Fulminant course of a Trousseau syndrome

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Keywords
Trousseau syndrome, thrombophlebitis saltans, thrombosis, paradoxical embolism, thromboembolic event, fulminant

Summary
The Trousseau syndrome is a clinical challenge and can be multi-faceted and often fulminant. We report a clinical case of a patient who initially presented with a thrombophlebitis saltans in our outpatient clinic. The further clinical course was dramatic and rapidly progressive in arterial and venous thrombosis and possible paradoxical embolisms. In staging, there was an urgent suspicion of the presence of metastatic cervical carcinoma. With continued rapid clinical worsening with progressive reduction of vigilance in recurrent thromboembolic events, persistent anuria and progression of ischemic areas, it was decided not to continue with the medical treatment given the severe and complex disease pattern. In a synopsis of the clinic and the diagnostic apparatus, we diagnosed a Trousseau syndrome. The patient died 15 days after the first presentation in our angiological consultation. In atypical clinic with recurrent episodic or foudroyant thrombophlebitis, venous and arterial thrombosis or thromboembolisms should be thought of paraneoplastic events and a malignant underlying disease secured or excluded.

Schlüsselwörter
Trousseau-Syndroms, Thrombophlebitis saltans, Thrombose, paradoxe Embolie, thromembolisches Ereignis, fulminant

Zusammenfassung
Das Trousseau-Syndrom ist eine klinische Herausforderung und kann facettenreich und nicht selten fulminant verlaufen. Wir berichten über einen klinischen Fall einer Patientin die sich initial mit einer Thrombophlebitis saltans in unserer Ambulanz vorstellte. Der weitere klinische Verlauf stellte sich bei arteriellen und venösen Thrombosen und möglichen paradoxen Embolien dramatisch und rasch progredient dar. Im Staging ergab sich der dringende Verdacht auf das Vorliegen eines metastasierten Zervixkarzinoms. Bei weiter zunehmender schneller klinischer Verschlechterung mit progredienter Vigilanzminderung bei rezidivierenden thrombembolischen Ereignissen, persistierender Anurie und Progredienz der ischämischen Areale entschied man sich in Anbetracht des schweren und komplexen Erkrankungsmusters gegen eine Fortsetzung der medizinischen Maßnahmen. In Zusammenschau der Klinik und der apparativen Diagnostik stellten wir die Diagnose eines Trousseau-Syndroms. Die Patientin verstarb 15 Tage nach Erstvorstellung in unserer angiologischen Sprechstunde. Bei rezidivierenden episodischen oder foudroyant verlaufenden Thrombophlebitiden,venösen und arteriellen Thrombosen bzw. Thrombembolien sollte an ein paraneoplastisches Geschehen gedacht und eine maligne Grunderkrankung gesichert bzw. ausgeschlossen werden.

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Case history

A 76-year-old woman first presented to our angiology outpatient clinic with a four-day history of cordlike erythema and pain in her distal left leg and forefoot. The symptoms had occurred spontaneously without any previous trauma or surgery. She had not previously experienced any similar changes. Oral antibiotic therapy with cefuroxime 500 mg twice daily and prophylactic anticoagulation with fondaparinux 2.5 mg had been prescribed elsewhere but had not improved the symptoms.

In addition to hypertension, she was a long-term smoker and had chronic kidney disease. She did not have a past history of thrombosis. No allergies.

Diagnostic investigation and treatment

At the time she first presented, the patient was in good general health and well nourished. She denied any chest pain or dyspnoea and had no B symptoms. Apart from the pain in her left leg, the patient had no complaints. The distal left leg showed cordlike erythema, warm and tender to the touch, along the course of the great saphenous vein and over the medial and lateral forefoot. The area was tender on palpation. The entire lower leg showed mild oedematous swelling (▶ Fig. 1).

As well as a leucocytosis value of 14.6 x109/l and C-reactive protein (CRP) of 6.82 mg/dl (reference range < 0.5 mg/dl), laboratory testing showed abnormal renal function tests with creatinine at 3.0 mg/dl and GFR at 15.2 ml/min. Duplex ultrasound scanning showed a deep vein thrombosis (DVT) of the left popliteal vein and the tributaries of the peroneal, gastrocnemius and soleus veins on the left, as well as a long segment of thrombophlebitis af-

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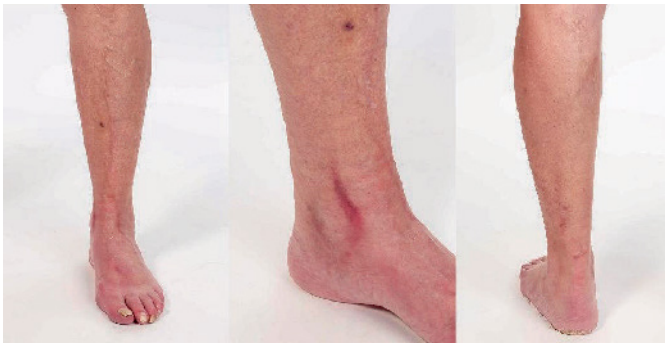

Fig. 1
The patient's distal left lower leg and forefoot showing the three-pronged distribution of warm erythematous cordlike induration.v

fecting the left great saphenous vein below the knee and extending as far as the dorsum of the foot.

