CASE REPORT

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Primary hyperfibrinolysis as the presenting sign of prostate cancer – A case report

Primarna hiperfibrinoliza kao prezentujući znak karcinoma prostate

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Abstract

Introduction. A bleeding syndrome in the setting of primary hyperfibrinolysis in a prostate cancer patient is only 0.40–1.65% of cases. The laboratory diagnosis of primary hyperfibrinolysis is based on the increase of biomarkers like D-dimer, fibrinogen split products, plasminogen, and euglobulin lysis test. These tests are not specific for primary hyperfibrinolysis. We reported a rare case of hemorrhagic syndrome caused by primary hyperfibrinolysis as the first clinical symptom of metastatic prostate cancer. **Case report.** A 64-year-old male was admitted to our hospital with large hematomas in the right pectoral and axillary areas (20 × 7 cm), right hemiabdomen (30 × 30 cm) and the left lumbal area, (25 × 5 cm). The patient had no subjective symptoms nor used any medication. Initial coagulation testing, prothrombin time (PT), and activated partial thromboplastin time (APTT) were within the normal range, while fibrinogen level was extremely low (1.068 g/L) (normal range 2.0–5.0) and the D-dimer assay result was high 1.122 mg/L (normal range < 0.23). The results obtained by rotation thrombelastometry pointed to primary fibrinolysis. Further clinical and laboratory examination indicated progressive malignant prostate disease. First line treatment for the patient was a combined administration of tranexamic acid (3 × 500 mg *iv*) and transfusion of ten units of cryoprecipitate (400 mL). Next day, fibrinolytic function measurements by rotation thrombelastometry were within the normal ranges. Fibrinogen level was normalized within two days (2.4 g/L). There were no newly developed hematomas. **Conclusion.** This case report shows primary hyperfibrinolysis with bleeding symptoms, which is an uncommon paraneoplastic phenomenon within expanded prostate malignancy. Rotation thrombelastometry in this severe complication helped to achieve the prompt and proper diagnosis and treatment.

Key words:
prostatic neoplasms; blood coagulation disorders; fibrinolysis; hemorrhage; diagnosis; thrombelastography; treatment outcome.

Apstrakt

Uvod. Hemoragijski sindrom uzrokovan primarnom hiperfibrinolizom kod bolesnika sa karcinomom prostate javlja se kod samo 0,40–1,65%. Laboratorijska dijagnoza hiperfibrinolize je bazirana na povećanju biomarkera kao što su: D-dimer, fibrin degradacionih produkata, plazminogena, kao i na testu euglobinske fibrinolize. Prikazali smo bolesnika sa retkom formom hemoragijskog sindroma uzrokovanog primarnom hiperfibrinolizom, koji je bio prva klinička manifestacija metastaskog karcinoma prostate. **Prikaz bolesnika.** Bolesnik, star 64 godine, primljen je u našu ustanovu sa velikim hematomima u desnoj pektoralnoj i aksilarnoj regiji (20 × 7 cm), desnom hemiabdomenu (30 × 30 cm) i levoj lumbalnoj regiji (25 × 5 cm). Bolesnik je negirao subjektivne simptome i uzimanje lekova. Inicijalni skrining testovi koagulacije pokazali su normalne vrednosti protrombinskog vremena (PT) i aktiviranog parcijalnog tromboplastinskog vremena (APTT), dok su vrednosti fibrinogena bile veoma niske (1.068 g/L), a D-dimer visoko pozitivan 1,122 mg/mL. Rezultati dobijeni rotacionom trombelastometrijom ukazali su na postojanje primarne hiperfibrinolize. Dalja klinička i laboratorijska ispitivanja dovela su do saznanja o postojanju progresivne maligne bolesti prostate. Lečenje je započeto kombinovanom primenom traneksamične kiseline (3 × 500 mg *iv*) i transfuzijom 10 jedinica krioprecipitata (400 mL). Sledećeg dana, fibrinolitička funkcija merena rotacionom tromboelastometrijom normalizovala se, dok su se vrednosti fibrinogena regulisale drugog dana (2,4 g/L). Nije došlo do razvoja novih hematoma. **Zaključak.** Ovaj prikaz bolesnika predstavlja primarnu hiperfibrinolizu sa krvarenjem, što je neuobičajeni paraneoplastični fenomen kod progresivne maligne bolesti prostate. Rotaciona tromboelastometrija u ovoj teškoj komplikaciji pomogla je u postizanju pravovremene dijagnostike i primene adekvatne terapije.

