Novel treatment (new drug/intervention; established drug/procedure in new situation)

Massive hypercoagulable state despite full-dose anticoagulant treatment in a patient with occult malignancy: considerations concerning chemotherapy without definitive diagnosis

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Summary

A 55-year-old female patient presented with recurrent deep venous thrombosis and pulmonary embolism while on oral anticoagulant treatment using the vitamin K antagonist phenprocoumon. Hypercoagulable state was regarded to be paraneoplastic, but no underlying malignancy could be identified despite extensive screening for cancer, including gastroscopy and colonoscopy, a bone marrow biopsy, thoracoabdominal CT scans with subsequent biopsies of possibly malignant findings, octreotide scintigraphy, skeletal scintigraphy and gynaecological screening. In the course of her hospital stay she developed progressive right cardiac insufficiency due to the formation of new thromboses despite aggressive anticoagulant treatment and died of right-sided heart failure. The autopsy showed a poorly differentiated adenocarcinoma in the middle lobe of the right lung. In addition, pulmonary lymphangiosis carcinomatosa, pleural and pericardial carcinosis, and lymph node metastases and osteoblastic vertebral body metastases were shown.

BACKGROUND

Hypercoagulable state is a common finding in patients with cancer due to the production of substances with procoagulant activity. Approximately 10% of patients who present with unprovoked or idiopathic vein thrombosis are diagnosed with cancer within a few years after their thrombotic event. Here we present a case of a patient with massive hypercoagulable state with recurrent thromboses despite anticoagulation due to adenocarcinoma of the lung, which could not be identified *in vivo*. It will be discussed whether chemotherapy should be considered as a last-line treatment in such patients even in the absence of a definitive diagnosis of malignancy to ameliorate the hypercoagulable state.

CASE PRESENTATION

Past medical history

A 55-year-old female patient was transferred to our tertiary care university hospital for evaluation of extensive and recurrent thrombosis despite anticoagulant treatment.

In July 2006 at age 54 years she had a first deep vein thrombosis. During following months, recurrent thromboses and superficial vein vasculitis predominantly of the extremities occurred despite treatment with phenprocoumon and international normalised ratio (INR) values within the therapeutic range. Screening for inherited or acquired

thrombophilic risk factors identified a heterozygous factor V (FV) Leiden mutation. Substitution of phenprocoumon with warfarin was not successful.

In August 2007 she was admitted to hospital for diagnostic workup as neoplasia was suspected as underlying disease. Slightly elevated tumour markers carcinoembryonic antigen, neuron-specific enolase and cancer antigen 15-3, a gastric ulcer without suspicion of malignancy, a nodular goitre and a most likely benign lesion of the right breast were the only findings of the extensive diagnostic workup, including broad laboratory testing, gastroscopy, colonoscopy, a thoracoabdominal CT scan, gynaecological screening with mammography and octreotide scintigraphy. However, no definite diagnosis could be established. In November 2007, she developed thrombotic occlusions of the left axillary and subclavian veins and peripheral lung embolism. After switching the antithrombotic treatment to low molecular weight heparin (LMWH; 1 mg/kg body weight/day enoxaparin) plus aspirin (100 mg/day) she was transferred to our hospital for further diagnostic workup and escalating antithrombotic treatment.

INVESTIGATIONS

Laboratory testing showed elevated d-dimer levels and anti-Xa-activities within the therapeutic range (table 1).

Table 1 Laboratory results at time of admission

Blood count	
Platelet count (G/l)	396 (150–350)
Leucocytes ($\times 10^9/l$)	9.6 (3.0–10.0)
Haemoglobin (g/dl)	11.6 (12.0–16.0)
Haematocrit (%)	35 (37–48)
Clotting analyses	
Activated partial thromboplastin time (s)	25.6 (25–36)
INR	1.16
Quick (%)/prothrombin time (s)	72/10 (78–164)/(9–12)
Fibrinogen (mg/dl)	476 (177–376)
Factor II (%)	129 (87–127)
Factor V (%)	132 (67–145)
Factor VII (%)	117 (77–154)
Factor VIII (%)	229 (70–157)
Factor X (%)	105 (80–140)
Antithrombin (%)	111 (85–130)
Protein C (%)	108 (80–150)
d-Dimers (mg/l)	9.77 (0–0.49)

