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Case Report

Squamous cell carcinoma lung: Presented with bilateral lower limb deep venous thrombosis with gangrene formation

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Abstract

Bilateral venous thrombosis due to underlying malignancy is a rare entity. It is worthy to search for malignancy in patients of bilateral venous gangrene. Our patient presented with severe bilateral leg pain as a result of venous gangrene. There was associated left sided massive pleural effusion with scalp nodule. Fine needle aspiration cytology of scalp nodule revealed metastatic squamous cell carcinoma and fiber optic bronchoscopy guided biopsy from growth at left upper lobe bronchus confirmed the case as squamous cell carcinoma lung. It was rare for squamous cell carcinoma lung to present as bilateral venous gangrene with anticardiolipin antibody negative.

Key words: Bilateral deep venous thrombosis, squamous cell carcinoma lung, venous gangrene

Introduction

Venous thrombosis is a common problem, especially deep vein thrombosis involving the extremities. Among the risk factors for venous thromboembolisms (VTE), cancer is an important and well-established risk factor, leading to a 2- to 4-fold increased risk. Patients with lung cancer have long been recognised to be at a high risk of venous thromboembolism. However, cancer induced venous gangrene is extremely rare condition and it is associated with a worse prognosis. Till now there has been one case reported in English literature where venous gangrene is associated with adenocarcinoma lung. Here we present a case of squamous cell carcinoma complicated with venous gangrene on the right foot associated with bilateral deep vein thrombosis.

Case Report

A 41-year-old non diabetic non hypertensive non smoker woman was brought to our department with complain of dry cough, progressive shortness of breath for 2 weeks along with pain and swelling of both feet for 1 week. On examination there was bilateral pitting pedal oedema and raised body temperature of 101°F. Blackening of skin of all the toes on both feet with decreased local temperature and tenderness were revealed on local examination of feet. [Figure 1] Multiple nodules over scalp were seen as incidental finding. For evaluation of respiratory symptoms, chest X-ray and CT scan thorax were done and revealed left sided massive pleural effusion with atelectasis of left lung. [Figure 2] Pleural fluid study came as lymphocytic, exudative, ADA level 14 IU/ml with presence of malignant cell. Closed pleural biopsy and report suggested as metastatic squamous cell carcinoma. FNAC from scalp nodule was also positive for metastatic squamous cell carcinoma [Figure 3a]. On fiber optic bronchoscopy, there was an infiltrating growth in left upper lobe bronchus and biopsy suggestive of squamous cell carcinoma [Figure 3b]. USG doppler of venous system of both lower limbs revealed an organized thrombus in common iliac veins extending into superficial femoral vein with complete occlusion of venous system distal to it. Doppler angiography showed patency of bilateral arterial system like common iliac, internal iliac, external iliac, femoral, popliteal, anterior tibial, posterior tibial, and arteria dorsalis pedis and any arterial occlusion as a cause of gangrene had been ruled out. However, a coagulation profile did reveal the existence of hypercoagulable state with prothrombin time 14.4 s (control 12.5 s), partial thromboplastin time 43.5 s (control 32.2 s), International Normalized Ratio (INR) 1.16, D-dimer raised to 1030 µg/L and a fibrin degradation product 286 µg/ml (normal < 10 µg.ml). Serum for antinuclear antibody (ANA), Ig M and Ig G anticardiolipin antibodies, protein C and protein S was within normal limits. Patient was put on low molecular weight heparin (LMWH) enoxaparin sodium injection subcutaneously at a dose of 40 IU twice daily. After 5 days of treatment with LMWH, INR was repeated and found to be 2.5. Patient was shifted to oral warfarin 5 mg daily from LMWH after 7 days of treatment. She was diagnosed as a case of stage IV squamous cell carcinoma lung and treated with palliative chemotherapy regimen consisting of carboplatin and gemcitabine. After 1st cycle of chemotherapy patient was discharged in stable condition with oral warfarin at a dose of 5 mg daily and asked to check INR regularly.

