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Case Report

Disseminated Intravascular Coagulation as the First Manifestation of Metastatic Prostate Adenocarcinoma

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Abstract

Malignancy may be complicated by Disseminated Intravascular Coagulation (DIC), a syndrome that is characterized by intravascular activation of coagulation ensuing in fibrin deposition and depletion of coagulation factors and platelets favouring bleeding diathesis. When a subclinical coagulopathy accompanies malignant states, it can be the coagulopathy itself the unique sign of the underlying systemic disease [1].

Herein, we cite a case of a 75-year-old man who was hospitalized in the cardiac care unit, suffering a myocardial infarction, and developed acute onset distal ischemia, microangiopathic hemolytic anemia and thrombocytopenia. He transferred to the internal medicine department where after thorough investigation, bone marrow biopsy revealed neoplastic cells that stained positive for prostate specific antigen (PSA). Hence, the diagnosis of acute onset DIC as a result of metastatic prostate cancer was posed. Malignancy may be the substrate for the development of DIC and DIC may be the first manifestation of an underlying malignancy [2].

Keywords: Distal ischemia; Thrombocytopenia; Haemolytic anaemia; Disseminated intravascular coagulopathy; Prostate cancer

Introduction

Disseminated Intravascular Coagulation (DIC) is a syndrome that accompanies a variety of pathological conditions. In cases of DIC, an underlying disorder is always the culprit for the systemic activation of coagulation cascade. There are two main ‘’hits’’; widespread fibrin deposition intravascularly and consumption of platelets and clotting factors. The former attenuates microvascular thrombotic obstruction and organ failure results, while the latter leads to thrombocytopenia and coagulation factor deficiencies, conditions that accentuate bleeding diathesis. When laboratory abnormalities indicate coagulopathy that is probably DIC-related, appropriate investigation is guaranteed in order to reveal the underlying clinical condition. There are not a few the causative factors of DIC; infections, malignancy, trauma, burns, liver diseases, obstetric disorders, envenomation, transfusion reactions as well as vascular disorders. In regards to malignant states, solid tumors and hematological malignancies are related to DIC; particularly adenocarcinoma of the pancreas and prostate and acute promyelocytic leukemia respectively. Characteristically, in DIC due to cancer there is abundant release of pro-coagulant material through cancerous cells to the systemic circulation; tissue factor and a cancer pro-coagulant, which is a cysteine protease with factor X activating properties are the principal molecules for the initiation of coagulation cascade. Therefore, establishing a causative factor for DIC development along with laboratory abnormalities supports further the diagnosis. Typical laboratory characteristics of disseminated intravascular coagulopathy are the following; thrombocytopenia, elevated fibrin degradation products (D-dimers), prolonged PT, a PTT and low fibrinogen levels. In this case-scenario, a 75-year-old male patient, who developed acute onset distal ischemia, thrombocytopenia and microangiopathic hemolytic anemia was eventually diagnosed with metastatic prostate cancer to the bone marrow. Interestingly, DIC was the first manifestation of the aforementioned systemic disease.

Case Presentation

A 75-year-old Caucasian male was hospitalized to the Cardiac Care Unit (CCU) for an acute coronary syndrome. During his hospitalization, he developed acute onset distal ischemia, progressively deteriorating thrombocytopenia and microangiopathic haemolytic anaemia. He was finally transferred to the internal medicine department for further investigation and treatment support.

Hence, upon his arrival at the emergency room, he complained of chest pain. Cardiac auscultation revealed tachycardia with no murmurs while crackles were noted during pulmonary auscultation. Electrocardiogram showed ST segment depressions in precordial leads (V3-V6) suggesting anterolateral ischemia. High-sensitive cardiac troponin levels were markedly elevated. His clotting times were undeterminable on two consecutive determinations, while the rest of laboratory results revealed anaemia, thrombocytopenia, and impaired renal and liver function tests. Urinary test analysis unveiled microscopic haematuria. Based on the aforementioned laboratory abnormalities he did not undergo immediate coronary angiography in order thrombolysis to be performed. He was transfused with one unit of fresh frozen plasma, after which his clotting times were: PT 24.4 sec, INR 2.1, APTT 35.2 sec. Coronary artery angiography revealed stenosis both of the left main and the right coronary artery. He also underwent total body Computed Tomography (CT) scan which displayed multifocal leukoencephalopathy, infiltrates at the lower base of the right lung denoting active infection and a 4 cm-diameter aneurysm of the aorta below the renal arteries. During the fifth day of his hospitalization, he developed ischemia on distal phalanges of his left hand and both feet (Figures 1 and 2). His platelet count dropped to 53.000 with no deterioration of his anaemia or his kidney function, but with concurrent appearance of schistocytes on the peripheral blood smear.

