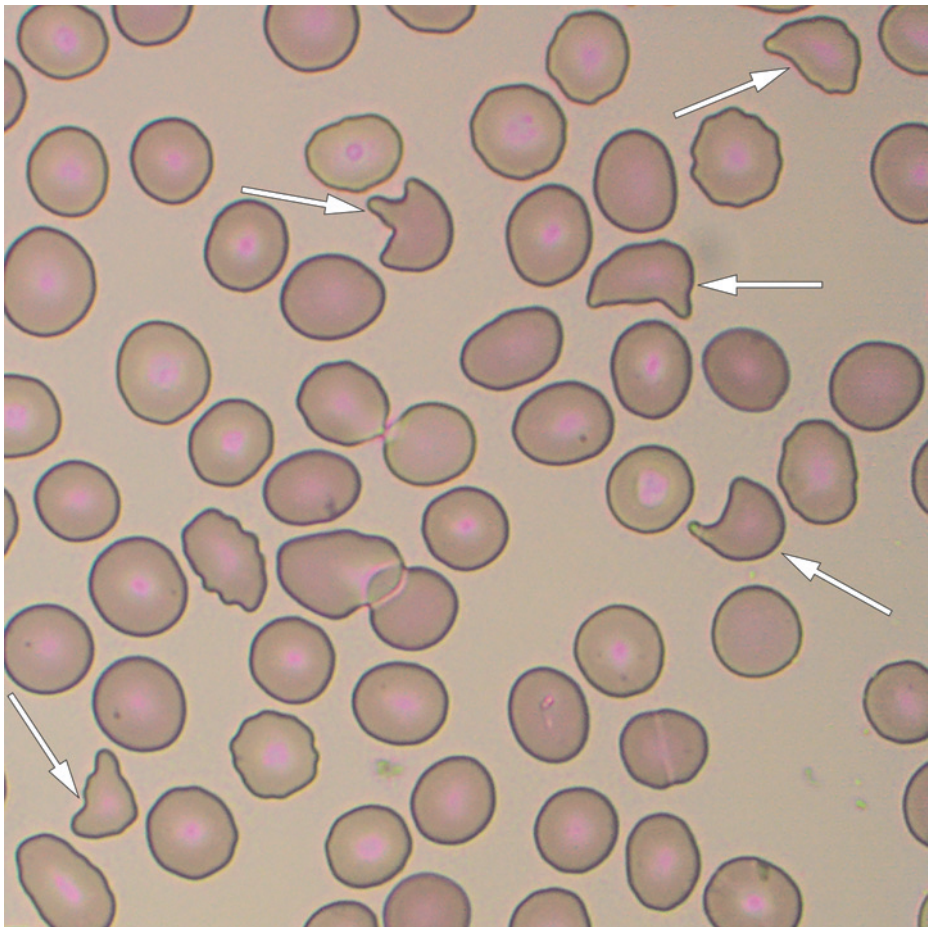

Figure 2 *Blood smear with schistocytes (arrows)*

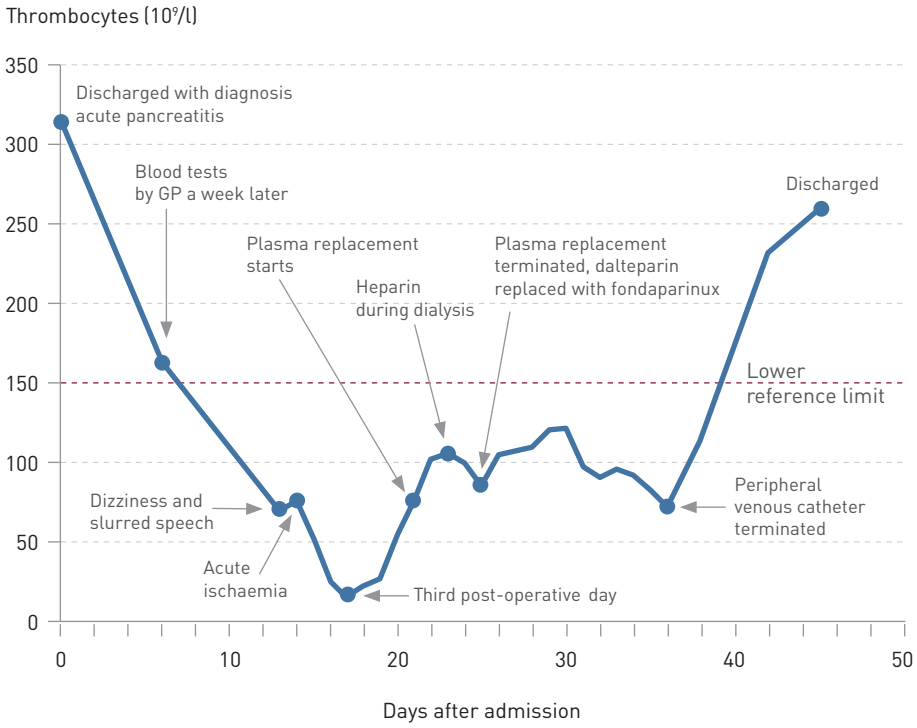

Figure 3 *Thrombocyte values from initial discharge (Day 0) and until the patient is discharged for the third time, 45 days later*

Table 2 4T score for estimation of pre-test probability of heparin-induced thrombocytopenia. Based on Warkentin & Heddle (15)

Category	2 points	1 point	0 points
Thrombocytopenia	> 50 % thrombocyte fall or nadir 20–100 · 10^9/l	30–50 % thrombocyte fall or nadir 10–19 · 10^9/l	< 30 % thrombocyte fall or nadir < 10 · 10^9/l
Time of thrombocyte fall	Day 5–10 or < 1 day if heparin therapy in the past 100 days	> Day 10 or uncertain (e.g. not measured until later, but fits with heparin-induced thrombocytopenia)	Thrombocyte fall comes before day 4 (and no recent heparin therapy)
Thrombosis or other sequelae	Detected thrombosis/es, skin necrosis or anaphylaxis after intravenous heparin	Progressive/recurrent thrombosis, non-necrotising skin lesions or suspected not proven thrombosis	No thrombosis or other suspicious symptoms
Other cause of thrombocytopenia	No other probable causes	Other cause possible	Other cause probable

let factor 4, which in turn causes the formation of more immune complexes, increased platelet activation and release of microparticles from the platelets. The immune complexes bind to the surface of the endothelium and trigger a cascade that results in platelet aggregation and thrombosis. Thrombocytes are consumed in the process, and typically fall more than 50 % from their level at the outset. Half the patients develop thrombosis in addition. This is normally venous; arterial thrombosis most commonly affects the large arteries of the lower limbs, more rarely cerebral vessels and the cardiac arteries (11).

