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REVIEW

Coagulopathy in prostate cancer

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ABSTRACT

Patients with metastatic hormone-refractory prostate carcinoma may have dramatic and life-threatening coagulation complications from their disease. We report here the case of a man with relapsing disseminated intravascular coagulation, and review the different coagulation disorders that may occur during prostatic carcinoma evolution. We focus mainly on disseminated intravascular coagulation (DIC), the most frequent coagulation complication. Other coagulopathies associated with prostate cancer are thrombocytopenic thrombotic purpura, thrombosis, Trousseau's syndrome and acquired factor VIII inhibitor development.

INTRODUCTION

Prostate cancer is the most common cancer in men after skin malignancies. When metastatic, it becomes incurable and only palliative treatment can be offered. The most frequent metastatic sites are bone, then lymph nodes and the viscera. Patients with metastatic prostate cancer may experience complications due to widespread extension. Here we report the case of a man with relapsing disseminated intravascular coagulation, then review the different coagulation disorders possibly occurring in prostatic carcinoma. Their clinical presentations vary from haemorrhage to thrombotic manifestations. We will successively describe disseminated intravascular coagulation, thrombocytopenic thrombotic purpura, thrombosis, Trousseau's syndrome and acquired factor VIII inhibitor occurrence.

CASE REPORT

A 61-year-old man with hormone-refractory prostate cancer and bone metastases was admitted with extensive chest-wall ecchymoses, bleeding at venipuncture sites, gingival haemorrhage and epistaxis. The platelet count was 54,000/ml (normal 130,000 to 400,000) and fibrinogen 0.09 g/l (normal 2 to 5). Clotting times were prolonged: prothrombin rate 20% (normal 60 to 100) and activated partial thromboplastin time 60 sec (normal 28 to 38), consistent with the diagnosis of acute disseminated intravascular coagulation (DIC). D-dimer test was positive (D-dimer >500 ng/ml) and soluble fibrin monomers were detected in blood. Prostate specific antigen (PSA) rate was 269 µg/l (normal 0 to 4). The patient was treated with intravenous high-dose diethylstilbestrol diphosphate (Fosfestrol®), 1 g a day for five days. He was also transfused with packed red blood cells, platelets and fibrinogen. Within two weeks of treatment, the platelet count had increased to 96,000, and the fibrinogen count and clotting times had returned to normal. Subsequent oral oestrogen therapy was administered between intravenous (IV) courses. After three cycles of diethylstilbestrol diphosphate every three weeks, an attempt was made to interrupt the treatment but the patient was readmitted a few days later with biological findings of DIC. The platelet count was down to 19,000/ml, fibrinogen 1.1 g/l, and activated partial thromboplastin time was prolonged to 54 sec. There was no bleeding. Intravenous high-dose diethylstilbestrol diphosphate and heparin therapy were started. A positive response to the treatment was observed, then the patient remained well for several weeks. He was further re-admitted with ecchymoses and gingival haemorrhages. Laboratory analyses at entry showed low platelets

(22,000/ml), prolonged prothrombin time (PT) and partial thromboplastin time (PTT), as well as decreased fibrinogen level. A new cycle of diethylstilbestrol diphosphate was started but the patient died from cerebromeningeal bleeding two days after admission. Clinical history and biological results are summarised in *table 1*.

DISSEMINATED INTRAVASCULAR COAGULATION

Disseminated intravascular coagulation represents the result of a widespread activation of coagulation pathways. Different clinical conditions, including solid tumours and haematological cancers, are associated with DIC. Other causes include infectious diseases (gram-negative sepsis), severe trauma, obstetric disorders, vascular diseases, reaction to toxins and immunological disorders.[1]
DIC is the most frequent coagulation complication in prostate cancer.[2,3] The first reports published in the 1950s were presented as cases of apparent primary fibrinolysis.[4] But medical observations by Rapaport in 1959 and Straub in 1967 recognised them as DIC with secondary fibrinolysis.[5,6]

