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Case Report

Gall bladder carcinoma associated with anticoagulation-resistant, progressive, multi-focal venous thrombosis and gangrene of all limbs: a case report and review of literature

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ABSTRACT

Cancer being a prothrombotic state, frequently has vascular complications, venous thrombosis, embolism, recurrent venous thromboembolism and a high frequency of anticoagulant failure. We present a rare case of anticoagulant-resistant, progressive, multifocal venous thrombosis and gangrene in all four limbs in a patient with carcinoma gallbladder. A 49 year old lady with locally advanced gallbladder cancer who had been on routine perioperative deep venous thrombosis (DVT) prophylaxis presented two months later with deep venous thrombosis of both lower limbs progressing to venous gangrene of both feet, despite being on anticoagulation. 7 days later, she presented with venous gangrene of both hands. Shortly thereafter, she developed right facial paralysis due to thrombus in the segmental branch of the left MCA despite being on anticoagulation. The hypercoagulable state in cancer involves procoagulant molecules produced by tumor cells, suppression of fibrinolytic activity and platelet activation and is contributed by interactions between the coagulation cascade, complement pathway and immune system. Upto 15% of patients with cancer will develop DVT following surgery, despite standard DVT prophylaxis. Extended DVT prophylaxis should be considered in high-risk patients. Patients with metastases should continue with indefinite anticoagulant therapy after a thrombotic event. In patients without metastasis, anticoagulant treatment is recommended for as long as the cancer is active and while the patient is receiving antitumor therapy. This rare case has been presented to highlight the hypercoagulable state of cancer, the importance of long-term anticoagulation in advanced and metastatic cancers and the high rate of anticoagulation failure associated with unfavourable tumor biology.

Keywords: Cancer-associated thrombosis, Venous thrombosis, Gangrene, Pulmonary thromboembolism, Prothrombotic state

INTRODUCTION

Cancer being a prothrombotic state can frequently lead to vascular complications, especially DVT and pulmonary embolism (PE) and have a three-fold higher risk of recurrent venous thromboembolism (VTE).[1,2] Arterial thrombosis can also occur, including stroke and myocardial infarction.[3] Recent data suggest that this thrombotic state is due to the close linkage between regulation of angiogenesis and coagulation and is integral to cancer growth and metastasis.[3]

The complex synergistic relationship between the coagulation cascade, complement pathway and the immune system in enhancing tumor growth likely contributes to the hypercoagulability in malignancy and

the high frequency of anticoagulant failure in malignancy associated thrombosis.[3-6]

We here presented a rare case of anticoagulant-resistant, progressive, multifocal venous thrombosis and gangrene with resultant devastating clinical consequences in a patient with advanced carcinoma of the gallbladder.

CASE REPORT

X, a 49 year old lady, presented to our surgical outpatient with complaints of a continuous, dull aching pain in right upper abdomen along with anorexia and weight loss for 6 months. There was no history of jaundice, biliary colic, fever or vomiting. On examination there was no pallor or jaundice. Abdominal examination revealed no palpable abnormality. Her liver function tests showed a normal serum bilirubin level and serum alkaline phosphatase. An ultrasound of the abdomen showed a heterogeneous mass in the gallbladder neck along with intraluminal sludge. A CECT abdomen showed a circumferential, heterogeneously enhancing mass at the gallbladder neck. The CBD was of normal caliber. There were periportal and peripancreatic lymph nodes present, largest being 2.8×2.2 cm. There was no evidence of infiltration to liver or duodenum. CT impression was of a carcinoma gallbladder T3N1Mx.

Patient was planned for laparotomy, frozen section of the paraaortic and aortocaval lymph nodes and possible extended cholecystectomy. Patient was put on routine DVT prophylaxis with intraoperative pneumatic calf compression and low molecular weight heparin (LMWH-enoxaparin) which was continued postoperatively till she was fully ambulant. During laparotomy, large paraaortic and paracaval LNs was present, which was positive for metastasis on frozen section, so only a cholecystectomy was done. Patient was referred for palliative chemoradiation.

After 2 months patient presented again with complaints of pain and swelling in both lower limbs. A bilateral lower limb venous Doppler revealed thrombus in superficial femoral (SFV), common femoral (CFV) and popliteal vein (PV) suggestive of bilateral chronic DVT. Patient was started on enoxaparin and tablet warfarin to maintain the INR between 2 and 3.

Despite being on anticoagulation, she presented again after 1 month with venous gangrene of both feet. Venous Doppler showed bilateral CFV, SFV and PV having echogenic thrombus with partial recanalization and patchy venous flow. Bilateral lower limb arterial Doppler showed biphasic arterial waveform, however velocity appeared grossly normal with normal colour flow. In view of progressive venous gangrene of bilateral feet, she was taken for bilateral below knee amputation. Anticoagulation was continued postoperatively.