Heparin-induced thrombocytopenia affects 0.2–5.0 % of patients who receive heparin for more than four days (6). The condition normally manifests itself while the heparin treatment is still in progress, but in rare cases it may occur later – up to several weeks after the termination of the heparin treatment. This is called delayed-onset HIT (6). Delayed-onset heparin-induced thrombocytopenia may be the explanation for why this patient's thrombocytes were halved a week after her initial discharge (Fig. 3) and fell further in the following days, while she developed arterial thrombi in the aorta and pelvic arteries. The symptoms, which were interpreted as transitory ischaemic attacks, may also have been associated with heparin-induced thrombocytopenia, with transitory platelet aggregation in cerebral vessels (12).

In 30 % of patients with heparin-induced thrombocytopenia, the condition may develop within 24 hours of heparin exposure. This type affects those who have received heparin in the course of the past three months and have already developed autoantibodies (11). Heparin-induced thrombocytopenia is up to ten times as common in patients who receive unfractionated heparin as in those who receive the low-molecular form (13). In a study involving orthopaedic patients, 5 % developed heparin-induced thrombocytopenia after having unfractionated heparin administered as thrombosis prophylaxis, but only 0.9 % after low-molecular heparin (14). Surgical patients are affected more often than medical patients, women more often than men, and the risk of heparin-induced thrombocytopenia is higher with therapeutic doses than with prophylactic doses.