Incidence

DIC incidence in prostate cancer was historically found to be close to 25%.[7] More recently, Ruffion reported this rate to be 13 to 30%, but clinical signs of DIC are actually found in only 0.4 to 1.65% of patients with prostate cancer.[8]
Prostate adenocarcinoma is the second solid malignancy, after gastric or pancreatic cancer, responsible for inducing DIC. In prostate cancer, the incidence of DIC is dependent on the tumour stage, and it is enhanced in metastatic hormone-refractory disease.[9] Some authors have even proposed using coagulation indices as tumour markers in prostate cancer.[10]

Pathophysiology

The pathogenesis of DIC proceeds from the simultaneous occurrence of systemic fibrin formation resulting from an increased generation of thrombin, impaired physiological anticoagulation mechanisms (low level of antithrombin III (ATIII) impaired function of the protein-C system, insufficient TPFI (tissue factor-pathway inhibitor)) and inadequate fibrinolysis.[11] The combination of increased formation and impaired removal of fibrin results in thrombotic occlusion of small and midsize vessels.[12] At the same time, there is a consumption of platelets and coagulation proteins at the site thrombosis, leading to possible bleeding. The difference between chronic (laboratory findings) and acute (severe clinical manifestations) (*table 2*) DIC depends on the balance of intravascular clotting and on the platelet and clotting factor depletion. In chronic DIC, there is a slow generation of thrombin and a mild decrease in platelets and coagulation factors. In acute DIC, there is a massive generation of thromboplastic material, as well as a consumption of haemostatic elements. Compensatory mechanisms are not sufficient to restore coagulation proteins and platelets. This worsening could be explained by sepsis, radiation or chemotherapy, but it is also related to disease evolution.[13] It may also be spontaneous.
The actual mechanism of this coagulopathy occurring in

Table 1
Clinical and laboratory data of patients with prostate cancer and relapsing DIC

	EPISODE I				EPISODE II		EPISODE III
Physical examination	**Extensive chest-wall ecchymosis Bleeding at venipuncture sites Gingival haemorrhage Epistaxis**				**No clinical signs**		**Epistaxis Gingival haemorrhage Pretibial ecchymoses Cerebromeningeal haemorrhage Death**
Biological signs	17/09/02	19/09/02	20/09/02	25/09/02	18/12/02	23/12/02	06/02/03
Platelets	54,000	18,000	5,000	39,000	19,000	50,000	22,000
Fibrinogen	0.09	0.2	0.5	2.8	1.1	2.3	<0.1
PT (%)	20.7	30	32	78	70	81	21
APT (s)	60	57	52	31	54	32	49
D-dimer assay (ng/ml) n<500			>10,000		8912		5668
Treatment	Diethylstilbestrol diphosphate Blood and platelet transfusions Fibrinogen concentrates				Diethylstilbestrol diphosphate Heparin		Diethylstilbestrol diphosphate Heparin Blood and platelet transfusions

PT = prothrombin time, APT = activated partial thromboplastin time, Diethylstilbestrol diphosphate = Fosfestrol®, 1g/d 5d.

Table 2
Clinical and biological findings in different coagulopathies

	CLINICAL FINDINGS	LABORATORY FINDINGS
DIC	Underlying clinical situation (cancer, sepsis ...) Haemorrhages and/or thrombosis Shock	Thrombopenia ↓ PT ↑ APT Positive D-dimer test ↓ Fibrinogen
Thrombosis	Venous thrombosis Pulmonary embolism	Increased platelet count Positive D-dimer test
Anti-FVIII	Haemorrhages	↑ APT ↓ FVIII Elevated FVIII inhibitor level Normal platelet count PT normal Fibrinogen normal
TTP	Haemorrhages Fever Renal failure Neurological abnormalities	Thrombopenia Normal D-dimer test Microangiopathic haemolytic anaemia ↑ LDH Decreased ADAMTS13 activity

