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Disseminated Intravascular Coagulation with Hyperfibrinolysis as the Initial Manifestation of Prostate Cancer with Disseminated Carcinomatosis of Bone Marrow

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Abstract

Cancer is one of the most common causes of disseminated intravascular coagulation (DIC), and the clinical course of cancer-related DIC is relatively less intense. However, DIC with hyperfibrinolysis is a rare and life-threatening manifestation in metastatic prostate cancer. This 68-year-old male presented with bruises over his entire body. Laboratory findings revealedpancytopenia, coagulopathy, and hypofibrinogenemia, and the peripheral blood smear showed a leucoerythroblastic reaction, suggesting DIC associated bone marrow occupying disease. The bone marrow biopsy revealed a carcinoma, and prostate-specific antigen was elevated to 1,062 ng/mL. Imaging findings suggested prostate cancer withmultiple bonemetastases. Final diagnosis was prostate cancer with disseminated carcinomatosis of the bone marrow, and androgen deprivation therapy plus denosumab was administered.At the same time, blood products, such as donor platelets, fresh frozen plasma, and cryoprecipitate, were transfused several times.However, despite the transfusions of blood products and the initiation of anti-cancer treatment, thrombocytopenia, hypofibrinogenemia, and coagulopathy were not improved, and the patients expireddue tosevere brain hemorrhage at 15 day after starting anti-cancer treatment.

Keywords: disseminated intravascular coagulation; hyperfibrinolysis; prostate cancer; disseminated carcinomatosis of the bone marrow

Introduction

Disseminated intravascular coagulation (DIC)is a systemic process that can potentially cause thrombosis and hemorrhage. It is characterized by the systemic activation of blood coagulation, which leads to a widespreadintravascular deposition of fibrin and depletion of platelets and coagulation factors. Consequently, the thrombotic obstruction of small and midsized vessels and the activation of fibrinolysis may occur, contributing to multiple organ dysfunction and often excessive bleeding. DIC is always secondary to several underlying conditions, including sepsis, malignancy, trauma, obstetric complication, and intravascular hemolysis [1].

Cancer is one of the most common causes of DIC. Thachil et al. suggested that cancer-related DIC may present in three forms; procoagulant, hyperfibrinolytic, andsubclinical types. Most solid tumors have a subclinical type of DIC which only shows laboratory abnormalities, and no obvious clinical symptoms. The hyperfibrinolytic type of DIC occursin acute promyelocytic leukemia and metastatic prostate cancer, and widespread bruising and bleedingare common in these cases [2].This case study reports a patient diagnosed with prostate cancer with disseminated carcinoma of the bone marrow (DCBM) who had DIC with hyperfibrinolysis as an initial manifestation.

Case Report

A 68-year-old male was hospitalized to the department of hemato-oncologyof our hospital,due tobruises over his entire body. One month ago, a small amount of melena occurred after colonicendoscopic mucosal resections due to multiple colonic polys. Since then, ecchymosesstarted to appear on his chest and both legs, accompanied by left flank pain. The patient was prescribed with non-steroidal anti-inflammatory drugs (NSAIDs) for suspected leftrib fractures. However, bruises gradually worsened and appeared over his entire body. He had a history of hypertension and had been taking atorvastatin and aspirin for three years. On physical examination, multiple ecchymoses were observed on his chest, abdomen, back, and both upper and lower extremities, and there was a left upper flank tenderness.

Upon admission, NSAIDs and aspirin were discontinued immediately. The initiallaboratory findings were as follows. Complete blood count showed a hemoglobin level of 9.2 g/dL (normal, 14.0–16.7 g/dL), platelet count of 22,000/μL (normal, 144,000–350,000/μL), white blood cell count of 6,460/μL (normal, 4,700–9,600/μL), reticulocyte of 7.2% (normal, 0.5%–1.8%). In the peripheral blood smear,a leucoerythroblastic reaction with fragmented erythrocytes and immature cells of neutrophilic series was noted. Schistocytes and helmet cells were also observed.Blood coagulation tests revealed a prolonged prothrombin time (PT) of 22.3 s (normal, 11.0–15.0 s), international normalized ratio of 1.94 (normal, 0.80–1.20), and activated partial thromboplastin time (aPTT) of 54.7 s (normal, 27.0–45.0 s).The D-dimer (>20μg/L; normal, 0–0.5μg/L) and fibrin degradation product (119 μg/mL; normal, 0–0.5μg/mL) were increased, while fibrinogen (<60 mg/dL; normal, 200–400mg/dL) was decreased (Table 1).In blood chemistry analysis, lactate dehydrogenase and alkaline phosphatase levelwere elevated to 2,368 IU/L (normal, 200–450IU/L) and 170 IU/L (normal, 25–100 IU/L). Chest x-ray showed amass-like pleural lesion involving right 8th rib (Figure 1A).