Thromboses of the inferior vena cava, the right external and common iliac veins and the right femoral vein, an occlusion of the left subclavian vein and peripheral lung embolisms on both sides were confirmed (figure 1). A repeated thrombophilic workup confirmed activated protein C resistance caused by a heterozygous FV Leiden mutation. Screening for antithrombin deficiency, protein C/S deficiency, prothrombin G20210A mutation, JAK2-mutation and antiphospholipid antibodies, including lupus anticoagulants, was negative. An underlying malignancy of unknown origin was considered to be the most likely explanation for the prothrombotic state. Since malignancies of the lung, thyroid, breast and pancreas are associated with the occurrence of thrombosis, further diagnostic procedures focused on these entities.

After aggravation of the patient's clinical condition and suspicion of further lung embolism, we repeated a thoraco-abdominal CT scan, which presented following findings possibly indicating malignancy:

- ▶ nodule of the left thyroid gland
- ▶ suspected area of the first lumbar vertebra body consistent with osteoblastic metastasis
- ▶ right-sided intramammary lymph node measured 9 mm.

Osteoblastic metastasis located in the lumbar spine was shown for the first time and strongly confirmed the clinical suspicion of malignancy (figure 2). A skeletal scintigraphy demonstrated multiple accumulations in several vertebral bodies. Subsequent biopsy of a lumbar vertebra provided necrotic tissue material but no evidence for malignancy. Although the thyroid gland nodule scintigraphically turned out to be rather non-malignant we performed a biopsy. There was no proof of malignant cells.

Repeated gastroscopy due to the gastric ulcer in the history showed a gastric erythema with no proof of malignancy.

Gynaecological screening and repeated mammography and MRI showed no evidence for malignancy and we did not pursue a biopsy because of the complex clotting situation and low clinical probability.

In summary, no clinical diagnosis could be established although obvious metastatic cancer was present.

TREATMENT

The course of anticoagulant treatment is shown in figure 3.

We started a d-dimer tailored anticoagulant treatment regimen combining phenprocoumon and enoxaparin 40 mg twice a day. We induced high-dose treatment with phenprocoumon with a target INR of 4–6 and due to further increment of d-dimers we adjusted enoxaparin doses to 60 mg twice a day. During this treatment, the increase of d-dimer was effectively stopped with d-dimer levels below 1 $\mu\text{g/l}$ and no further thromboembolic events occurred. On day 15 of this high-dose anticoagulant treatment, she developed pericardial effusion and was admitted to the intensive care unit. Pericardiocentesis showed a non-haemorrhagic effusion with few cells consistent with a malignant effusion. During the first 48 h of the intensive care unit stay, anticoagulant phenprocoumon and enoxaparin treatment was stopped and anticoagulation continued with 500 IU/h of unfractionated heparin (UFH). During this anticoagulant regimen she developed deep vein thrombosis of the right vena femoralis associated with an increase of d-dimer levels above 10 $\mu\text{g/l}$ and a decrease of fibrinogen, factor V and platelet count indicative for systemic activation of the coagulation system. Heparin-induced thrombocytopenia as a possible cause of thrombosis despite heparin treatment was ruled out. To achieve efficient antithrombotic treatment, the direct thrombin inhibitor argatroban at a dosage of 0.5 $\mu\text{g/kg/min}$ was given. During this combined anticoagulant approach, the thrombus growth was stopped and a sufficient reduction of d-dimers could be achieved. Medication with argatroban and heparin was continued and formerly mentioned biopsies of the thyroid gland and the vertebral body and endoscopy could be performed. Stopping anticoagulant treatment to perform these diagnostic procedures induced a rapid rise of d-dimer levels.

During her hospital stay, dyspnoea and congestive heart failure worsened. After the first exacerbation with pericardial effusion her clinical condition remained critical and she needed continuous oxygen treatment. In January 2008 she developed a progressive right cardiac insufficiency and died of right-sided heart failure.

OUTCOME AND FOLLOW-UP

A poorly differentiated adenocarcinoma in the area of the middle lobe of the right lung was proven by autopsy (figure 4). Moreover, pulmonary lymphangiosis carcinomatosa, pleural and pericardial carcinosis and metastases of the hilary lymph nodes and osteoblastic vertebral body metastases were shown. Breasts and thyroid gland showed no evidence for malignancy.

