CASE REPORT

Prostate cancer: beware of disseminated intravascular coagulation

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SUMMARY

Disseminated intravascular coagulation (DIC) is a pathological systemic condition resulting from aberrant activation of the coagulation system. It is characterised by the release and activation of procoagulants into the blood, with an associated consumption coagulopathy. Its association with solid and haematological malignancies is well described in literature. This case describes an elderly man, known to have prostate cancer, who following transurethral resection of the prostate developed DIC with haematuria, spontaneous ecchymoses and mucosal bleeding. Subsequent investigations revealed a prostate-specific antigen (PSA) >1000 μg/L, and staging CT showed multiple sclerotic metastatic lesions affecting the thoracic and lumbar vertebra, as well as infiltration into his left femur. Coagulation normalised with blood products and vitamin K within 1 week, and the patient responded to antiandrogen therapy with a reduction in pain and PSA on discharge.

BACKGROUND

This case highlights disseminated intravascular coagulation (DIC) as a complication of metastatic prostate cancer following transurethral resection of the prostate (TURP). DIC is known to be associated with number of solid malignancies, including prostate cancer. This paper serves to discuss presentation, investigation and management of DIC with respect to prostate cancer.

CASE PRESENTATION

An 80-year-old Caucasian man, presented to hospital with non-specific gradual decline in well-being. On assessment in the emergency department, he was found to be in urinary retention. He was catheterised, and subsequently underwent a TURP in saline operation the following day.

The patient had a known background history of localised prostate cancer, partially treated previously with radical radiotherapy (10 years prior to presentation). Treatment was discontinued due to ongoing anxiety and depression resulting in a temporary admission to a psychiatric institute. Since then the patient had been followed up in clinic, and a slow rising prostate-specific antigen (PSA) noted, which was last tested 9 months prior to this presentation at 67 μg/L but had not been started on luteinizing hormone-releasing hormone (LHRH) agonists. His last CT and bone scan at this time showed no evidence of metastatic disease.

The patient's medical history included chronic obstructive pulmonary disease, diverticular disease, previous transient ischemic attack, anxiety and depression.

On presentation, the patient described a gradual deterioration in function over the last few months, as well as significant lower urinary tract symptoms and examination at the time of TURP revealed local progression of his prostate cancer, with a fixed pelvic mass. Preoperative bloods revealed a normal clotting profile (prothrombin time (PT) 14.6 s, activated partial thromboplastin time (APTT) 26.7 s and platelets 350×10^9/L), and since there was no recent evidence of metastatic disease, he went to have a standard channel TURP with no immediate postoperative complication.

On the second postoperative day, the patient failed a trial without catheter, and on day 3, he was found passing fresh blood and clots requiring bladder washouts and irrigation. At the time, the patient was afebrile—temperature 37°C, had a blood pressure of 140/80, tachycardic with pulse of 110 and maintaining oxygen saturations of 99% on 2 L of oxygen. Diffuse spontaneous ecchymoses were noted, and as clotting function worsened, bleeding from his mouth and nose was observed.

INVESTIGATIONS

Laboratory results postoperatively showed haemoglobin (Hb) 86 g/L (130–180), platelets 50×10^9/L (150–400)—which subsequently dropped to 38×10^9/L, haematocrit 0.260 ratio (0.4–0.5), white cell count 8.5×10^9/L. PT was 36.6 s (12–16), APTT 87.9 s (22–35), fibrinogen <0.10 g/L (1.90–4.30), thrombin time 121.9 s (13–20) and reptilase time >100.0 s (14–19). He had normal renal function—creatinine 75, urea 5.4, estimated glomerular filtration rate (MDRD) 88 units, raised alkaline phosphate 1201 U/L (30–130), raised bilirubin 33 (0–29) and raised C reactive protein 110 (<10 mg/L).

Blood film showed leucoerythroblastic picture with myelocytes and nucleated red cells. Seven-two hours postadmission PSA result was >1000 μg/L and D-dimer 656.4 (0.05–0.5).

DIFFERENTIAL DIAGNOSIS

The grossly deranged coagulation profile including low levels of fibrinogen and leucoerythroblastic blood film were suggestive of a diagnosis of DIC. The high alkaline phosphate result suggested likely bone and marrow infiltration. Subsequent diagnosis of postoperative DIC provoked by TURP in the presence of metastatic prostate cancer was made.