After 7 days she developed venous gangrene of both hands despite being on anticoagulation. Venous Doppler showed normal cephalic and basilic veins, but echogenic thrombus was present in bilateral radial and ulnar veins. Arterial Doppler of both upper limbs showed normal flow and velocity.

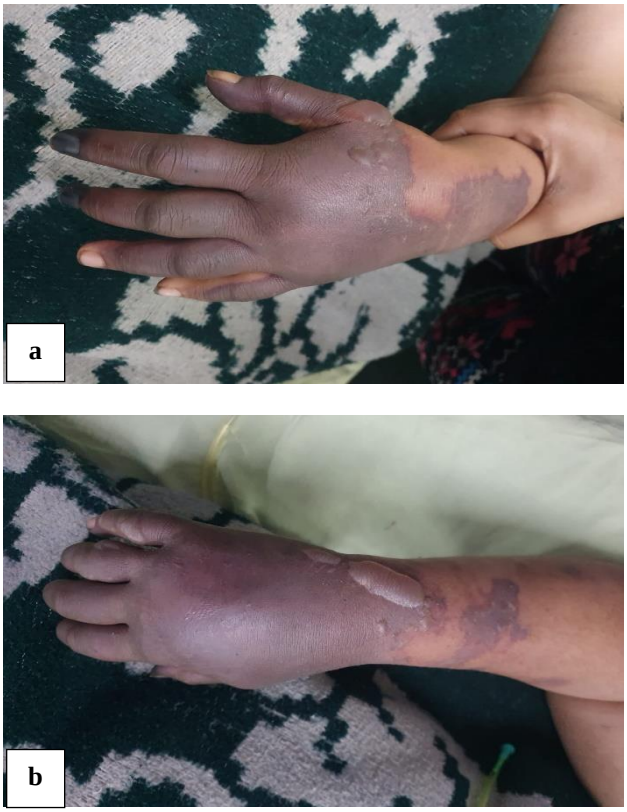

Figure 1 (a and b): Venous gangrene of both hands.

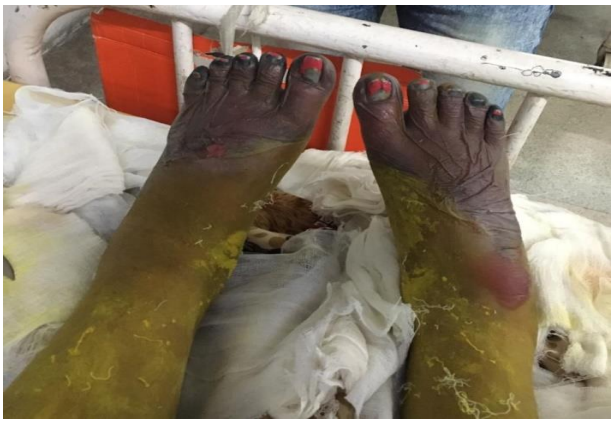

Figure 2: Venous gangrene of both feet.

After 4 days patient developed deviation of angle of mouth to the right side and deviation of tongue to the left side. MR angiography brain showed acute to early subacute infarct in left frontal and insular region with loss of flow related enhancement and intra-arterial thrombosis in insular branches of M2 segment of left MCA.

In view of the inoperable locally advanced carcinoma gallbladder and anticoagulant-resistant, progressive, multi-focal venous thrombosis and gangrene, the patient and relatives refused any further operative intervention and opted to be discharged on anticoagulation.

DISCUSSION

Mechanism of hypercoagulability in cancer

The complex pathogenesis of the prothrombotic state in cancer involves procoagulant molecules produced by tumor cells, suppression of fibrinolytic activity and platelet activation.[3] The most important procoagulant expressed by tumor cells is tissue factor (TF) present on neoplastic cells as well as on tumor-associated endothelial cells.[7] TF contributes to tumor growth, metastasis and angiogenesis by a variety of mechanisms and its expression is associated with increased angiogenesis, tumor invasiveness and worsened prognosis in various malignancies.[8,9] Secretion of TF-containing microvesicles into the circulation may also account for the systemic coagulopathy of cancer.[3]

Tumor cells also express plasminogen activator inhibitor-1, a potent inhibitor of the fibrinolytic system which has prothrombotic properties and also promotes tumor growth and angiogenesis. Elevation of proinflammatory cytokines such as tumor necrosis factor, interleukins-1 and 6, and interferons which activate coagulation are also elevated in malignancy. In addition, platelet P-selectin mediates interactions between circulating carcinoma mucins and platelets leading to platelet aggregation and platelet-rich thrombus formation and may also contribute to the prothrombotic state in cancer.[3,10]