Immediate cause of death was right heart failure due to recurrent microthromboembolism, which led to an increment of pulmonary vessel resistance and pressure on the right heart with central venous blood congestion.

DISCUSSION

Venous thromboembolism is a common complication in patients with cancer and may be the first manifestation of

Figure 1 Pulmonary embolism. Dedicated CT pulmonary angiography performed after admission displays pulmonary embolism (white arrow) with recurrent thrombosis.

malignancy.¹ The spectrum of haemostatic abnormalities in patients with cancer ranges from abnormal coagulation tests in the absence of clinical manifestations to massive thromboembolism. Clinical presentations include:

- ▶ migratory superficial thrombophlebitis (Trousseau's syndrome)
- ▶ deep venous thrombosis and other venous thrombosis
- ▶ thrombotic endocarditis (marantic endocarditis)
- ▶ disseminated intravascular coagulation
- ▶ thrombotic microangiopathy
- ▶ arterial thrombosis.

Approximately 10% of patients who present with unprovoked or idiopathic thrombosis are diagnosed with cancer within a few years after their thrombotic event.² Most common cancers associated with venous thromboembolism include lung cancer, colon cancer, brain cancer, prostate cancer in men, and ovarian and breast cancer in women.^{3,4} Among non-small-cell lung cancers the incidence of venous thrombosis in patients with adenocarcinoma is considerably increased compared to patients with squamous cell carcinoma.⁵ Observational data indicate that patients with cancer and venous thrombosis have a worse prognosis than those with cancer alone.^{3,4} Up to 40% of patients with cancer diagnosed within 1 year after venous thrombosis have distant metastases by the time of their cancer diagnosis.⁶ Considering these observations, earlier cancer diagnosis is likely to be associated with improved treatment possibilities and prognosis. However, there is no evidence for better prognosis due to earlier diagnosis. One recent randomised controlled trial (RCT) of 201 patients with symptomatic idiopathic thromboembolism showed no survival benefit with extensive screening compared to routine testing for malignant disease in patients with idiopathic venous thromboembolism.⁷ In this trial, extensive screening

included ultrasound of the abdomen, followed by CT scan of the abdomen, gastroscopy or double contrast barium swallowing, colonoscopy or sigmoidoscopy followed by barium enema, haemoccult, sputum cytology, tumour markers (including carcinoembryonic antigen, α -fetoprotein and cancer antigen 125), mammography and Pap smear for women, and transabdominal ultrasound of the prostate and total specific prostatic antigen for men. Although in the extensive screening group a single (1%) malignancy became apparent during 2-year follow-up whereas in the control group a total of 10 (9.8%) malignancies became symptomatic, it is uncertain whether the earlier detection of the cancer improves the prognosis due to the limited sample size. Despite the extensive screening, one of the overall detected fourteen malignancies of the extensive screening group was not identified for a sensitivity of 93%. This shows the difficulty of finding the suspected malignancy as, in our case, no definite diagnosis could be established although repeated CT scans and biopsies were performed.

During hospitalisation we did not perform a positron emission tomography (PET) scan despite its increasing value in diagnostics of malignancies. It possibly would have helped us to locate the primary; however, PET scan still has hardly any significance in screening for unknown malignancy in Germany due to its costs. As all findings possibly indicating malignancy via CT scan did not provide evidence performing invasive diagnostics, we would have considered a PET scan as one of our next steps. Anyway, the rapid aggravation of the clinical condition left no opportunity to complete the diagnostic workup.

The FV Leiden mutation is an established thrombophilic risk factor that increased the cancer-associated risk of thrombosis. A large population-based case control study of 3220 consecutive patients showed a twofold increased risk

Figure 2 Vertebral body metastases. Parasagittal T1-weighted (A) and fat-suppressed T2-weighted (B) MR images show an infiltrative process within the L1 vertebral body consistent with osteoblastic metastasis.

of venous thrombosis for patients with FV Leiden mutation with cancer compared to non-carriers with cancer.⁸ However, the enormous activation of the coagulation system in this case cannot be explained by the FV Leiden mutation.