Patient was supported with blood products including fresh frozen plasma (FFP), cryoprecipitate, packed red cells, platelets and vitamin K. Over

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the subsequent 5 days, clotting gradually normalised and haematuria resolved; however, platelets have remained low—PT 15.2 s, APTT 27.7 s, platelets 50×10^9/L and Hb 105 g/L.

A subsequent CT of the chest, abdomen and pelvis showed focal sclerotic lesions in T12, L4 and L5 vertebral bodies as well as the left acetabulum and proximal left femur.

TREATMENT

He was started on antiandrogen therapy (bicalutamide 50 mg once daily). Repeat PSA testing 2 weeks later showed a reduction to 749 μg/L.

OUTCOME AND FOLLOW-UP

Following initial therapy with bicalutamide, he was started on an LHRH agonist. The patient was discharged under the care of the oncology and palliative care teams at his local hospital.

DISCUSSION

Pathophysiology of DIC

DIC occurs due to systemic activation of clotting, resulting from release of procoagulants, formation of microthrombi which can compromise organ blood supply, and an increased propensity to bleed secondary to a consumption coagulopathy. It is known that a number of conditions—inflammatory, infectious and malignant—cause activation of clotting to some degree.[1]

Testing for DIC

There is no isolated diagnostic test for DIC. Instead it is characterised by the clinical picture with the presence of deranged clotting function tests, including prolonged APTT, and PT, low fibrinogen, raised fibrin degradation products or D-dimer, and low platelet count. Importantly, fibrinogen is seen as a useful marker; however, it is also an acute phase reactant, so it is important to note that plasma levels can remain within normal ranges, with serial measurement suggested as more reliable indicator.[1] In light of a lack of specific test, a scoring system was developed by International Society of Thrombosis and Haemostasis in the identification of DIC in 2001.[2] Validated in subsequent studies,[1 3 4] the scoring system results from the analysis of retrospective data of patients in DIC. It is based on an initial assessment of the clinical picture, followed by a zero to eight score using widely available laboratory results which include platelet count, fibrin markers—D-dimer, or fibrin degradation products, PT, and fibrinogen level. A score greater or equal to five is suggestive of DIC.[2] Table 1 below shows the International Society of Thrombosis and Haemostasis scoring system for DIC.

Table 1 International Society of Thrombosis and Haemostasis Scoring System for DIC[2]

	Result	Score
Platelet count	>100×10⁹/L	0
	<100×10⁹/L	1
	<50×10⁹/L	2
Elevated fibrin-related marker (FDP/D-dimer)	No increase	0
	Moderate increase	2
	Strong increase	3
Prothrombin time	<3 s	0
	>3 but <6 s	1
	>6 s	2
Fibrinogen level	>1.0 g/L	0
	<1.0 g/L	1

DIC, disseminated intravascular coagulation.

DIC and solid tumours

Significantly, DIC is always secondary to an underlying condition and as a result treatment is largely aimed at ameliorating the underlying cause. In cases of no apparent cause, it is important to consider an underlying malignancy. An association with solid and haematological malignancies is well known, and has been well described in literature[5–7]—with procoagulants secreted by cancer cells suggested as a potential mechanism of action.[8 9]

DIC and prostate cancer

DIC as a feature of metastatic prostate cancer has been recognised in several published case reports with manifestations that include spontaneous intracranial, retroperitoneal and skin haemorrhage.[5 10–12]

Prostate cancer can be complicated by various coagulopathies, of which the most common is DIC,[13 14] with others including primary fibrinolysis, thrombocytopaenic thrombotic purpura, thrombosis, Trousseau's syndrome and acquired factor VIII inhibitor development.[13]

Typically, as in this case, these can be provoked by surgical intervention[12] or secondary to infiltrative metastatic prostate cancer.[15] Surgery results in the release of procoagulants such as tissue factor, whose expression by malignant glands in prostate cancer is common.[16]

Treatment of the coagulopathy with blood products is dependent on platelet count, extent of derangement and presence of bleeding.[5] Since DIC involves formation of microthrombi, there has been some literature suggesting a role for heparinisation[17]; however, this should only be considered where thrombosis dominates the clinical picture.[18]