Ključne reči:
prostata, neoplazme; krv, poremećaji koagulacije; fibrinoliza; krvarenje; dijagnoza; tromboelastografija; lečenje, ishod.

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Introduction

Hemostatic capacity of a patient depends on the stability in the processes of formation and degradation of a blood clot. Disturbances in the mechanisms of fibrinolysis may lead in some cases to primarily clinical bleeding without the initial thrombotic events that characterize disseminated intravascular coagulation (DIC) syndromes. Malignant disease results in a prothrombotic imbalance of the host hemostatic system. Hematologic disorders are commonly seen in patients with prostate cancer (PCa). The most frequently observed disorder in PCa patients is acute or chronic DIC. The incidence of DIC complication in PCa ranges from 13% to 30%, and can be presented as catastrophic bleeding or various thrombotic events. In contrast, bleeding symptoms in the setting of primary hyperfibrinolysis in this malignancy are seen in only 0.40–1.65% patients, usually provoked by surgical procedures [1]. Laboratory diagnosis of hyperfibrinolysis is based on the increase of biomarkers like D-dimer; fibrin/fibrinogen degradation products (FDP), plasminogen, and euglobulin lysis test (ELT). These tests are not specific for primary hyperfibrinolysis and they are also elevated in other pathological conditions [2]. We presented a rare case of hemorrhagic syndrome caused by primary hyperfibrinolysis, which was the presenting paraneoplastic phenomenon of metastatic PCa.

Case report

A 64-year-old male was admitted to our hospital with a large hematomas in the right pectoral and axillary areas, size 20 × 7 cm, the right hemiabdomen, size 30 × 30 cm and the left lumbal area, size 25 × 5 cm. Hematomas developed two days before hospitalization. The patient denied subjective symptoms and any medication. Performed laboratory analyses showed mild normocytic anemia of chronic disease hemoglobin (Hb) 108 g/L [normal value (NV), 135–175 g/L), mean corpuscular hemoglobin (MCV) 90 fL (NV 80–90 fL), red blood cell (RBC) 3.72 × 10^{12}/L (NV 4.32–5.72 × 10^{12}/L), hematocrit (Hct) 0.331% (NV 38.8–5.0%), platelet (Plt) 419 × 10^{9}/L (NV 150–450 × 10^{9}/L), white blood cell (WBC) 9.5 × 10^{9}/L (NV 3.5–10.5 × 10^{9}/L), neutrophils 60% (NV 50–70%), serum iron 12.9 µmol/L (NV 11–32 µmol/L), ferritin 7,820 µg /L (NV 24–336 µg /L), highly elevated alkaline phosphatase (1,390 U/L, NV 50–130 U/L), lactate dehydrogenase (1,740 U/L, NV 140–280 U/L) and prostate specific antigen (above 150 ng/mL)]. Viral tests were negative (HBs Ag, anti HCV and anti HIV). Initial coagulation testing was performed with: IL ELITE PRO® and ACL 300® analyser. Prothrombin time (PT) and activated partial thromboplastin time (APTT) were within the normal limits (12.4 s and 31.9 s, respectively) as well as anti-thrombin III (86.6%), while fibrinogen level was very low (1.068 g/L, NV 2–5) and the D-dimer assay result was 1.122 mg/L (NV 0.1–0.23) (Table 1).

The thrombin time was prolonged (24.0 s). A reduced level of fibrinogen, and high positive D-dimer with the absence of dramatic disturbances in coagulation screening tests indicated the high level of fibrinolytic activity. The results obtained by rotation thrombelastometry pointed to primary fibrinolysis. The clotting time, clot formation time, maximum clot firmness, alpha angle, and 60-minute lysis index were pathologically changed in INTEM, EXTEM, FIBTEM and APTEM tests (Figure 1).