DIC = disseminated intravascular coagulation, PT = prothrombin time, APT = activated partial thromboplastin time, TTP = thrombotic thrombocytopenia purpura, LDH = lactate dehydrogenase.

cancer patients is not clear. A number of studies indicate that different procoagulant substances such as tissue factor (TF) expressed at the surface of tumour cells and a cancer procoagulant (CP) may be involved.[14,15] Elsewhere, some authors have demonstrated that prostate tumour cells are rich in thromboplastin.[16] Several proinflammatory cytokines, such as interleukin-6 and tumour necrosis factor, are supposed to be involved in DIC.[17,18]

Diagnosis

The diagnosis of DIC combines the following three features: any disease known to be associated with DIC, clinical manifestations, and a combination of laboratory tests. In 2002, Levi *et al.* proposed a scoring system using a five-step diagnostic algorithm to facilitate DIC diagnosis. This score can be obtained from routinely available laboratory tests (platelet count, fibrin-related markers such as fibrin(ogen)-degradation products (FDPs) and D-dimer, prothrombin time and fibrinogen level).[19] The platelet count is typically decreased in DIC with often less than 100,000 platelet per cubic millimetre (normal count between 150,000 and 450,000).
Prolongation of clotting times, such as prothrombin time and activated partial thromboplastin time, is found in 70% and 50% of patients, respectively.[20] Fibrinogen concentration is low in only 50% of the patients, and it is usually associated with severe cases of DIC.[12] A normal plasma fibrinogen level can be seen, particularly when the concentration prior to DIC was elevated due to neoplasia or sepsis.[21] Fibrinolytic activation is documented by various tests. FDPs are increased in 85 to 100% of the patients with DIC.[1] They reflect both fibrin and fibrinogen degradation and are only representative of the presence of plasmin. Circulating soluble fibrin monomers can be detected but, like FDP, are not specific for DIC. D-dimer assay by the ELISA method is more reliable for detecting DIC because it reflects fibrin (and not fibrinogen) degradation. In some situations, other laboratory tests are required. Evidence of procoagulant activity is demonstrated by elevated levels of prothrombin fragment 1 + 2 and fibrinopeptide A. Plasma levels of coagulation inhibitors such as ATIII and protein C are found to be decreased.[12] These abnormalities are not specific but characteristic of DIC.[12] They have been used to predict fatal outcome.
Other biological abnormalities, such as the presence of schizocytes, can be seen but are not essential or specific to the diagnosis of DIC.
The differential diagnosis between DIC and primary fibrinolysis is made on the absence of elevated D-dimers and the normal platelet and ATIII levels in primary fibrinolysis. The differential diagnosis with thrombotic thrombocytopenic purpura (TTP) is made on the normality of coagulation times in TTP.

Clinical presentation

Clinical features of DIC may vary from bleeding to thrombosis, or involve both. Schematically, four clinical situations can be discriminated.[21]

1. The patient is asymptomatic and chronic DIC is diagnosed by laboratory tests.
2. The patient presents with a thrombotic episode which is a manifestation of DIC (Trousseau's syndrome).[22] Thrombosis presentation is not the commonest clinical feature of DIC but is often found at patient autopsy.[23]

3. Perioperative bleeding or minor bleeding (confined to the tumour area) occurs and patient presents a biological pattern of DIC.[20,24]
4. Acute, severe DIC with life-threatening haemorrhage can be observed. In this situation, hypovolaemia, hypotension and shock are probably related to cytokine production.[25] Intravascular coagulation can then contribute to organ failure by compromising the blood supply. Renal failure or dysfunction of the pulmonary or central nervous system may also occur in patients with acute DIC.