Guidelines from the *British Journal of Haematology* (2009)[18] state that only in patients with low platelet counts $<50\times10^9$, who are bleeding or at high risk of bleeding, should platelet transfusion be given. In patients with prolonged PT and APPT, FFP may be useful. Furthermore, in cases where fluid overload may be an increasing problem, factor concentrates may be useful. Fibrinogen concentrate or cryoprecipitate may be used in cases where low fibrin levels (<1 g/L) persists despite FFP replacement. However, importantly cryoprecipitate despite a being good source of fibrinogen, its associated risks of viral transmission has seen its use curtailed.[19]

Significantly as in this case, the extremely low fibrinogen is suggestive of DIC with prominent hyperfibrinolysis—in such cases this can be reflected by measuring plasminogen plasma levels and α2-antiplasmin complex levels. With ongoing high consumption of plasminogen resulting in high α2-antiplasmin complex levels.[20]

In such cases of ongoing severe bleeding with prominent hyperfibrinolysis, fibrinolytic inhibitors—lysine analogues, for example, tranexamic acid—may be considered. However, its use is generally not recommended with risks of widespread fibrin deposition, and resulting impairment of organ perfusion.[18]

Mainstay of treatment of underlying prostate cancer is initially with complete androgen blockade and/or deprivation. Steroidal androgen-receptor blockers such as cyproterone acetate and non-steroidals such as bicalutamide were the most commonly used drugs in the initial treatment of metastatic prostate cancer. This also enabled the addition of a gonadotropin-releasing hormone (GnRH) analogue such as leuprolide or goserelin later. Degarelix is a new rapidly acting

GnRH antagonist that brings down testosterone levels to castrate levels within 72 h without the associated risk of clinical flare and has taken over as the drug of choice for initial management.[21 22]

In cases of life-threatening DIC, ketoconazole has been trialled in high doses to decrease circulating androgen levels.[23] Ketoconazole, an antifungal agent, inhibits both adrenal and testes androgen production. Acting to non-specifically inhibit 17 α-hydroxylase (CYP17A1), a key enzyme involved in the hydroxylation of pregnenolone and progesterone, and their subsequent conversion to dehydroepiandrosterone and androstenedione, together with inhibiting aromatase in testes.[24] Abiraterone acetate is a selective, irreversible inhibitor of CYP17A1[25] (the same enzyme ketoconazole non-specifically inhibits) and has now been licensed for castration-resistant metastatic prostate cancer. It represents the first of novel drugs having passed clinical trials, acting to rapidly inhibit extragonadal androgen production[26] and improve overall survival.[27 28]

In cases of hormone refractory prostate cancer, the prognosis is poorer; however, chemotherapy combinations may be considered, such as docetaxel and paclitaxel.[29–33]

Recently driven by a greater understanding of the importance androgen receptor signalling and its role in prostate cancer, novel therapies targeting extragonadal androgen synthesis have been developed.[34] As prostate cancer evolves, gene mutations result in androgen receptor overexpression and amplification—meaning circulating levels of androgens from the tumour itself or adrenal production can be enough for androgen receptor activation despite castration.[25 34]

In summary, this case reflects on the unusual presentation of an elderly gentleman with known prostate cancer in DIC. Treatment should focus on supportive therapies to treat the coagulopathy and underlying prostate cancer. In the case described, coagulopathy was corrected within 1 week and the patient responded to antiandrogen therapy with a reduction in symptoms and PSA noted prior to discharge.

Learning points

- Disseminated intravascular coagulation (DIC) is the most common coagulopathy associated with prostate cancer.
- Patients with untreated advanced prostate cancer (or those progressing on treatment) undergoing prostate surgery should be monitored for development of DIC if they develop bleeding or a low platelet count.
- Initial treatment must be to control any active bleeding with concurrent initiation of androgen deprivation, for example, with a gonadotropin-releasing hormone (GnRH) antagonist. An alternative to GnRH antagonists is surgical castration with bilateral orchidectomy.
- Development of DIC is a poor prognostic indicator, although in certain cases a period of remission can be achieved with hormone therapy.
- Novel therapies are in development for castration-resistant metastatic prostate cancer.

Competing interests None.

Patient consent Obtained.

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