Penile gangrene in lung cancer

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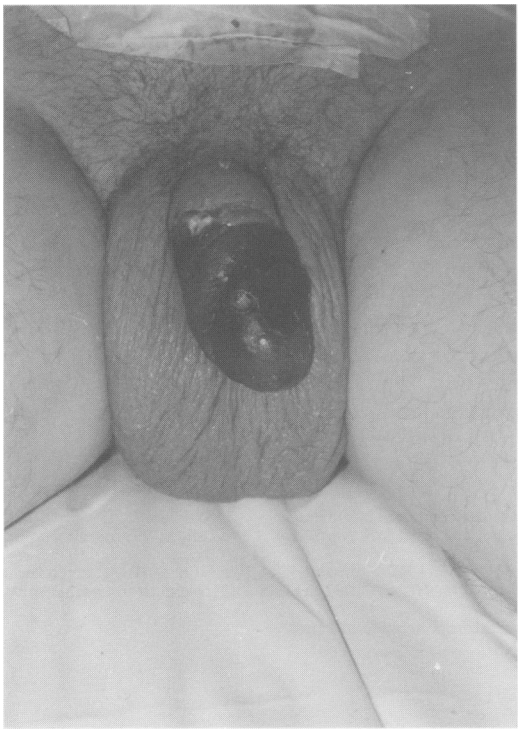
A 41-year-old man was admitted to the emergency service with complaints of pain and swelling in right calf, dyspnoea and haemoptysis. Hypoxaemia and hypocapnia were identified on arterial blood gases analysis: pO_2 53.9 mmHg, pCO_2 30.6 mmHg, O_2 saturation 88.5% and pH 7.42. An infiltrative mass in the right lower lobe with mediastinal and hilar adenopathies was seen on chest X-ray and subsequently on computed tomography. Right popliteal vein thrombosis and pulmonary thromboemboli were diagnosed with Doppler ultrasonography and pulmonary ventilation-perfusion scanning, respectively. Basal prothrombin levels, activated partial thromboplastin time and blood counts were within normal limits. Anticoagulation was started with intravenous heparin and later with subcutaneous low molecular weight heparin. The patient improved and bronchoscopic transbronchial lung biopsy was performed which revealed bronchioloalveolar carcinoma. Chemotherapy was administered as cisplatin plus etoposide.

A few days after completion of the treatment, the patient suffered from acute penile pain and cyanosis which progressed to gangrene (figure). Coagulation tests were as seen in the table. Over the next few days oliguric acute renal failure and distal femoral arterial embolism developed. Blood urea nitrogen and creatinine levels progressively increased. There was bilateral renal ischaemia on radionuclide renal scan. Sudden left leg pain, pallor, coldness and absent popliteal and pedal pulses led to the diagnosis of arterial embolism, which was confirmed with Doppler ultrasonography. The patient died due to respiratory insufficiency, shock, and subsequent cardiopulmonary arrest. At necropsy, multiple thromboemboli in peripheral organs including brain, kidneys, lung, left femoral artery, and penile vasculature were confirmed.

Table Coagulation data (and normal values)

Prothrombin time (s)	37.5 (13±2)
Activated partial thromboplastin time (s)	88.7 (29–45)
Thrombin time (s)	23.4 (18±3)
D-dimer (ng/ml)	1500 (0–250)
Antithrombin III antigen (mg/ml)	19.2 (18–28)
Fibrinogen (mg/ml)	130 (150–350)
Platelet count ($\times 10^9$/l)	103 (150–440)



Figure

Questions

1 What is the coagulation problem summarised in the table?
2 What is the most probable clinical diagnosis that explains the emergence of multiple peripheral thromboembolism in this patient?

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Answers

QUESTION 1

Disseminated intravascular coagulation (DIC). Significantly elevated D-dimer levels, laboratory evidence of depletion of clotting factors and platelets, and the presence of a disorder known to cause DIC allow the diagnosis to be made with certainty. Therapy should be determined on an individual basis, considering the clinical manifestations, precipitating events, severity, etc. Three sequential steps should be followed[1]:

- treatment or removal of the precipitating process
- if elimination of the triggering events is not possible within a feasible timeframe or haemorrhage and/or thrombosis continues despite accomplishing the first step, the intravascular coagulation process should be blocked by heparin, antithrombin, etc
- if any patient with DIC continues to bleed despite the first two steps, depleted coagulation components should be replaced. In a minority of patients, inhibition of an associated severe fibrinolysis may be required as a last resort for continued bleeding.