Published cases often describe bleeding episodes corresponding to clinical situation 3. Moderate haemorrhage is generally consecutive to manipulations of prostate tumour tissue, at either the metastatic or primary site, or may also be spontaneous.[4] Haematuria after prostate biopsy is the most frequent revealing sign of DIC in these cases.[26,27] Perioperative bleeding in the course of decompressive laminectomy has also been reported.[28] Unusually, gastrointestinal bleeding is the first manifestation of DIC.[29] Impaired warfarin dose adjustment as an early manifestation of prostate cancer can be the first sign of chronic DIC.[30]

Therapeutic options

The dogma in DIC management is to first treat the underlying disorder.[31] When laboratory signs of DIC are predominant or when bleeding is moderate (see above, clinical situations 1 and 3), initial treatment is directed specifically to the prostate carcinoma. But because of its occurrence in the course of metastatic hormone-refractory disease, causal DIC treatment is often difficult. The few specific therapeutic options published are hormonal manipulations (oestrogens, ketoconazole, orchiectomy), chemotherapy and radiopharmaceutical treatments. Hormonal treatment is the basis of advanced metastatic prostate cancer treatment. In the hormone-refractory stage, third-line hormone treatment with oestrogens (diethylstilbestrol (DES) and diethylstilbestrol phosphate) has been proposed.[32] Diethylstilbestrol phosphate has been found to be active in DIC related to prostate cancer[29,33] but also to exacerbate signs.[34] Hormone treatment is generally associated with antiaggregation treatment. In 1987, Lowe successfully used ketoconazole as an antiandrogen in one case of DIC due to metastatic prostate cancer.[35] Epsilon aminocaproic acid has also been shown to be active in some situations, though in association with high-dose intravenous DES;[27] the drug is theoretically contraindicated because of the thrombotic risk, and not largely used. Chemotherapy has induced some results, particularly mitoxantrone[36] but also more recently docetaxel and cisplatin.[37] Radiopharmaceutical treatment is controversial: two publications have reported two patient deaths related to strontium-89 therapy.[38,39] However, in 2000, Ruffion *et al.* described the case of a 61-year-old man with symptomatic DIC due to metastatic prostate carcinoma that could be controlled by treatment with samarium 153.[8]

Anticoagulant and particularly heparin treatment is still debated in the management of DIC. Few, small, nonrandomised studies have shown a benefit and no increase in bleeding with heparin in patients with DIC.[40,41] No studies have been specifically conducted in patients with cancer, except in Trousseau's syndrome.[42] Continuous infusions of low-dose heparin are recommended (300-500 U/h).[12] A treatment strategy involving antithrombin III (ATIII) replacement or protein C concentrates has also been used, but only in small nonrandomised studies.[43-46] Most of theses studies were performed in patients with sepsis or septic shock and in obstetrical circumstances.[47] Some authors have used direct thrombin inhibitors (i.e. independent from ATIII) such as recombinant hirudin (r-hirudin) in haematological malignancies.[48] But the clinical benefit of these treatments has not been clearly established.

Replacement treatment with blood components is determined by the importance of bleeding, the platelet count or coagulation factor levels. There is no evidence of prophylactic administration of platelets or plasma in patients with DIC.[10] Some authors advocate replacing platelets when their count is below 50 x 10^9/l if the patient is bleeding or if an invasive procedure is needed.[20] In case of important and life-threatening bleeding, fresh frozen plasma can be used. Because fresh frozen plasma contains more fibrinogen than cryoprecipitates, and cryoprecipitates are possibly contaminated with traces of procoagulation factors which could worsen the phenomenon, FFP should be given primarily.[12]

THROMBOCYTOPENIC THROMBOTIC PURPURA

Thrombocytopenic thrombotic purpura (TTP) is an acquired or congenital thrombotic microangiopathy, classically characterised by a pentad of signs: thrombocytopenia, microangiopathic haemolytic anaemia, neurological abnormalities, renal failure and fever.[48] These abnormalities are the consequence of widespread microvascular thrombi, consisting in platelet aggregates with large amounts of von Willebrand factor and little or no fibrin (contrary to DIC).[49] Its causal factor is a severe deficiency of von Willebrand factor-cleaving protease (1-4) known as ADAMTS13.[50] Because of this deficiency, a large number of multimers of von Willebrand factor accumulate in the flowing blood, inducing platelet aggregation. TTP is sparsely described in prostate carcinoma.[51] Other associated