Table 1

Results of coagulation testing

Coagulation test	Values	Normal ranges
PT (s)	12.4	9.1–12.1
APTT (s)	31.9	24.3–35.0
TT (s)	24.0	11.0–17.8
Fibrinogen (g/L)	1.068	2.0–5.0
D-dimer (mg/L)	1.122	< 0.23

PT – prothrombin time; APTT – activated partial thromboplastin time; TT – thrombin time.

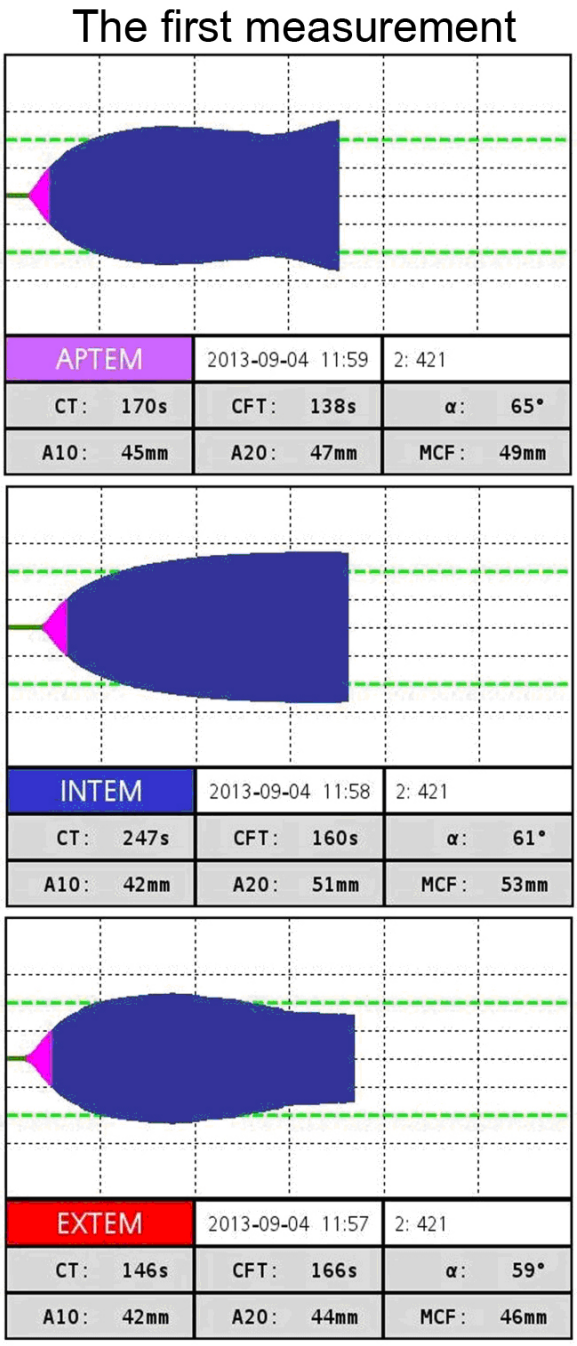

Fig. 1 – Diagnosis of hipefibrinolysis by ROTEM® tests.

First line treatment for the patient was a combined administration of tranexamic acid (3 × 500 mg *iv*) and transfusion of ten units of cryoprecipitate (400 mL). Next day, fibrinolytic function measurements by rotation thrombelastometry were within normal ranges. APTEM test was not registered pathological fibrinolysis (Figure 2).

