

# Recurrent epistaxis as a presenting sign of androgen-sensitive metastatic prostate cancer

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## ABSTRACT

**Prostate cancer is a common cancer, especially among elderly men. It is sometimes not diagnosed until it has metastasised. Disseminated intravascular coagulopathy (DIC) can be the presenting manifestation of prostate cancer, and can present with bleeding (varying from isolated epistaxis to generalised haemorrhage), intravascular thrombosis, or both. A case of recurrent epistaxis from DIC due to metastatic prostate cancer occurring in an 84-year-old Caucasian man is presented, and the pathophysiology and management of DIC in association with androgen-sensitive prostate cancer are discussed.**

**Keywords: androgen-sensitive prostate cancer, disseminated intravascular coagulation, epistaxis, metastatic prostate cancer, prostate cancer**

*Singapore Med J 2009;50(5):e178-e180*

## INTRODUCTION

Prostate cancer is a common cancer, especially among elderly men. It is sometimes not diagnosed until it has metastasised. Disseminated intravascular coagulopathy (DIC) can be the presenting manifestation of prostate cancer, and can present with bleeding (varying from isolated epistaxis to generalised haemorrhage), intravascular thrombosis, or both. Recurrent epistaxis has not been reported as a presenting sign of metastatic prostate cancer. We present a case of an elderly man with recurrent epistaxis from underlying DIC due to androgen-sensitive metastatic prostate cancer.

## CASE REPORT

An 84-year-old Caucasian man was admitted to our hospital with a 15-day history of recurrent epistaxis. The first episode resolved with direct pressure. The next episode required packing and silver nitrate cauterisation. With a third episode, he was seen by the otolaryngology service at a regional hospital, where Bovie monopolar electrocautery was performed on two separate days.

Epistaxis recurred, and he was transferred to our university hospital. Other than epistaxis, he had no complaints. His past medical history was notable for a history of hypopituitarism requiring supplementation with levothyroxine, hydrocortisone and testosterone for 20 years.

The examination was remarkable for packing inside both nostrils. He had no hepatosplenomegaly or bony tenderness. Laboratory data included: haemoglobin 11 g/dL, haematocrit 29.6%, platelet count 109 k/ $\mu$ L and white blood cell count 7.9 k/ $\mu$ L. Serum electrolytes were normal. Serum alkaline phosphatase was elevated at 207 U/L. Other liver enzymes, albumin and bilirubin were normal. Coagulation profile revealed: elevated prothrombin time (PT) 18.2 seconds, international normalised ratio (INR) 1.6, partial thromboplastin time (PTT) 48 seconds, D-dimer 62.7  $\mu$ /ml and low serum fibrinogen 140 mg/dL. Serum prostate-specific antigen (PSA) was elevated at 252 (normal range 0–4) ng/ml.

The patient was diagnosed with DIC causing epistaxis. He received fresh frozen plasma, vitamin K and packed red blood cell infusion, and underwent embolisation of his bilateral internal maxillary and left facial arteries, resulting in the resolution of epistaxis. Further testing was done. A urinalysis, chest radiographs and blood cultures were negative. Computed tomography (CT) of the chest, abdomen and pelvis revealed a markedly enlarged prostate and ill-defined areas of sclerosis and lucency, raising concerns of widespread metastatic bone disease. A bone scintiscan showed widespread osteoblastic bony metastases involving the axial, appendicular, or skeletal space, including the skull and calvarium.

With the diagnosis of DIC and metastatic prostate cancer, the patient was started on bicalutamide, ketoconazole and hydrocortisone. Four days later, he received a dose of long-acting leuprolide. His coagulation parameters gradually improved, and his epistaxis did not recur. At discharge seven days later, his haemoglobin and platelets were normal. The coagulation profile revealed improved D-dimer 39.8  $\mu$ /ml, PT 15.6 seconds, INR 1.2, PTT 47 seconds, and normal fibrinogen. Four

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weeks after discharge, he was asymptomatic with no recurrence of epistaxis and no bleeding manifestations. The serum PSA was 24 ng/ml. Coagulation parameters were normal.