diseases are metastatic malignancies, chronic inflammation, liver cirrhosis and systemic lupus erythematosus.[52] Thrombocytopenic thrombotic purpura may also be induced by chemotherapy, particularly mitomycin C and cytotoxic associations such as bleomycin-cisplatin.[49] Laboratory evaluations most commonly demonstrate haemolytic anaemia with the presence of schistocytes (fragmented erythrocytes), thrombocytopenia, elevated serum levels of lactate dehydrogenase and normal coagulation parameters. In acute episodes of thrombotic thrombocytopenic purpura, ADAMTS13 activity is found low in citrated plasma, and antibodies to ADAMTS13 may be detected.[50]

TTP is discriminated from DIC by pathogenesis and biological findings. It differs from haemolytic uraemic syndrome (HUS) by the presence of neurological or renal abnormalities (neurological traditionally predominant in TTP, renal in HUS), by ADAMTS13 level (normal in HUS).[53] TTP is also differentiated from tumour micro-angiopathic haemolytic anaemia.

The essential treatment for acquired TTP with ADAMTS13 deficiency consists of plasma exchange (plasmapheresis + infusion of fresh-frozen plasma or cryosupernatant). Additional treatment involving immune suppression by glucocorticoids, vincristine or splenectomy is considered in patients with high titres of inhibitor not responding to plasma exchange. Platelet transfusions may exacerbate intravascular thrombosis and must be restricted to life-threatening haemorrhage.[49]

THROMBOSIS

Activation of coagulation and predisposition to thrombosis is classically associated with most cancers, particularly prostatic carcinoma. In 1967, a large study of patients with advanced prostatic carcinoma showed that the incidence of thromboembolic disease was 2 to 3% in early-stage disease and 8 to 9% in more advanced forms.[54] This hypercoagulability status results from several factors.[55] Firstly, there are specific tumour properties including direct or indirect induction of thrombin generation either by cytokines or by tumour cell procoagulants (tissue factor (TF) and cancer procoagulant (CP)). Secondly, there are nonspecific factors, such as inflammatory state, tissue damage from tumour burden or necrosis leading to the activation of systemic coagulation. This clotting predisposition may have clinical expression or may remain latent with blood coagulation abnormalities.

Several biological parameters are known to be a sign of hypercoagulability but none are specific. The most commonly seen are markers of platelet activation and thrombocytosis, markers of coagulation cascade activation (elevated levels of fibrinogen, modifications of prothrombin time and partial thromboplastin time), and suppression of fibrinolytic activity. All these phenomena lead to the activation of coagulation (elevation of fibrinopeptide A (FPA), presence of D-dimer (DD) and fibrinogen degradation products (FDP)).[56] Some studies involving only few patients have shown that decreased ATIII levels may be associated with thromboembolic complications in patients with prostate cancer.[57,58] Tumour procoagulant activity is principally reflected by two factors, namely cancer procoagulant (CP) and tissue factor (TF). Their role in the activation of coagulation is well known, but their plasma level is not well correlated with clinical thromboembolic disease.[56] Another aspect of hypercoagulability is the inflammatory response. It has been studied in cancer patients, and studies have demonstrated the thrombotic role of two proinflammatory cytokines: tumour necrosis factor (TNF) and interleukin-I (Il 1). However, the role of these laboratory abnormalities is unclear. If many cancer patients have markers of coagulation activation, few will ultimately develop thrombosis. In 2002, Kohli showed an increase in coagulation markers (D-dimers, prothrombin fragment 1+2 (F1+2)) in 30 patients with advanced prostate cancer, as compared with age-matched control patients.[59] Unfortunately, the clinical significance of these findings was not studied in these patients. In addition to these biological factors, extrinsic factors such as surgery, radiotherapy and chemotherapy can increase hypercoagulability characteristics. Besides, cytotoxic treatments and, particularly in prostatic carcinoma, hormone treatments can also induce hypercoagulability and be a source of thrombosis. Antiandrogenic compounds and oestrogens are known to enhance the thromboembolic risk. Oestrogens have been shown to decrease ATIII levels in DES-treated prostate carcinoma patients.[58] Within more advanced-stage prostate cancer patients, the risk of thromboembolic disease is, however, heightened by the decreased mobility due to bone metastases and other comorbidities. In conclusion, cancer is associated with a complex multifactorial hypercoagulation status. No biological marker is actually sufficient for predicting thromboembolic accidents and identifying patients who may benefit from low-molecular-weight heparin prophylaxis.