QUESTION 2

Nonbacterial thrombotic endocarditis (NBTE), characterised by sterile thrombotic vegetations on cardiac valves, predominantly aortic and mitral. The major clinical manifestations are those related to systemic embolisations. Multiple arterial emboli, and sometimes heart murmurs in a disease process known to be associated with NBTE, establish the clinical diagnosis.[2,3] There is no specific treatment other than to deal with the complications and underlying disease and controlling coagulation with heparin.[2] Heparin-induced thrombocytopenia and thrombosis syndrome (the 'white clot' syndrome) should be considered in patients with thrombocytopenia and thrombotic complications on heparin treatment. Rarely, a similar syndrome is also caused by low molecular weight heparin.

Discussion

Hypercoagulability is a common paraneoplastic occurrence. Clinically apparent thrombosis occurs in 1 to 11 % of patients with cancer and the incidence is much higher in *post-mortem* studies, especially in mucinous cancers, eg, gastrointestinal, pancreatic and lung.[4] Inappropriate activation of the coagulation cascade due to interaction of malignant cells with endothelium, platelets, coagulation and fibrinolytic systems is the principle pathophysiological basis of the hypercoagulability that occurs in cancer.[5] Cancer cell-derived procoagulants and antigens, cytokines, chemotherapy and antiphospholipid antibodies can induce coagulation by different mechanisms in malignant neoplasms.[4,5] Superficial thrombophlebitis, deep venous thrombosis, pulmonary embolism, NBTE, visceral thrombosis, thrombotic microangiopathic haemolytic anaemia, digital and cerebral microvascular arterial thrombosis and apparent DIC are the clinical manifestations of cancer-associated hypercoagulability.[3]

Clinical manifestations of cancer-associated hypercoagulability

- superficial thrombophlebitis
- deep venous thrombosis
- pulmonary thromboembolism
- visceral thrombosis
- nonbacterial thrombotic endocarditis
- microvascular arterial thrombosis
- microangiopathic haemolytic anaemia
- disseminated intravascular coagulation

NBTE is frequently missed in clinical practice. The major clinical manifestations that should lead to the diagnosis are those related to systemic embolisations.[2,3] NBTE is most frequently encountered in lung cancer.[2] The incidence is highest in bronchiolo-alveolar carcinoma and other adenocarcinomas of the lung. NBTE is commonly associated with DIC.[2] Transthoracic echocardiography is useful for *pre-mortem* confirmation.[2] However, false-negative results may occur due to small valvular vegetations. Transoesophageal approach and magnetic resonance imaging may be more sensitive. In our patient, NBTE was suspected due to the emergence of thromboembolic complications and the diagnosis was confirmed by the appearance of vegetations on the mitral valve on transthoracic echocardiography. There were no signs of infection. NBTE was confirmed on autopsy.

Final diagnosis

Bronchiolo-alveolar carcinoma, disseminated intravascular coagulation, and nonbacterial thrombotic endocarditis.

Keywords: bronchiolo-alveolar carcinoma, disseminated intravascular coagulation, nonbacterial thrombotic endocarditis.

1 Bick RL. Disseminated intravascular coagulation. Objective criteria for diagnosis and management. *Med Clin North Am* 1994; **78:** 511-43.
2 Lopez JA, Ross RS, Fishbein MC, Siegel RJ. Nonbacterial thrombotic endocarditis: A review. *Am Heart J* 1987; **113:** 773-84.
3 Luzzato G, Schafer AI. The prethrombotic state in cancer. *Semin Oncol* 1990; **17:** 147-59.
4 Rickles FR, Edward RL. Activation of blood coagulation in cancer. Trousseau's syndrome revisited. *Blood* 1983; **62:** 14-31.
5 Donati MB. Cancer and thrombosis: from phlegmasia alba dolens to transgenic mice. *Thromb Haemost* 1995; **74:** 278-81.