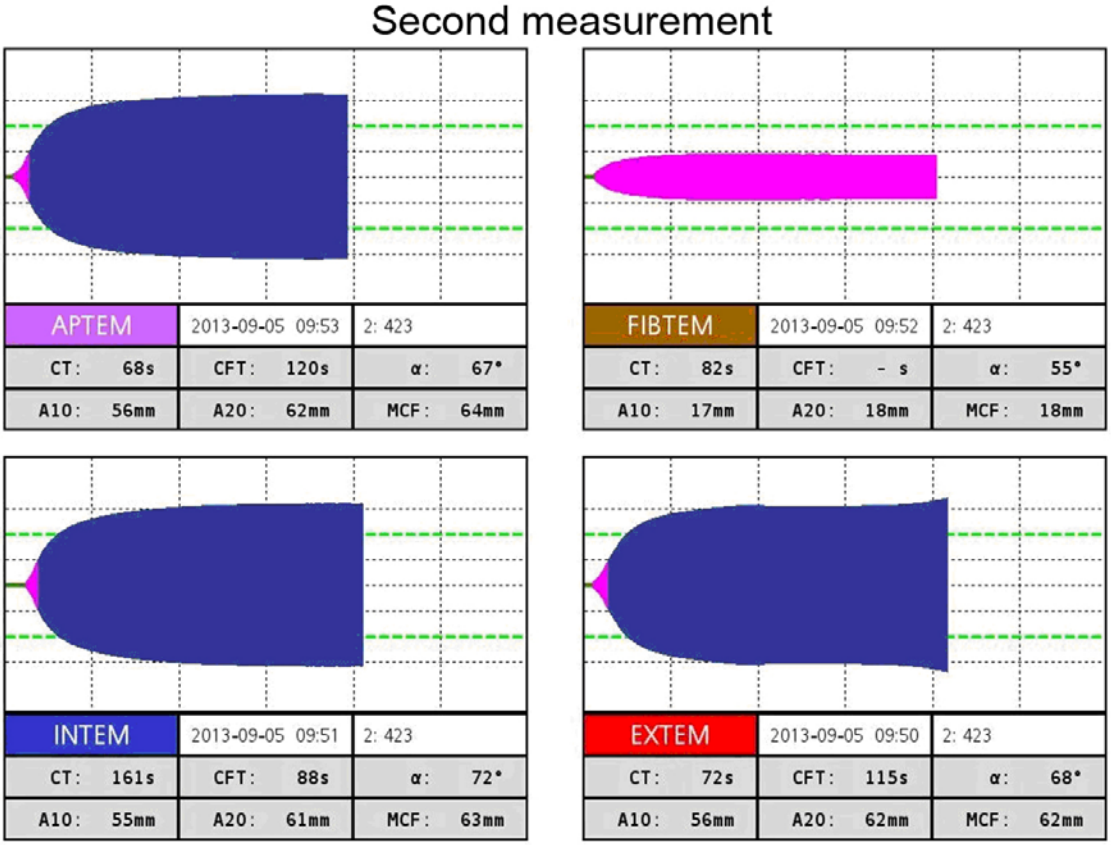

Fig. 2 – ROTEM® test after the treatment.

The fibrinogen level was normalized within two days (2.4 g/L). There were no newly developed hematomas.

The existence of pathological fibrinolysis with a high value of alkaline phosphatase and lactate dehydrogenase directed the diagnostics to detecting malignancy. Laboratory evaluation of patients included determination of prostate specific antigen (PSA), of the values higher than 150 ng/mL (NV 0–4.5 ng/mL). Digital rectal examination established the enlarged prostate with bumps, painless to palpation. The definitive diagnosis of prostate cancer was only possible after the treatment of hyperfibrinolysis which was the cause of hemorrhagic syndrome. Transrectal biopsy of prostate was successfully performed without any hemorrhagic complications, revealing prostate adenocarcinoma G3, Gleason score 9, and bone scans confirmed bone metastases. Afterwards, the patient was referred to the oncologist for further treatment with androgen deprivation therapy and by *per os* administration of tranexamic acid.

Discussion

Paraneoplastic syndromes represent a constellation of conditions that are caused by the presence of malignancy, but not associated with direct tumor invasion or compression. In patients with advanced prostate cancer paraneoplastic syndrome is expressed through a variety of different clinical symptoms [3, 4]. One of them are disorders of hemostasis ranging from bleeding to thrombosis or embolic complications. This case report presented primary hyperfibrinolysis with bleeding symptoms, which is an uncommon paraneoplasic phenomenon within expanded prostate malignancy. The only clinical manifestation of primary hyperfibrinolysis in the presented patient was the presence of large subcutaneous hematoma.