Curative initial treatment of thrombotic events is based on heparin.[60] Low-molecular-weight heparins, which have been shown to be as effective and safe as unfractionated heparin, are ideal for outpatient management.[60-62] Oral anticoagulant treatment is then ideal for long-term management. Theoretically, the treatment of venous thromboembolic events lasts six months but it should be continued indefinitely in patients with residual disease.[63] The clinical management of long-term oral anticoagulant treatment in cancer patients is difficult because patients often require surgical procedures, have a therapy-related decrease in platelets and frequent therapy-related inter-

actions with the metabolism of vitamin K antagonists. Haemorrhagic complications are estimated at 2 to 3% annual risk.[64]

Trousseau's syndrome is an association of migratory superficial phlebitis and underlying malignancy. It is now known to be a manifestation of chronic DIC.[21] First described by Trousseau (1801-1867) in 1865, it is the condition most frequently associated with pancreatic and gastric carcinoma. It has also been reported in metastatic prostate carcinoma.[65,66] The therapeutic attitude in Trousseau's syndrome is similar to that of 'classic' DIC requiring the treatment of the underlying disorder. The use of intravenous heparin is always recommended when the tumour cannot be controlled. Oral treatment with anticoagulants such as warfarin is not adequate.[67]

ACQUIRED FACTOR VIII INHIBITOR

Apart from DIC, bleeding manifestations in prostate carcinoma could result from the presence of acquired factor VIII inhibitor.[68-70] This acquired inhibitory activity against clotting factor VIII is rare in prostate cancer and not clearly explained.[69] In 2001, Sallah *et al.* reviewed all publications addressing acquired factor VIII inhibitor between 1974 and 2000 (41 patients) and found five cases (12%) associated with prostate cancer.[71] The onset of this coagulopathy is often associated with a progressive disease.[69,70] The diagnosis is generally made in the presence of unexplained bleeding. Laboratory tests show prolonged partial thromboplastin and kaolin coagulation times. Prothrombin time, platelet count and fibrinogen level are normal, therefore excluding a DIC. Diagnosis is confirmed by a decrease in factor VIII clotting activity and by the presence of FVIII inhibitors. Antibody titre is not directly related to bleeding complications and some patients are known to have had fatal bleeding with low-titre inhibitors.[71]

Therapeutic options include factor replacement, immunosuppressive drugs and/or plasmapheresis. Treatment of the underlying malignancy is also required. Good therapeutic responses could be achieved with immunosuppressive drugs such as steroids, cyclophosphamide, cyclosporine or azathioprine. Best responses are obtained in patients with low-titre antibody.[71] Human or porcine FVIII are indicated to treat haemorrhage and control acute episodes. When bleeding is persistent, additional use of prothrombin-complex concentrates that bypass the inhibitor (FVIII Inhibitor Bypassing Activity, FEIBA) or recombinant factor VIIa (Novoseven) is indicated. More recently, some authors have used rituximab in association with cytotoxic therapy in the management of patients with active bleeding and/or high-titre FVIII inhibitors.

CONCLUSION

Coagulation disorders are frequently associated with disseminated prostate cancer and should be known to urologists and oncologists because they may compromise short-term prognosis and influence therapeutic strategies. Disseminated intravascular coagulation is the most frequently reported disorder but, in spite of its long-time recognition, its treatment remains controversial.

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2 bijsluiters A