The patient developed recurrent deep vein thrombosis while on full-dose anticoagulant treatment. Therefore, we suspected an underlying malignancy of unknown origin. As the clinical condition of the patient worsened rapidly we discussed treatment with chemotherapeutic agents like 5-FU and carboplatin as a last resort. Retrospectively, chemotherapy probably leading to a reduction of tumour size and, therefore, to an improvement of thrombophilia could have ameliorated her condition as autopsy showed the recurrent lung microembolism with subsequent right heart failure were direct causes of death. However, the use of chemotherapeutic agents should be considered carefully as

these agents are also associated with increased risk of venous thrombosis. Cytotoxic agents can alter coagulation protease levels and may directly injure the endothelium. Clinical data prospectively collected on the population of Olmsted County, Minnesota, suggest a 4.1-fold risk of thrombosis for cancer alone compared to the absence of cancer. Chemotherapy increased the risk for thrombosis 6.5-fold;⁹ thereby, questioning the empiric use of chemotherapy in our case without a definite diagnosis. Further investigation using a multivariate model to estimate the attributable risk in this study showed 18% of venous thromboembolism cases were attributable to active malignant neoplasm. Malignant neoplasm without chemotherapy was responsible for a larger percentage of the risk of venous thromboembolism (12%) than was malignancy with chemotherapy (6%).¹⁰ Although there are few comments in

Figure 3 Course of anticoagulant treatment and clotting surrogates.

literature indicating an improvement of thrombophilia by chemotherapy,¹¹ this effect is poorly proved and all recent studies suggest an increase of risk within populations with neoplasms by using chemotherapeutic agents.^{12,13}

Existing studies focus on anticoagulant treatment rather than the use of chemotherapeutic agents. Concerning anticoagulation, the largest reported RCT study (CLOT) comparing LMWH with vitamin K antagonist treatment in patients with cancer with venous thrombosis showed a RR reduction of 49% for treatment with dalteparin compared to vitamin K antagonists.¹⁴ Recent guidelines recommend treatment with LMWH rather than with vitamin K antagonists or UFH as several studies demonstrate a positive effect on survival.¹⁴ Current evidence suggests that the

best-characterised cancer procoagulant tissue factor is also an important mediator between activation of coagulation and tumour growth. LMWH releases tissue factor pathway inhibitor, a physiological inhibitor of the tissue factor pathway,¹⁵ and should even be considered in patients with cancer without venous thromboembolism.^{14,15} After the occurrence of pericardial effusion we temporary changed antithrombotic regimen to heparin and argatroban due to facilitate monitoring during invasive procedures. This also led to an adequate reduction of d-dimers but probably did not have the same effect on tumour growth compared to LMWH.

In summary, our case illustrates that despite the knowledge of a metastatic disease with multiple bone metastases and paraneoplastic hypercoagulation no

Figure 4 Cancer histopathology. (A) Lung tissue revealed extensive lymphangiosis carcinomatosa (arrowhead: visceral pleura surface) (100 × H&E). (B) In addition, spinal tumour metastases (tu) with a desmoplastic and osteoplastic reaction were detectable (bm, unaffected bone marrow) (100 × H&E). Immunohistochemical analyses revealed expression of (C) lung surfactant protein A (SP-A) (200 × H&E) and (D) cytokeratine 7 (200 × H&E).

definite diagnosis could be established in vivo. We considered chemotherapeutic treatment but could not decide for it due to the additional risk and the lack of experience in using chemotherapeutic agents in such special cases. Diagnosis and management of these patients still remains a challenging issue in medical care and further experience is needed.

Learning points

- ▶ Venous thromboembolism is a common complication in patients with cancer and may be the first manifestation of malignancy.
- ▶ The case illustrates the difficulty of establishing a definite diagnosis despite the knowledge of a metastatic disease with multiple bone metastases and paraneoplastic hypercoagulation.
- ▶ Concerning anticoagulative treatment existing guidelines recommend treatment with LMWH rather than with vitamin K antagonists or UFH as several studies show a positive effect on survival.
- ▶ The impact of chemotherapy on cancer-related recurrent thromboembolism is poorly investigated. Considering the negative effects of chemotherapeutic agents on protease levels and the endothelium with potentially increased risk of venous thrombosis further experience is needed.

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