In malignancy hiperfibrinolysis can be activated in two ways. Firstly, tumor cells can produce all the proteins of the fibrinolytic system including the urokinase-type plasminogen activator (uPA) and the tissue-type plasminogen activator (tPA). Secondly, cancer cells also carry on their membranes the specific urokinase plasminogen activator receptor (uPAR), which favors the assembly of all the fibrinolytic components, facilitating the extreme activation of the fibrinolytic cascade [5].

The central event of hyperfibrinolysis is the generation of plasmin within the general circulation [6]. The presence of high activity of the plasmin causes a pathological degradation of fibrin and fibrinogen. It leads to rapid clot breakdown with consequent bleeding. Probably, severe hypofibrinogenemia in the presented patient was caused by fibrinogenolysis due to extreme production of uPA and tPA by prostate cancer cells.

Acquired fibrinolysis occurs as primary process during lung, and gland surgery, in malignant diseases of blood and liver disorders [6]. Other type of acquired hyperfibrinolysis is

DIC. Fibrinolytic process in DIC is always secondary to another underlying pathological state. Clinical presentation of DIC depends on the underlying condition that triggers this medical disorder. In some patients, activation of the fibrinolytic system may dominate over the excessive coagulation, resulting in massive generation of thromboplastic material and consumption of hemostatic elements [7]. In DIC coagulation test the results are obtained with decreasing probability in this order: platelets decreased, FDP increased, PT prolonged, APTT prolonged and fibrinogen decreased. D-dimer test in DIC is highly positive [7, 8]. In patients with prostate cancer DIC is the most frequent coagulation disorder while primary hyperfibrinolysis is unusual. The low fibrinogen with markedly elevated D-dimer and negative test for fibrin soluble monomer complex with no depletion of the coagulation factors can point to primary hyperfibrinolysis. D-dimer is a specific degradation product formed by FXIIa from cross-linked fibrin monomers, followed by plasmin hydrolysis [9], but elevated D-dimer level can be seen in different diseases and it is not specific for primary hyperfibrinolysis. The diagnosis in the presented case was confirmed by rotation thromboelastometry.

Rotation thromboelastometry (ROTEM®) is a viscoelastic point-of-care hemostatic assay designed for full perception of the hemostatic capacity of patients. Also, the method is sensitive for detection and the diagnosis of early fibrinolysis in trauma patients [10]. In contrast to plasmatic coagulation tests, viscoelastic assays like ROTEM® can estimate speed and quality of clot formation, including detection of hyperfibrinolysis, and are performed in whole blood, thus closely reflecting the *in vivo* situation [11]. Comparing the parameters in EXTEM and APTEM test we could detect the moderate form of hiperfibrinolysis.

In the literature we could not find similar examples of hyperfibrinolysis in a prostate cancer patient with the diagnosis made using rotation thrombelastometry. Rotation thrombelastometry is intended for perioperative monitoring of coagulation at active bleeding trauma patients. In cancer patients it was applied in order to detect alterations in the hemostatic capacity, primarily in identification of those patients who are at risk of cancer-induced thromboembolic events [12]. Due to the possibility of rotation thrombelastometry to review all elements of the hemostatic system, particularly the role of platelets and fibrinogen in the formation and stability of a blood clot, its wider application can significantly help in the diagnosis of hemostasis disorders in non-trauma patients.

The diagnosis of primary hyperfibrinolysis is complex and requires the knowledge of the fibrinolytic process nature and clinical circumstances of this pathological condition.

Conclusion

This case report presented primary hiperfibrinolysis with bleeding diathesis as the first clinical sign of previously undiagnosed metastatic PCa. Clinical application of rotation thrombelastometry in a combination with coagulation tests at non-trauma patients, especially oncology patients, can greatly facilitate the diagnosis and therapy of primary hiperfibrinolysis. Rotation thrombelastometry in this severe complication helps to achieve the prompt and proper diagnosis.

The management of hyperfibrinolysis was done within a short period of time thanks to the adequate diagnostic procedure.

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