Severe Hemorrhagic Diathesis in a Patient with Prostate Adenocarcinoma and Diagnostic Approach

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ABSTRACT
Disseminated intravascular coagulation, acquired hemophilia, and hyperfibrinolysis induced by prostate adenocarcinoma were first considered in the differential diagnosis of a patient who had been diagnosed with prostate adenocarcinoma and complicated with hemorrhage. Clinical progression and lack of response to other treatments directed us toward the diagnosis of hyperfibrinolysis and tranexamic acid therapy was initiated. Clinical and laboratory findings resulted in a partial improvement, but the response was insufficient. This situation was associated with metastasis and not initiating the treatment for the primary disease. This case was presented to emphasize the importance of treatment arrangement on the basis of differential diagnosis for hemorrhagic diathesis occurring in the clinical course of prostate adenocarcinoma.

Keywords: Hemorrhage, prostate cancer, treatment

INTRODUCTION
Hemorrhagic diathesis is an important complication in solid organ cancers and hematological malignancies, and can develop because of hyperfibrinolysis, acquired hemophilia, or disseminated intravascular coagulation.

Disseminated intravascular coagulation is a disease that manifests itself due to overconsumption of coagulation factors and presents with hemorrhagic diathesis. Acquired hemophilia also causes hemorrhagic diathesis and approximately 50% of the cases present with autoimmune diseases, lymphoproliferative diseases, solid tumors, gestation, or the use of drugs such as penicillin and sulfonamide. Factor replacement and immunosuppressive drugs are used in its treatment.

Fibrinolysis can be primary or secondary. When it is primary, direct activation occurs; when it is secondary, fibrinolysis occurs after coagulation activation. Diagnosis is set by clinical and laboratory findings. D-dimer is considered as the indicator of fibrinolysis. Hypofibrinogenemia is also an expected finding but there is no specific laboratory test for diagnosis. Prostate gland is rich in lytic activators (1). Cancer cells in prostate cancer can secrete urokinase plasminogen activator (U-PA) where cells contact each other. U-PA induces cell proliferation and migration via plasmin-dependent and -independent mechanisms. As a result, when the mechanism that increased fibrinolytic activity plays a role, prostate cancer can present with hemorrhagic diathesis.

Deficiency of plasminogen activator inhibitor-1 (PAI-1), which is an important regulator in fibrinolytic system and which inhibits tissue type and urokinase type plasminogen activators, is associated with hemorrhage, which is also responsible for hyperfibrinolysis in the elderly (2, 3). Congenital PAI-1 deficiency is quite rare. It manifests itself with trauma at a young age and with post-surgical hemorrhage. In such cases, a family history of hemorrhagic patient supports the diagnosis. However, the absence of a family history does not exclude the possibility of congenital hyperfibrinolysis, because the disease can occur with spontaneous mutations.

This case presented with disseminated hemorrhage in muscle, soft tissue, and retroperitoneal region that occurred after the diagnosis of prostate adenocarcinoma, and differed from other cases in resisting the treatment and in multiple possible mechanisms causing hemorrhagic diathesis.

CASE REPORT
In May 2008, upon pathological investigation following the transurethral prostate resection (TURP), a 70-year-old male patient was diagnosed with prostate adenocarcinoma. In the first two months following the diagnosis, the patient was committed because of deep anemia, macroscopic hematuria, and prevalent bruises and swelling in the body, especially in the extremities that were discovered during staging procedures. Thoracolumbar magnetic
resonance (MR) imaging detected lesions that may be significant in favor of metastasis in thoracic and lumbar spines.

There was no known hemorrhagic diathesis in the patient's history. He was diagnosed with atrial fibrillation, chronic obstructive lung disease, and coronary artery disease, and was under no medication that may cause hemorrhagic diathesis, except for acetylsalicylic acid (100 mg/day, for longer than a year). In his physical examination, paleness, rhonchi, via listening the lungs, in the left of abdomen in hypochondrium with approximately 15 centimeter palpation ecchymotic lesion, and ecchymoses in arms and legs were detected.