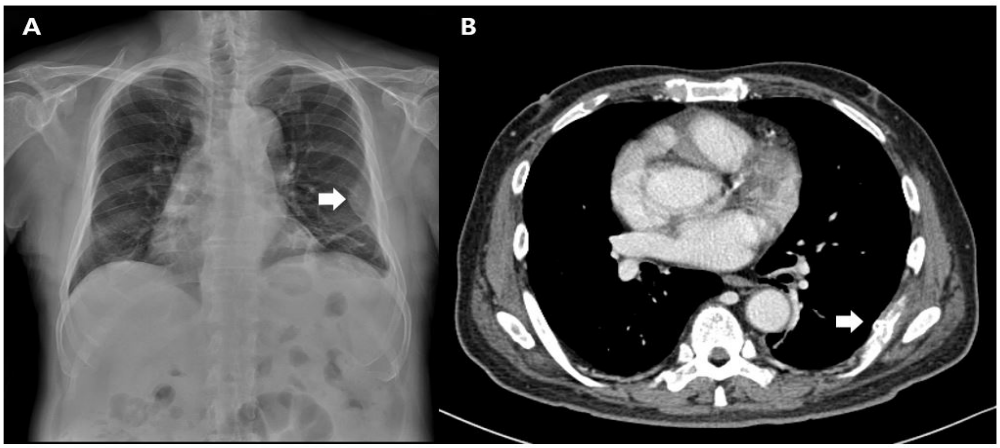

Figure 1: (A) Chest x-ray shows a mass-like lesion on the left pleura (arrow). (B) Chest CT scan shows the destruction of the left 8thrib (arrow).

DIC associated bone marrow occupying disease was suspected. Bone marrow aspiration and biopsywere done. The bone marrow aspiration was not adequate for evaluation due to drytapping. The bone marrow biopsy revealed a carcinoma.Chest and abdominal computed tomography (CT) showed a mass involving left 8thrib and splenomegaly (Figure 1B). Disseminated bone metastases were observed in a bone scan (Figure 2A).The prostate-specific antigen (PSA) level was elevated to 1,062 ng/mL (normal, 0.0–4.0ng/mL). In the magnetic resonance imaging of the prostate, a T2-hypointense lesion was observed in prostate (Figure 3). Whole-body proton emission tomography CT showed hypermetabolic lesions on the prostate and whole bone marrow (Figures 2B). Based on these finding, prostate cancer with bone and bone marrow involvement was diagnosed. Prostate biopsy was not performed due to the risk of bleeding. On the immunohistochemical staining of the bone marrow biopsy specimen,PSA was weekly positive.

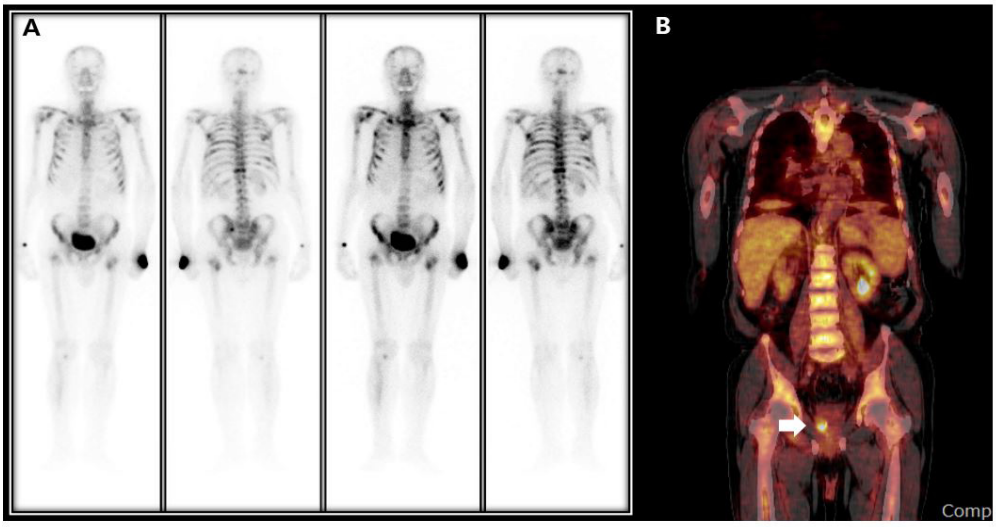

Figure 2: (A) Disseminated bone metastasis is observed. (B) A focal hypermetabolic lesion is noted in the prostate (max SUV 6.2) (arrow), and diffuse hypermetabolism is observed in the whole bone marrow.