Discussion

The incidence of venous thromboemboli sm in cancer population is 1 in 200 in comparison with 1 in 100,000

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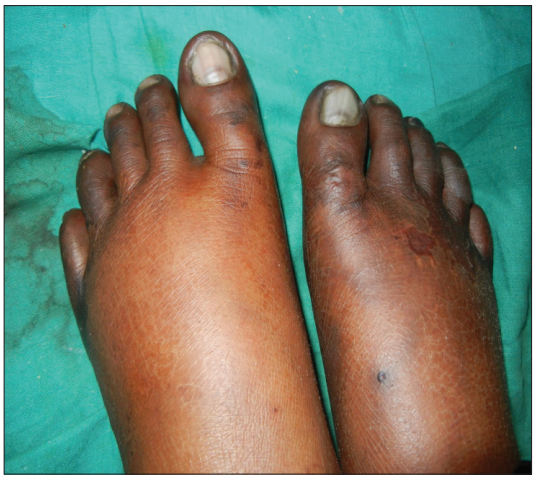

Figure 1: Blackening of skin of all the toes on both feet with swelling suggesting venous gangrene

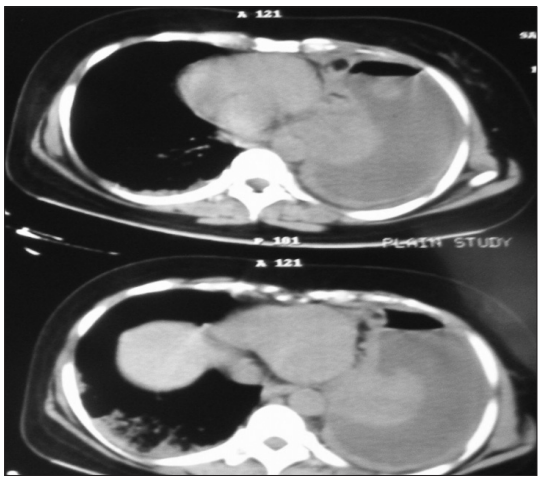

Figure 2: CT scan thorax showing left sided massive pleural effusion with atelectasis of left lung

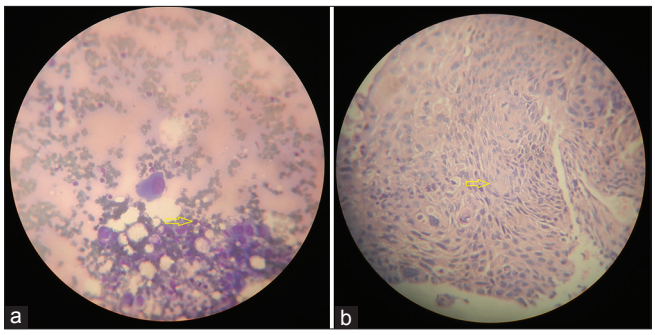

Figure 3: (a) FNAC from scalp nodule showing atypical cells (yellow arrow) suggestive of metastatic squamous cell carcinoma (H and E x200). (b) Bronchial biopsy showing nuclear hyperchromasia with pleomorphism and keratinisation pearl (yellow arrow) suggestive of squamous cell carcinoma of lung (H and E, ×200)

in the general population.[1] Cancers of the pancreas, lung, stomach and adenocarcinoma of unknown primary, are strongly associated with thrombosis.[2] Lung cancer is associated with a 20-fold increased risk for thrombosis.

Most important and dominant theory of pathophysiology for thrombosis is Virchow's theory [Table 1]. Patients with various cancers frequently demonstrate abnormalities in each components of Virchow's triad, leading to a prothrombotic or hypercoagulable state. Tumor cells can activate blood coagulation through multiple mechanisms, including production of procoagulant, fibrinolytic, and proaggregating activities, release of proinflammatory and pro-angiogenic cytokines, and interacting directly with host vascular and blood cells (e.g., endothelial cells, leukocytes, and platelets) through adhesion molecules.[3] Decreased level of antithrombin III and acquired deficiency of protein C or protein S have previous been reported in cancer patients.[4] Membrane bound tissue factor on cancer cell also stimulate the extrinsic blood coagulation pathway.[5] There are some studies reported that there is association between anticardiolipin antibodies related coagulopathy in cancer. Yang MH *et al*. reported one case of venous gangrene in a patient of adenocarcinoma lung with raised anticardiolipin antibodies.[6] Zuckerman E *et al*. reported that anticardiolipin positive cancer patients have significantly more chance of developing thrombosis than anticardiolipin antibodies negative patients (28% compared to 14%).[7] VTE risk appears two-fold higher in non small-cell lung cancer than in small-cell lung cancer patients. Venous thrombosis in lung cancer patients is mostly associated with adenocarcinoma rather than squamous cell carcinoma.[8] Interaction of circulating carcinoma mucins with leukocyte L-selectin and platelet P-selectin without requiring accompanying thrombin generation is a probable molecular explanation for the increased incidence of venous thrombosis in patients with adenocarcinoma.[9] Other than tumor type, risk factors for VTE are stage of the disease, metastatic disease, venous stasis from immobility, sepsis, local inflammation and/or infection, use of specific chemotherapeutic drugs in combination with novel targeted drugs such as antiangiogenic agents, elevated prechemotherapy platelet counts, surgery and interventions such as central venous catheter placements.