Prior to prostate surgery, hemoglobin (Hb), platelet, prothrombin time (PT), and active partial thromboplastin time (aPTT) values were normal. In his first laboratory evaluation, normochromic normocytic anemia was present and in his hemogram, Hb value was 6.19 g/dL, leukocyte count was 16,700/mm³, and platelet count was 352,000/mm³. There was no abnormality in his blood biochemistry except for lactate dehydrogenase (LDH) and indirectly dominant mild bilirubin elevation. In his coagulation tests; PT was 12.7 seconds (normal value: 10.4-13), aPTT was 43 seconds (normal value: 24.35-31.25), INR was 1.1 (normal value: 0.85-1.15), hemorrhage time was 3 minutes (normal value: 1-9 minutes), and coagulation time was 15 minutes (normal value: 8-18 minutes). Reticulocyte was 15% and direct and indirect Coombs tests were negative. Peripheral smear was normal except for the existence of rare burr cells.

In abdominal ultrasonography, a 9 x 7 centimeters retroperitoneal hematoma was detected in an area that matches the projection of the ecchymosis in left hypochondrium. Fresh frozen plasma was started with the dose of 10 mL/kg/day and aPTT reached 75 seconds even though the dose was increased to 30 mL/kg. Furthermore, antibiotic therapy was started because of non-specific lung infection.

D-Dimer was always high (5 mg/L), whereas fibrinogen was normal in some measurements but was generally high (3.8 g/L). During the fresh frozen plasma treatment, intermuscular hematomas appeared in left thigh, right arm, right breast, and left forearm soft tissue and there was a macroscopic hematuria attack in this period. Patient’s factor VII level was 47% (normal: 50-150%), factor VIII level was 6% (normal: 50-150%), and factor IX level was 103% (normal: 50-150%). With an early diagnosis of acquired hemophilia, steroid (methylprednisolone) was started with a dose of 1 mg/kg/day. Fresh frozen plasma and steroid treatments continued for 20 days. After the treatment, aPTT was 46 seconds, D-Dimer was 5.6 mg/L (0.00-0.50 mg/L), and fibrinogen was 4.2 g/L (1.8-3.5 g/L).

Because of a lack of clinical and laboratory improvement, after informing the patient and obtaining written consent, factor VIII replacement, with a factor level target of 100%, was performed. Steroid and fresh frozen plasma continued with the same doses. After the factor replacement, aPTT was 50 seconds (increased), PT was 19 seconds (increased), INR was 2.2 (increased), D-Dimer was 6.7 mg/L (increased), and fibrinogen was 4.3 g/L (increased). After steroid and factor VIII replacement, factor V was 54%, factor VII was 16%, factor VIII was 5.6%, factor IX was 76%, and factor X was 56%. Levels of factor VIII and VII are not deemed low enough to account for the clinical picture. Factor VIII inhibitor level was measured as <0.9 Bethesda Unit (BU)/mL (negative).

Because factor treatment was unresponsive and factor VIII levels were only slightly low, it is believed that the diagnosis in this case cannot be explained with hemophilia. Patient’s pronounced heart failure and pulmonary edema was attributed to intense transfusion.

Because the patient’s clinical and laboratory findings did not meet the criteria for disseminated intravascular coagulation, acquired hemophilia treatment did not elicit a response, and D-Dimer increased along with aPTT, it is believed that acquired hemophilia cannot, explain the clinical picture and that, given the underlying malignant neoplasm, hyperfibrinolysis was believed to be added to the picture. After acquiring patient’s written consent, tranexamic acid was started intravenously with a dose of 10 mg/kg. Fresh frozen plasma and steroid treatments were stopped. Tranexamic acid treatment was partially responsive but there was no obvious improvement. Even though soft tissue and intramuscular hematoma generation frequency decreased, a right retroperitoneal hematoma developed. After a month of tranexamic acid treatment, aPTT (48 seconds) did not notably improve; D-Dimer value (30 mg/L) decreased. However, these values were not within the normal range. In the clinical observation, hemoptysis and additional respiratory distress emerged. Patient was lost within hours because of alveolar hemorrhage.