Antineoplastic therapy can further exacerbate the prothrombotic state in cancer. Several studies have documented changes in the markers of thrombin generation within hours of chemotherapy administration.[11] Chemotherapy can induce endothelial cell activation which in turn lead to increased TF expression, elevated levels of plasma von Willebrand factor and factor VIII coagulant protein and decreased levels of natural anticoagulants antithrombin and proteins C and S.[12]

The complex interactions between the coagulation cascade, complement pathway and the immune system, and their synergistic effect on tumor growth are now being investigated. The cooperation among these pathways contributes to the hypercoagulability in malignancy and the high frequency of anticoagulant failure in cancer associated thrombosis.[4-6]

Risk factors

There are known cancer-related, treatment-related and patient-related risk factors for cancer-associated thrombosis.[3]

Cancers of the pancreas, stomach, brain, ovary, kidney, lung and haematological malignancies like lymphomas, and metastatic disease have a 2-fold to 20-fold increased risk of VTE.[13-16] Major surgery, hospitalization and chemotherapy are also common risk factors.[3] The risk is higher in elderly, African race and in patients with comorbidities like obesity, infection, renal disease, pulmonary disease, arterial thromboembolism and prior history of thrombosis.[3] Prechemotherapy leukocyte count >11,000/mm^3, prechemotherapy platelet count ≥350,000/mm^3, hemoglobin <10 g/dl also predispose to thrombosis.[17]

Prevention

Overall, upto 15% of patients with cancer will develop DVT following surgery, despite standard prophylaxis with unfractionated heparin (UFH) or LMWH. Extending pharmacological prophylaxis beyond hospitalisation for 4 weeks has been shown to further reduce the risk of VTE in patients with cancer as the risk of post discharge symptomatic VTE has been shown to peak at 3 weeks after cancer surgery.[18-20]

The American society of clinical oncology (ASCO) and the American college of chest physicians (ACCP) recommend considering extended prophylaxis in patients undergoing cancer surgery, especially in those with high-risk features (previous history of VTE, anaesthesia lasting ≥2 hours, bed rest for ≥4 days, advanced malignancy and older age).[19,21,22]

Treatment

Anticoagulants are the mainstay of treatment of acute VTE.

Initial therapy

LMWH and UFH are equally effective in reducing recurrent thrombosis in patients with cancer, but LMWH is associated with a 3 month survival benefit over UFH and also with a lower risk of heparin-induced thrombocytopenia.[23]

Long term therapy

Vitamin K antagonists (VKA) were the mainstay of long-term anticoagulant treatment for VTE in patients with cancer for many years. However, treatment failures, serious bleeding and difficulties in maintaining the INR within the therapeutic range are common problems in patients with cancer.[2] Patients with cancer also experience recurrent VTE despite having therapeutic INR levels and suffer serious bleeding complications even without receiving excessive anticoagulation.[1] Clinical trials have now established LMWH as the preferred long-term treatment for VTE24 and is recommended by the ACCP consensus guidelines, the national comprehensive

cancer network clinical practice guidelines in oncology and ASCO.[21,24-26]

Recurrent VTE

In a series of cancer patients with recurrent thrombosis, 9% of patients treated with dose escalation of LMWH had a second thrombotic event and 1% had a major bleed over a 3 month follow-up period.[27] Mortality in patients who developed recurrent thrombosis was high, reinforcing the concept that activation of coagulation is associated with unfavourable tumor biology.

Duration of therapy

Although clinical trial evidence is lacking, it is generally recommended that patients with metastases should continue with indefinite anticoagulant therapy after a single thrombotic event because metastatic malignancy is a risk factor for recurrent thrombosis. In patients without metastasis, anticoagulant treatment is recommended for as long as the cancer is active and while the patient is receiving antitumor therapy.[3]

This rare case of anticoagulant-resistant, progressive, multifocal venous thrombosis and gangrene, with resultant devastating clinical consequences in a patient with advanced carcinoma of the gallbladder has been presented to highlight the hypercoagulable state of cancer, the importance of DVT prophylaxis during and after surgery, the importance of continuing long-term anticoagulation in advanced and metastatic cancers and the high rate of anticoagulation failure associated with unfavourable tumor biology.

CONCLUSION

This unusual case highlights the hypercoagulable state of cancer. In view of the life-threatening consequences of DVT and VTE, extended prophylaxis with LMWH for 4 weeks should be considered in high risk patients undergoing cancer surgery (previous history of VTE, anaesthesia lasting ≥2 hours, bed rest for ≥4 days, advanced malignancy and older age). LMWH is the preferred drug for initial treatment for prophylaxis, as well as for long-term treatment for VTE. It is also recommended that patients with metastases should continue with indefinite anticoagulant therapy after a single thrombotic event because metastatic malignancy is a risk factor for recurrent thrombosis. In patients without metastasis, anticoagulant treatment is recommended for as long as the cancer is active and while the patient is receiving antitumor therapy.

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