Chemotherapy for cancer is associated with a 2-to 6-fold increased risk for VTE compared with the general population. Platinum-based regimens, etoposide, methotrexate, hormonal therapies like medroxyprogesterone acetate are significantly associated with VTE.[10] Main mechanisms of thrombogenesis ascribed to chemotherapeutic agents are: Release of procoagulants and cytokines from damaged tumor cells, a toxic effect on vascular endothelium and the fall of naturally occurring anticoagulants due to hepatotoxicity.[11] Radiotherapy probably mainly has a thrombogenic effect by release of procoagulants and cytokines from damaged tumor cells.[12] To reduce the clinical burden of VTE associated with anticancer treatment, it is important to identify patients with cancer at highest risk for VTE for whom prophylaxis may be beneficial.

The clinical manifestations of cancer related thrombosis include spontaneous recurrent migratory venous thrombosis, arterial thrombosis, microangiopathy, nonbacterial thrombotic

Table 1: Virchow's triad in cancer

Abnormal blood flow
Increased plasma viscosity
Increased stasis due to immobility (e.g., being bed-bound, in a wheelchair)
Abnormal blood constituents
Increased platelet activation and aggregability, for example, increased soluble P selectin, beta thromboglobulin
Loss of haemostasis with increase in procoagulants for example, increased fibrinogen, cancer procoagulant, PAI-1
Abnormal blood vessel wall
Damaged or dysfunctional endothelium (e.g., increased soluble E selectin, increased soluble thrombomodulin, possibly also related to chemotherapy)
Loss of anticoagulant nature and therefore acquisition of a procoagulant nature (e.g., increased vonWillebrand factor, tissue factor, reduced tPA, possibly also related to chemotherapy)
Angiogenesis (altered release of, and response to, growth factors)

endocarditis and acute or chronic disseminated intravascular coagulation. For assessing the risk of VTE in cancer patients D-dimer assay is useful for screening purpose and if elevated, then doppler study is helpful to diagnose VTE.

According to the current guidelines, treatment for cancer-associated thrombosis is started with fixed dose LMWH for 5-7 days and continued with vitamin K antagonists, such as warfarin, for 3-6 months. Recurrence of VTE is more common in cancer patients than in non-cancer patients. In patients who develop a recurrence while on warfarin therapy, the recommended practice is to switch these patients to LMWH because it is more efficacious than warfarin. Insertion of a vena cava filter has been recommended for oncology patients with recurrent VTE despite adequate long-term LMWH therapy. On the other hand, cancer patients seem to be prone to have more frequently bleeding complications while receiving anticoagulant treatment. Patients should have their anticoagulant response (INR or PTT) monitored frequently in order to adjust the anticoagulant dose accordingly. Most bleeding events are observed in the first months of anticoagulation.[13] Cancer patients frequently have chemotherapy-induced cytopenias, including thrombocytopenia. In these patients reduction in dose of LMWH by half is required in patients with platelet counts between 20 and 50 $\times$ 10^9/L.[14]

In lung cancer patient's thromboembolic phenomenon is thought to be a sign of poor prognosis with an average survival of less than 6 months from the thrombotic events to death.[15]

To the best of our knowledge, no cases of paraneoplastic venous gangrene in a patient of squamous cell carcinoma lung with negative anticardiolipin antibodies have been reported. Our patient also had venous gangrene of both lower extremities which is rare to see on presentation in squamous cell lung cancer.

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