**DISCUSSION**

Patients with solid organ tumors can face many complications, and one of the most important of these is hemorrhagic diathesis. Although severe hemorrhage case may be caused due to many reasons, in cases such as ours, early diagnoses of disseminated intravascular coagulation, acquired hemophilia, and hyperfibrinolysis should be considered.

Disseminated intravascular coagulation can be differentiated from hyperfibrinolysis by the existence of thrombocytopenia and prolonged PT and aPTT. D-dimer does not increase as notably as it does with hyperfibrinolysis and fibrinogen does not decrease notably. Given these findings, disseminated intravascular coagulation was ruled out in our case as the main cause of hemorrhage.

Given the laboratory and clinical findings, the initial, most likely diagnosis was acquired hemophilia. Acquired hemophilia exhibits a more serious hemorrhage pattern compared to inhibitor congenital hemophilia. In the treatment of these patients’ acute hemorrhages, high dose factor VIII concentrate can be considered for those with inhibitor titer <5 BU, active prothrombin complex concentrate (aPCC) or recombinant factor VIIa (rFactor VIIa) can be considered for those with >5 BU, and if no response can be elicited, plasma replacement with plasmapheresis and extracorporeal immunoadsorption can be considered as a treatment. In these cases, it is known that the combination of oral steroid and cyclophosphamide is the most efficient first treatment in the elimination of inhibitors. In non-responsive patients, intravenous immunoglobulin (IVIG), cyclosporine, or multiple chemotherapy can be recommended. Given that in our patient, inhibitor was detected negative, administered factor VIII and steroid treatment did not elicit a response, and D-Dimer increased alongside aPTT, it is believed that the case cannot be explained by acquired hemophilia and that, given the un-
derlying malignant neoplasm, hyperfibrinolysis may also be added to the case (4-6).

Increased fibrinolytic activity and corresponding spontaneous hemorrhages may occur in prostate carcinoma cases (7). This situation is more prominent in patients with multiple metastases. Hyperfibrinolysis more frequently occurs in prostate adenocarcinoma after surgical operations directed at prostate or metastasis. Increased D-dimer, which reflects plasmin activation, can also be present in metastatic cancer. Furthermore elevated U-PA values are correlated with metastasis. We believed that hyperfibrinolysis was included in our patient who was diagnosed with prostate carcinoma. The existence of metastases and revelation of the clinical findings following the surgical operation were consistent with that the literature. The fact that fibrinogen levels were not low in our case can be attributed to performing fresh frozen plasma transfusion.

Another mechanism that may cause hyperfibrinolysis is PAI-1 deficiency. A case with massive subhyaloid hemorrhage that arose alongside PAI-1 deficiency was reported in 2005 (8). Furthermore, there can be changes in fibrinolytic activity in the elderly because of an increase in PAI-1 levels (9). In patients, like our case, where advanced age and hyperfibrinolysis are considered among differential diagnoses, a PAI-1 level study will be appropriate. In our case, confirming diagnosis was difficult because we were unable to measure the PAI-1 level. The treatment of hyperfibrinolysis consists of antifibrinolytic treatment and treatment of the primary disease. Tranexamic acid and epsilon amino caproic acid are currently the preferred antifibrinolytic agents in the treatment of hyperfibrinolysis.

That hemorrhage control did not approach desired levels in our case. This situation may have occurred relative to hyperfibrinolysis due to metastases and yet not to be treated for primary disease.

**CONCLUSION**

This case demonstrates that severe hemorrhage diathesis during the course of prostate carcinoma can be fatal and that the appropriate treatments should be performed via differential diagnoses.

**Informed Consent:** Written informed consent was obtained from patient who participated in this study.

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**Authors’ contributions:** Conceived and designed the experiments or case: OSD, MŞ. Performed the experiments or case: OSD, MŞ, EP, EK. Analyzed the data: VÖ, FÖ, RA, AT. Wrote the paper: OSD, MŞ, VÖ, EK. All authors have read and approved the final manuscript.

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