## DISCUSSION

DIC is a syndrome characterised by uncontrolled activation of the clotting and fibrinolytic pathways, resulting in excessive release of thrombin and fibrin.<sup>(1)</sup> The end result is consumption of both coagulation factors and platelets, accompanied by diffuse intravascular deposition of fibrin. Clinical manifestations may vary from bleeding to thrombosis. In cancer patients, DIC more often presents as bleeding rather than thrombosis, suggestive of a dominant activation of fibrinolysis.<sup>(2)</sup> The pathophysiology of the derangement of the coagulation system in cancer-associated DIC is not clear. The exposure of tissue factor (TF) to blood and its subsequent binding with activated factor VII (FVIIa) already present in the circulation, may be the initiating event.<sup>(3)</sup> A platelet-dependent mechanism of action ensures that FVIIa does not cause systemic activation of coagulation, since the activated platelets on which FVIIa acts, remain localised to the sites of injury. However, in cases of sepsis, disseminated malignancy or similar states of generalised inflammation, widespread activation of platelets occurs, leading to the systemic activation of coagulation.

Expression of TF may be induced by tumour necrosis factor- $\alpha$  and vascular endothelial growth factor, both of which are up-regulated in cancer cells.<sup>(4,5)</sup> In addition to being a procoagulant, TF participates in intracellular signals, embryonic blood vessel development and cancer-associated angiogenesis.<sup>(6)</sup> Metastatic cancers, in addition to causing overexpression of TF, can also cause endothelial injury by abnormal angiogenesis in the marrow and direct invasion of the marrow, by the tumor cells.<sup>(7,8)</sup> Contrino et al initially reported *in situ* expression of TF on the surface of invasive breast cancer cells.<sup>(9)</sup> TF has been reported to induce abnormal tumour angiogenesis in transgenic mouse models of hepatocellular carcinoma.<sup>(10)</sup> Levels of TF expression on the human prostate cancer cells significantly correlate with the tumour angiogenesis (as measured by the microvessel density) and the preoperative PSA level.<sup>(11)</sup>

Overexpression of TF in cancer patients and subsequent persistent generation of thrombin lead 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 the eventual consumption of coagulation factors resulting in bleeding, thrombosis, or both. In a study of 1,117 patients with solid tumours, DIC was found in 7% of cases. The median age was 68.5 years. 66% of patients with DIC presented with bleeding. Male gender, older age (> 60 years), advanced stage of malignancy, breast cancer and necrosis on pathological examination of the tumour were independent factors correlated with occurrence of DIC. Thrombocytopenia, hypofibrinogenaemia, elevated fibrin degradation product and D-dimer, in descending order, were the most frequent laboratory abnormalities associated with DIC in this group.<sup>(2)</sup>

DIC, as the presenting sign of hormone-sensitive metastatic prostate cancer, has been described recently.<sup>(12)</sup> In that case, the patient presented with a four-day history of gum bleeding and easy bruising. His coagulation parameters returned to normal within seven days of receiving treatment with antiandrogen (bicalutamide), followed by gonadotrophin-releasing hormone (GnRH) agonist, leuprolide. Prostate biopsy is risky in the presence of prostate cancer-associated DIC, and has been reported to exacerbate the pre-existing coagulopathy.<sup>(13)</sup> Following administration, GnRH agonists bind to GnRH receptors in the pituitary gland, resulting in an initial release of leutinising hormone and follicle-stimulating hormone, and a transient rise in the serum testosterone level. Increase in the serum testosterone level can further stimulate prostate cancer cells and cause a worsening of the symptoms of metastatic prostate cancer, commonly known as flare reaction. A preceding short course of an antiandrogen (bicalutamide) is used to antagonise the initial surge of testosterone, and to prevent this flare reaction on treatment with a GnRH agonist.<sup>(14,15)</sup> Precipitation of DIC has also been reported following treatment of advanced prostate cancer with GnRH agonist, leuprolide, while receiving the androgen receptor blocking agent, flutamide.<sup>(16)</sup> Ketoconazole (with hydrocortisone) can be supplemented to antiandrogen (bicalutamide). Ketoconazole blocks steroidogenesis in the adrenal glands and gonads by inhibiting cytochrome P450-dependent enzymes. The onset of action of ketoconazole is very rapid.<sup>(17)</sup> Serum testosterone level falls to post-orchietomy levels within 24 hours, making ketoconazole valuable in conditions (such as DIC or spinal cord compression syndrome) where rapid onset of action is necessary. Because ketoconazole has no agonist action, flare reaction is not a concern.

In conclusion, unprovoked bleeding in an elderly man can be a manifestation of underlying

prostate cancer. Work-up should include digital rectal examination and serum PSA level. In a patient with bleeding manifestations, it is reasonable to avoid a prostate biopsy if the clinical suspicion is high. A thorough work-up to look for any other underlying cause of DIC, such as infection, should be done while continuing hormonal and other supportive treatment.

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