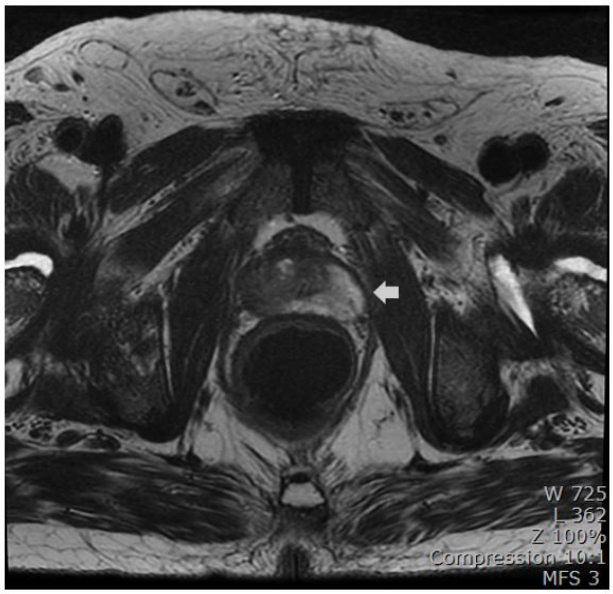

Figure 3: Pelvic MRI image shows a hypointesive lesion in the right peripheral zone and central gland of the prostate in T2 image (arrow).

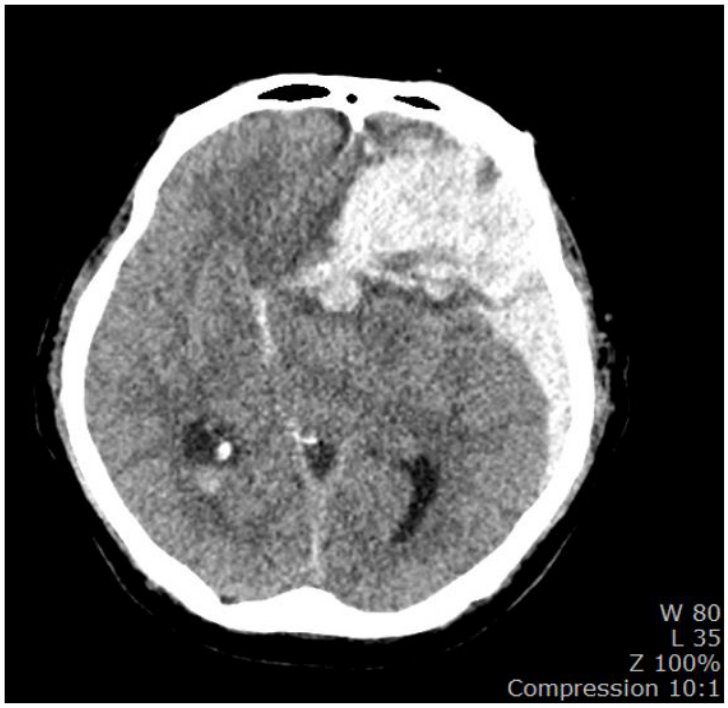

Figure 4: Non-enhanced brain CT scan. A high-signal density in the left frontal lobe and left cerebral convexity is noted.

Because of the bleeding tendency, such as gum bleeding, subcutaneous bleeding at injection sites, and small amount of hemoptysis, persisted after hospitalization, blood products. such as donor platelets, fresh frozen plasma, and cryoprecipitate, were transfused several times. Androgen deprivation therapy (ADT) with 3.6 mg subcutaneous monthly plus 50 mg oral bicalutamideonce daily was started9 daysafter the admission; 120 mgDenosumab was administered subcutaneously at the same time for the management of bone metastases. However, despite the transfusions of blood products and initiation of prostate cancer treatment, thrombocytopenia, hypofibrinogenemia,and prolongations of PTand aPTT were not improved (Table 1).

At day 15after starting the ADT, the patient was found unconscious in the restroom. His blood pressure was 170/80 mmHg. Anemergency brain CT scanwas performed, and it showed intracranial hemorrhage in the left frontal lobe, subdural hemorrhage in the left cerebral convexity, and intraventricular hemorrhage in all ventricles (Figure 4). The patient expired 6 h after the onset of brain hemorrhage.