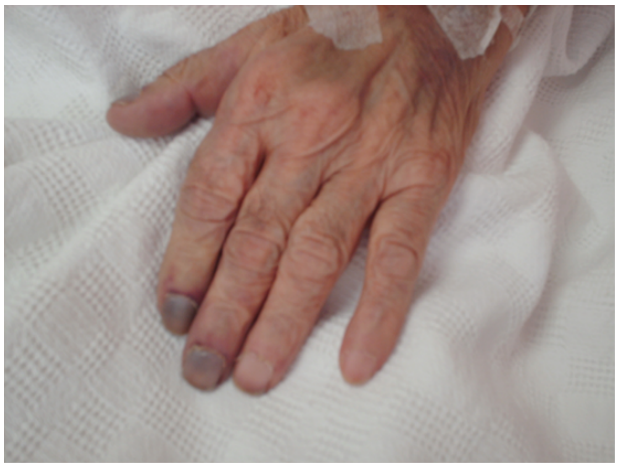

Figure 1: Signs of distal ischemia and venous thrombosis.

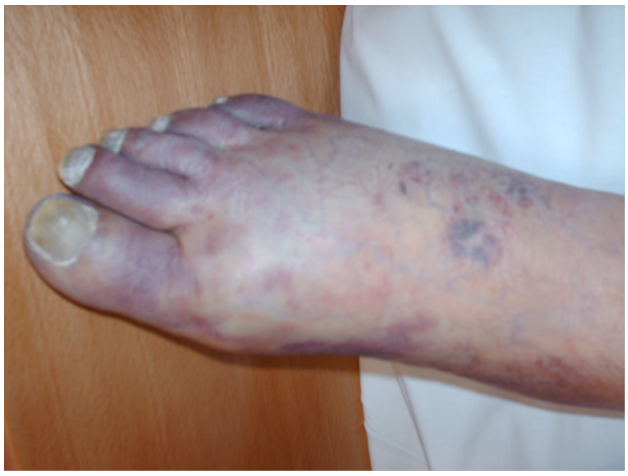

Figure 2: Signs of distal ischemia and venous thrombosis.

On the eight day of hospitalization he was transferred to the internal medicine department. At that time his vital signs were as follows: temperature of 36.6°C, blood pressure 180 mmHg over 100 mmHg, heart rate 110/min, respiratory rate 25/min and oxygen saturation (FiO_2 21%) 80% and 91% after the placement of an oxygen mask (Airmix 40%, 10 litres). Central Venous Pressure (CVP) was 4 cm H_2O.

Marked signs upon physical examination were tachycardia, prolonged expiratory phase, wheezing (both inspiratory and expiratory) and crackles in both lungs. He also had ecchymosis and superficial venous thrombosis signs, but not "wet" haemorrhages. He had thrombotic occlusion of small size vessels at the limbs, while the large size vessels were palpable. He showed intermittent confusion. The rest of the physical examination (abdomen examination, rectal examination, prostate palpation) revealed normal findings.

His laboratory findings were: ESR 69 mm, Hct 28,4%, Hb 9,5 g/dL, WBC 18,430/uL, PLT 106,000/uL, presence of schistocytes and reticulocytes 8%. Clotting times were prolonged: PT 15 sec (INR: 1.3), APTT 28 sec, D-dimer test was positive (D-dimer 4567 ug/L) and fibrinogen 540,3 mg/dl. The LDH level was elevated 1270 IU/mL, the kidney and liver function tests were abnormal: urea 275 mg/dL, creatinine 2.6 mg/dL, uric acid 11.7 mg/dL, SGOT 44 IU/mL, SGPT 101 IU/mL, ALP 273 IU/mL, γ-GT 168 IU/mL. Glucose levels were 214 mg/dL, CPK 2736 IU/mL, CPK-MB 261 IU/mL, Potassium 2.6 mEq/L, Sodium 145 mEq/L, Phosphorus 5.0 mg/dL, Magnesium 2.4 mg/dL, Chlorium 100 mEq/L, Calcium 7.8 mg/dL. Troponin levels were 1.74 ng/mL, CRP 21 mg/dL. His antithrombin III (AT III) levels were normal, ADAMTS13 activity was normal and anticardiolipine antibodies were negative. The patient also had monoclonal IgM gammapathy and kappa light chain excretion in the urine.

The differential diagnosis included Thrombotic Thrombopenic Purpura (TTP), Disseminated Intravascular Coangulation (DIC), for which an underlying disease had to be detected, cholesterol emboli, thrombotic vasculitis and catastrophic antiphospholipoid syndrome.