Course of the disease

In view of the renal function described above, the fondaparinux therapy had to be switched to aPTT-guided unfractionated heparin therapy. We felt that there was an indication for hospital admission to change the anticoagulant and carry out a full staging investigation. However, the patient did not wish to be admitted. She left the hospital against medical advice.

The patient returned as an emergency three days later, now in a poor general condition with increased dark bluish-red discolouration of her left foot and lower leg and, contralaterally, a cool mottled dark bluish-white right leg. There was no capillary refilling of the right lower leg and forefoot. Motor and sensory functions were intact. The clinical picture suggested critical limb ischaemia. This diagnosis was later confirmed on duplex ultrasonography.

Given the recent onset of the first occurrence of venous and arterial occlusion in this patient, we performed computed tomography (CT). The scan showed multiple thromboembolic lesions: complete occlusion of the popliteal artery vasculature and a short segment of moderate to severe stenosis of the right femoral artery. Thrombus adherent to the vessel wall was seen in the infrarenal and descending aorta, and there was thrombosis of the left common iliac vein extending as far as the inferior vena cava.

The CT scan also provided strong evidence of cervical cancer with local and regional peritoneal carcinomatosis and infiltration of the pararectal fascia and the uterus (▶ Fig. 2). The rapid clinical deterioration of the patient in this case meant that we were unable to obtain histological confirmation of the provisional radiological diagnosis.

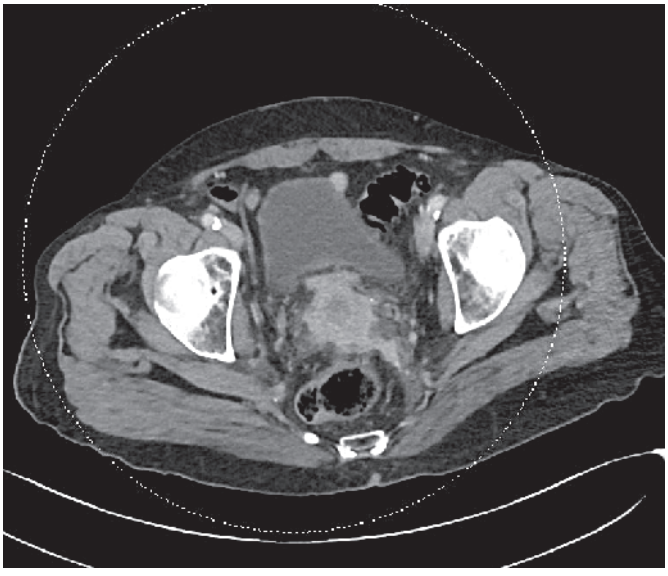

Fig. 2
Suspected cervical cancer – swollen, irregularly thickened cervix with clearly visible contrast medium enhancement. Adjacent mesenteric thickening, especially on the left.

Given the critical limb ischaemia, which threatened the viability of the leg, emergency thrombendarteriectomy of the right popliteal artery and the right femoral artery with subsequent patch plasty was performed. Early re-occlusion required revision surgery.

Both interventions were unsuccessful and necrosis rapidly set in, ultimately necessitating below-knee amputation of the right leg.

In the following days, similar sharply demarcated livid haemorrhagic changes appeared on the right hand and arm (▶ Fig. 3).

The patient's clinical condition deteriorated with steadily decreasing alertness, persistent anuria, and progression of the ischaemic areas. Given the severe and complex clinical picture, we decided not to continue active medical treatment. The patient died 15 days after we first saw her in our angiology outpatient clinic.

Summarising the overall clinical picture and the results of the diagnostic investigations, we diagnosed Trousseau's syndrome (TS) with a strong suspicion of metastatic cervical cancer.

Discussion

Armand Trousseau first described the association between episodic migratory thrombophlebitis and cancer in 1865 (1). Today we refer to the episodic occurrence of conditions such as thrombophlebitis migrans et saltans, venous thromboembolism (VTE), and arterial thrombosis in the presence of underlying malignant disease as Trousseau's syndrome.

Besides hereditary thrombophilia and a past medical history of VTE, malignant disease is the most important predisposing risk factor for developing venous thromboembolism. Patients with cancer have a higher incidence of VTE. Some 15% of this patient group have cancer at the time the thrombosis is diagnosed (2). In particular, patients with idiopathic thrombosis have a 3–15% greater risk of a previously unrecognised underlying malignant disease (3).

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VTE is a serious complication in patients with underlying malignant disease and is clinically manifest in up to 15% (4). The acute and long-term consequences of VTE play a significant role in mortality and represent the second most common cause of death in patients with cancer. For this reason, patients with malignant disease have to be classified as high-risk patients for VTE (5).

This acquired coagulopathy is associated particularly with patients who have solid adenocarcinomas and haematological cancers (6).