Table 1: Laboratory findings during admission

	Platelet (/μL)	PT (seconds)/INR	aPTT (seconds)	Fibrinogen (mg/dL)
Day 1 (Admission)	22,000	22.3/1.94	54.7	<60
Day 3	34,000	20.9/1.78	49.8	<60
Day 6	41,000	19.6/1.65	51.5	<60
Day 9 (ADT)	44,000	28.4/2.63	75.0	<60
Day 12	26,000	23.6/2.08	66.6	<60
Day 18	24,000	21.6/1.86	52.6	<60
Day 24 (Dead)	36,000	24.6/2.19	48.7	63

PT, prothrombin time; INR, international normalized ratio; aPTT, activated partial thromboplastin time; ADT, androgen deprivation therapy

Discussion

DICis a well-known hematostatic complication of cancer, but the incidence of overt DIC appears to be lower. In a cohort of 1117 patients with various solid tumors, DIC was found in 6.8% of patients and the risk factors for the development of DIC included older age, male gender, primary tumor necrosis, and advanced stage[3]. In prostate cancer, the incidence of DIC was 13%–25%, and most cases have chronic DIC, and they present with a low-grade bleeding tendency with or without venous thrombosis [4]. However, acute and decompensated DIC, which was manifested with a life-threatening bleeding due to hyperfibrinolysis, often occurs in somepatients with prostate cancer.Hyman et al. reported 42 patients with prostate cancer who were accompanied by DIC with hyperfibrinolysis; In the study, 40 of these patientshad a metastatic disease, and 39 had a castration-resistant disease when they developed DIC. The median survival of these patients was 4 weeks, and the prognosis of prostate cancer accompanied by DIC with excessive fibrinolysis was poor[5].

The pathophysiology of DIC in prostate cancer is not fully understood; however, tissue factor (TF) and urokinase-type plasminogen activator (uPA) produced by tumor cells are thought to have important roles. TF initiates the extrinsic coagulation pathways, and theoverproduction of TF induced by prostate cancer cellsleads to DIC[6]. uPAconverts plasminogen to plasmin, which activates fibrinolysis. Prostate cancer cells produce excessive uPA that increases circulating plasmin, thus resulting in hyperfibrinolysis and bleeding diathesis [7]. Additionally, the case presented herein was diagnosed as DCBM. The Infiltration of cancer cells in the bone marrow causes bone marrow suppression and extramedullary hematopoiesis, leading to pancytopenia. DCBM is accompanied by pancytopenia due to this, and the patients with DCBM have a bleeding diathesis. Cancer-related DIC could occur regardless of the existence of DCBM, and DCBM is not necessarily accompanied by DIC [8]. Althoughthere have been several case reports of DIC in prostate cancer,it is rare to diagnose DIC with DCMB in prostate cancer[9, 10]. Severe thrombocytopenia (< 50,000/μL) persisted in this case, and this was thought to bedue to bone marrow suppression and splenomegaly caused by DCMB and DIC. The combination of DIC with hyperfibrinolysis and severe thrombocytopenia exacerbated the bleeding diathesis, which might result in a fatal bleeding event in this present case.

The main management of DIC is the treatment of underlying causes, and this also applies to cancer-related DIC. In addition, supportive treatment to prevent complications is also needed in some patients with DIC.Thromboembolic complications are common in most cancer-related DIC, and anticoagulant therapy can be considered in patients who had evidence of venous or arterial thromboembolism. In contrast, patients with DIC with hyperfibrinolysis have severe bleeding episodes or are at high risk of bleeding; thus, aggressive replacements of coagulation factors and platelets should be given. The use of anti-fibrinolytic agents, such as tranexamic acid and ε-aminocaproic acid, are generally contraindicated in managing DIC because the blockage of the fibrinolytic system may increase the risk of thrombotic complications[1, 2]. However, these agents may have a role in life-threatening bleeding in patients with DIC with excessive fibrinolysis, as reported in several case reports [11-14].

Cancer-related DIC typically resolves if underlying cancer is effectively treated. In patients with castration-sensitive prostate cancer, ADT with gonadotropin-releasing hormone agonist and/or anti-androgen is a widely used treatment, and several case reports showed that these agents had an effect in the management of prostate cancer-related DIC with hyperfibrinolysis [13-17]. However, the present patientexpired due to severe brain hemorrhage at day 15 after starting the ADT.This was thought to be due to severe thrombocytopenia arising from DCBM and persistent hypofibrinogenemia due to hyperfibrinolysis. In the two case reports of prostate cancer with DCBM by Hiroshige et al, denosumab, a fully humanized monoclonal IgG2 antibody against the receptor activator of nuclear factor-kB ligand, combined with anti-androgen agents had effects[9]. Denosumab was administered in the present patient, but the effect could not be confirmed.

Conclusion

This case report illustrates a case of DIC with hyperfibrinolysis as the initial manifestation of metastatic prostate cancer with DCBM. The severehypofibrinogenemia and thrombocytopenia due to decompensated DIC and bone marrow suppression persisted, and the patient eventually expired due to fatal brain hemorrhage despite anti-cancer treatment and aggressive replacements of blood products. In cases ofDIC with hyperfibrinolysis that occurs in prostate cancer with DCBM, the risk of bleeding may be very high. Therefore, further clinical studies for a more aggressive and effective treatment strategy are needed.

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