The patient received empiric antibiotic treatment with piperacillin/tazobactam. The rest of his hospital regimen included methylprednisolone, omeprazole, diltiazem, furosemide, nitrates, allopurinol, nebulised budesonide and salvutamol/ipratropium. He was transfused with fresh frozen plasma and was put on LMWH (enoxaparin 40000x2). Within one week of treatment, his renal function had improved (creatinine 1.9 mg/dL), the platelet count had increased to normal, the fibrinogen count and clotting times had also returned to normal and schistocytes were eliminated. Nevertheless, his distal ischemia worsened and he started having epistaxis and macroscopic haematuria. Prostate Specific Antigen (PSA) rate was found to be 835 ng/mL (normal 0 to 4). The patient underwent bone marrow aspiration and biopsy the fifteenth day of hospitalization. Malignant cell clusters were found in the bone marrow smear that stained positive for prostate specific antigen (Figure 3). Unfortunately, the patient died the next day, before the initiation of any treatment for the underlying disease, which would be the only hope for DIC causal management. The findings were consistent with the diagnosis of acute DIC due to metastatic prostate cancer.

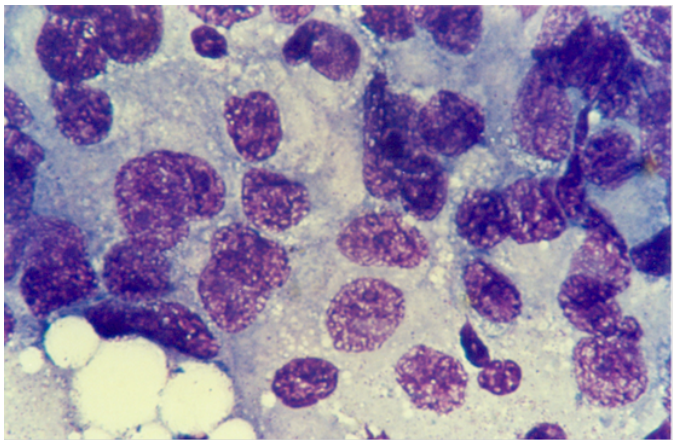

Figure 3: Malignant cells in the bone marrow smear.

Discussion

Disseminated Intravascular Coagulation (DIC) is the result of a widespread activation of coagulation pathways. It has been reported, that up to 25% of DIC cases are caused by metastatic carcinoma of the prostate [3]. On the other hand, DIC is the most prevalent coagulation complication in prostate cancer, as it occurs in 13-30% of the patients, [3] although overt clinical signs are found only in 0.4-1.65% of them [4]. It is more common in metastatic and hormone refractory disease [5]. The pathophysiology of the derangement of the coagulation system in cancer associated DIC is greatly based on procoagulant substances, such as Tissue Factor (TF) and Cancer Procoagulant (CP) [6,7]. Tissue factor is expressed in cells which are not normally exposed to flowing blood, such as subendothelial cells and fibroblasts. Endothelial cells do not express TF except when they are exposed to inflammatory molecules such as TNF-α and VEGF, which are both up regulated and expressed by cancer cells. Specifically, tissue factor is generated either by the tumor cells or the surface of monocytes or macrophages. When TF is released binds to factor VII, activating factors IX and X [8,9]. Thus, overexpression of TF in cancer patients and subsequent persistent generation of thrombin leads to the continued activation of coagulation factors and release of tissue plasminogen activator and fibrinolysis, with simultaneous activation of the anticoagulant pathway (through activated protein C). All these lead to eventual consumption of coagulation factors resulting in bleeding, thrombosis or both [8,9].

Other coagulopathies associated with prostate cancer are thrombocytopenic thrombotic purpura, thrombosis, Trousseau's syndrome and acquired factor VIII inhibitor development [10]. The patient also had monoclonal gammopathy and kappa light chain excretion in the urine. It is known that advanced prostate cancer may be associated with abnormal increase in immunoglobulin levels [11].

In the present case, both clinical (general condition and complications, normal prostate palpation etc.) and laboratory findings were confusing, rendering the differential diagnosis, of a common disease (prostate cancer), difficult and the immediate supportive care obligatory. Time was lost before the diagnosis became obvious and before any attempt for salvage chemotherapy could begin. This is what renders the case didactic for the clinical practice, helping thus in future improve of patients' care.

Conclusion

Coagulation abnormalities indicate a variety of disorders associated with bleeding and or thrombosis. DIC is a syndrome of coagulopathy that does not exist by itself but it accompanies underlying clinical disorders. When DIC is suspected always find the associated pathology that triggered it. It is not rare patients having a still undiagnosed underlying malignancy, presenting to the emergency department with coagulation abnormalities. It is of outmost importance for the clinician to early recognize such conditions because early diagnosis can certainly indicate early treatment of the underlying disease and this may be life-saving.

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