Thrombosis and thrombocytopenia may have many causes other than heparin treatment, and use of a scoring system is recommended to assess the probability of heparin-induced thrombocytopenia before an antibody test is ordered. Best validated is the 4T score (Table 2), which estimates the probability of the condition on the basis of thrombocyte count, time of onset, incidence of thrombosis, if any, and the probability of other diagnoses (15). If the point score is low (0–3), the condition can be excluded with a high degree of probability, while in the event of an intermediate (4–5) or high (6–8) point score, heparin should be terminated and replaced with a direct thrombin inhibitor (16). Our patient had a point score of 6–7, i.e. a high probability of heparin-induced thrombocytopenia.

A high 4T score should be verified through the detection of antibodies against PF4-heparin complexes. Functional tests, where the patient's serum and heparin are added to platelets taken from blood donors to see whether platelet aggregation takes place, are not conducted in Norway at present. However, a number of laboratories conduct immunological tests. Immunological tests for heparin-induced thrombocytopenia have a sensitivity of almost 100 %, but varying specificity (40–80 %) (17). A positive test does not mean that the antibodies are clinically relevant; they do not necessarily result in platelet aggregation and thrombosis in vivo. However, a negative test is a good means of excluding heparin-induced thrombocytopenia.

A blood smear from the patient revealed a number of schistocytes. This is unusual with heparin-induced thrombocytopenia (18), but usual with disseminated intravascular coagulation (19). Warkentin et al. examined twelve patients with late-onset heparin-induced thrombocytopenia and found that three of them also had disseminated intravascular coagulation. This is a rare complication of heparin-induced thrombocytopenia, but possibly more common in the late-onset form (20). On the patient's second admission, a slightly prolonged activated partial thromboplastin time of 50 seconds was noted, which normalised later in the clinical course. The prolonged thromboplastin time and schistocytes may also have been an expression of low-grade disseminated intravascular coagulation.

As a general rule, thrombocytes increase to above the lower limit of the reference range in the course of four days following the termination of heparin, but it may take up to two weeks in patients with very high antibody titres (6). In our patient, it took almost four weeks before the thrombocytes were normalised. Her thrombocyte count fell six days after heparin and dalteparin had been terminated (Fig. 3, day 31). This fall may be due to continued flushing of the peripheral venous catheter with heparin, probably because this was an established procedure, and it was not specified on the medication chart that heparin flushing must be avoided. Only when the intravenous treatment was completed, and the patient no longer needed a peripheral venous catheter, did her thrombocytes begin to rise again.

British guidelines recommend that the thrombocyte count should be checked before, during and after the termination of heparin exposure, particularly in the case of

more than four days' use, and in surgical patients, and particularly if they have received unfractionated heparin (16). As the condition may manifest itself several days after the termination of heparin exposure, it is important that also doctors in the primary health service are aware of the condition. If heparin-induced thrombocytopenia is suspected at an early stage, and thrombocytes are counted, complications can be limited and treated. In the absence of treatment, there is high morbidity and mortality associated with the condition (11).

The occurrence was entered in our reporting system as a serious adverse event and dealt with by the quality committee. The procedure of flushing peripheral venous catheters with heparin has now been changed at our hospital. Flushing with saline has proved to be just as effective as flushing with heparin (21), while severe heparin-induced adverse events are avoided. Most other hospitals in Norway only use saline to flush peripheral venous catheters.

In a Cochrane report from 2014 it was concluded that the risk of infection or blockage associated with flushing central venous catheters with saline is no greater than it is for heparin flushing (22). A national professional procedure under the Norwegian Knowledge Centre recommends that central venous catheters that are in daily use should only be flushed with saline (23). If the catheter is not in daily use, it is recommended that it be flushed weekly with saline and locked with heparin 100 IU/ml. Heparin flushing entails a small, but increased risk of the patient developing heparin-induced thrombocytopenia. Perhaps heparin flushing/heparin lock should be added to the medication charts to remind us of this?

The patient has consented to the publication of the article.

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