The pathogenesis of the haemostatic changes in patients with cancer is complex, apparently multifactorial, and not yet completely elucidated (7, 8). Besides classic causes including the patient's age, immobility, associated treatment such as chemotherapy or radiotherapy, and vascular compression or infiltration by the tumour, the discussion of acquired cancer-associated thrombophilia is focussing on the production of tissue-factor (TF), cancer procoagulant (CP), cytokines and tissue necrosis factor (TNF) (9). Glycoproteins that activate factor X have also been identified in cases of mucinous adenocarcinoma (10). These substances provide a possible explanation for the comparatively common tendency to thrombosis in patients with adenocarcinomas (11). The procoagulant factors mentioned above are not part of routine laboratory testing, so that TS is currently a clinical diagnosis based on the episodic occurrence of different thromboembolic events together with evidence of malignant disease.

The main therapeutic approach to TS, if at all possible, is curative treatment of the identified underlying malignancy. In addition, the VTE has to be adequately treated in accordance with the current guidelines. Adequate treatment can improve the survival of patients with cancer (12). Besides the primary cancer, the sequelae of VTE count as leading causes of mortality (13). The initial treatment of venous thrombosis in oncology patients includes compression therapy and heparin. The risks of recurrence, bleeding, and mortality are more favourable with low molecular weight heparin (LMWH) than with vitamin K antagonists (VKA) (14, 15). Initial antithrombotic therapy in patients with cancer should be continued for at least 3–6 months. The dosage and duration of subsequent maintenance therapy depends on the activity of the malignant disease and the risk of bleeding. Strategies for stepping up the anticoagulation in patients with advanced cancer when thromboembolic complications recur despite technically adequate treatment (refractory Trousseau's syndrome) should be determined by interdisciplinary discussion between the oncologists and specialists in haemostasis, in the light of palliative care for the individual (16).

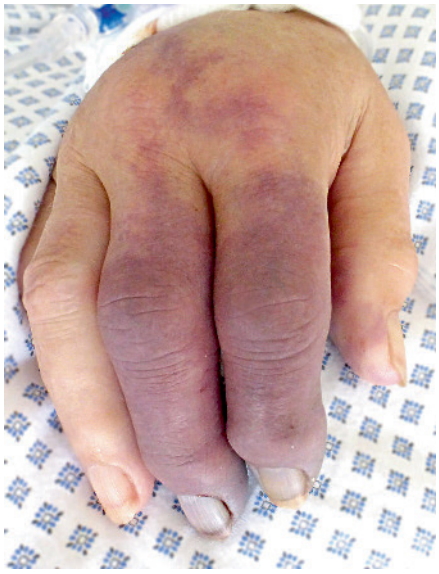

Fig. 3 Sharply demarcated livid haemorrhagic macula can be seen on the right upper limb. The hand is swollen and oedematous. There is no capillary refilling in the second or third finger of the right hand.

The demonstration of cancer alone is not a sufficient indication for long-term anticoagulation. If there are additional thrombogenic risk factors such as surgery, chemotherapy, radiotherapy, a central venous line, immobility, or vascular compression/infiltration by the tumour, then risk-adapted thromboprophylaxis with LMWH can be considered. Regular thrombosis screening in asymptomatic patients is not recommended. Asymptomatic pulmonary embolism is not uncommonly found in staging examinations. This condition should be treated in accordance with the VTE guidelines. Should there be any symptoms suggesting thrombosis, compression ultrasound scanning is the diagnostic investigation of choice. D-dimer testing is not worthwhile in active malignant disease because of its low specificity with frequent false-positive results.

If the patient is being treated with heparin, the differential diagnosis of heparin-induced thrombocytopenia (HIT) type II has to be considered when arterial and venous thromboembolism occurs in large and small vessels. HIT type II could be ruled out in the present case, as our patient was treated with fondaparinux when the acute venous and arterial events began and the platelet count at that time was in the normal range.

Heparin-induced thrombocytopenia type II is an immune-mediated reaction in which there is a pathological production of antibodies to the complex of platelet factor 4 and heparin. The platelet count clearly falls by at least half the baseline value in the first few days of treatment with unfractionated heparin (UFH) or LMWH. The reaction leads to platelet activation and agglutination with subsequent thromboembolism and, more rarely, haemorrhage. It is a dangerous adverse reaction to heparins, occurring ten times more frequently with UFH than with LMWH (18).

The differential diagnosis of arterial and venous thromboembolism also includes antiphospholipid syndrome and systemic vasculitis. Given the rapid and fulminating course in our patient, we did not include investigations relevant to these diagnoses (lupus anticoagulant, cardiolipin/antiphospholipid antibodies, ANCA). Other conditions in the differential diagnosis of superficial migratory thrombophlebitis are existing chronic venous insufficiency, thromboangiitis obliterans, Behçet's disease, systemic lupus erythematosus, granulomatosis with polyangiitis, and septic events (17).

Malignant disease must be considered and the appropriate screening carried out whenever there is an atypical clinical picture with recurrent episodic thrombophlebitis and venous thromboembolism.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Ethical guidelines

Data used in this manuscript were obtained in compliance with national laws and the current version of the Declaration of Helsinki. The patient gave her informed consent.

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