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Coagulopathy in the prostate cancer patient: prevalence and clinical relevance

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Carcinoma of the prostate has historically been associated with the bleeding diathesis which accompanies disseminated intravascular coagulation. We have performed a prospective study into the prevalence of coagulopathy in patients with untreated prostate cancer using matched patients with benign prostatic hypertrophy (BPH) as controls. Haemostatic activation was assessed by measuring fibrinopeptide A (FpA) by an ELISA and D-dimer by a latex agglutination assay. FpA and D-dimer levels were correlated with serum prostate specific antigen (PSA) and bone scan status. Of the cancer patients, 40% had elevated FpA, levels being higher in those with bone scan positive disease ($P < 0.05$). D-dimer was detectable in 24% of those with prostate cancer but in none with BPH. Neither FpA nor D-dimer were related to serum PSA but D-dimer appeared to be a predictor of bone scan status with a positive predictive value of 91%. It is concluded that changes compatible with subclinical DIC are common in patients presenting with prostate cancer and that measurement of FpA and D-dimer may have roles as tumour markers in this disease.

Since the original report of haemorrhagic diathesis in a patient with adenocarcinoma of the prostate *(1)*, this tumour, like others, has been associated with abnormalities of the haemostatic system. Clinically, the urologist is most aware of the catastrophic bleeding that may complicate disseminated intravascular coagulation (DIC), but thrombotic episodes may also be seen. Venous thrombosis, migratory thrombophlebitis, arterial emboli and non-bacterial endocarditis have all been reported in association with prostate cancer *(2)*. Thus, a whole spectrum of thromboembolic disease may be clinically manifest and this supports the current thesis that many patients with cancer are in a compensated state of chronic DIC *(3)*.

The exact mechanism of activation of coagulation in the cancer patient remains unclear. However, two different procoagulants have been identified and implicated as possible initiators of the coagulation cascade in malignant disease. Cancer procoagulant is a cysteine proteinase which appears to be produced only by tumour cells and is capable of activating blood coagulation factor X in the absence of factor VII *(4)*. Tissue factor (TF), on the other hand, requires factor VII to activate factor X and is the normal route of clotting activation, for example, when vascular integrity is compromised *(5)*. Since it is expressed by both host and tumour cells, the demonstration of TF is not specific for cancer, although malignant cells may produce increased amounts of this procoagulant *(6)*. Malignant change in the prostate has also been associated with increased expression of urokinase-type plasminogen activator (uPA) by the primary tumour *(7)* and plasma uPA levels are higher in those with metastatic prostate cancer *(8)*. There is, therefore, the potential for primary activation of the fibrinolytic pathway in prostate cancer patients.

There is also no doubt that DIC in cancer may also be an epiphenomenon, especially in patients with prostate cancer. Sepsis, uraemia and abnormal thrombopoeisis are all features of this disease and may result in abnormalities or activation of the coagulation mechanism *(9,10)*. In addition, the administration of exogenous oestrogens may also profoundly affect the naturally occurring anticoagulation mechanism by reducing plasma antithrombin III levels, increasing blood viscosity and potentiating the effect of endotoxin as a trigger of DIC *(11–13)*.

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Although there have been several reports on the incidence of coagulopathy in prostate cancer, most studies have evaluated heterogeneous groups of patients, often including those undergoing active treatment. In addition, two studies have failed to demonstrate differences in the coagulation profile of patients with benign and malignant prostatic disease *(14,15)*. The purpose of the present investigation was to establish the incidence of coagulopathy in a prospective study of patients presenting *de novo* with prostate cancer, relating changes to bone scan status and serum prostatic specific antigen (PSA). The clinical significance of these findings is also discussed.

Patients and methods

Patients

Local Ethical Committee approval was obtained together with informed consent from all patients. The study groups comprised patients presenting with untreated prostate cancer and age matched controls with histologically proven, benign prostatic hypertrophy (BPH). No patient had clinical evidence of thromboembolic disease and none developed haemorrhagic or thrombotic complications after operation.

Assessment of coagulopathy

Activation of haemostasis was assessed by the measurement of two markers, D-dimer and Fibrinopeptide A (FpA). D-dimer is produced as a result of cleavage of crosslinked fibrin by the fibrinolytic enzyme plasmin. Abnormal levels of D-dimer therefore reflect reactive fibrinolysis. FpA is formed by thrombin-mediated cleavage of the Aα-chain of fibrinogen. As a result of its very short half-life (a few min) it is a very sensitive marker of coagulation activation and ongoing fibrin formation.

D-dimer was measured in 55 patients with cancer and 37 patients with BPH using a widely available and technically simple semi-quantitative latex agglutination assay (Fibrinosticon®, Organon Teknika, Boxtel, The Netherlands). This assay is essentially equivalent in performance to the more time-consuming and expensive ELISA or immunoblot *(16)*. Within this group, 10 patients with cancer were managed without bone scan status being determined. Fibrinopeptide A was measured using an ELISA (Diagnostica Sago, Asnières, France) in 32 patients with BPH and 53 with cancer, of whom 43 had bone scans performed. PSA was measured using the Tandem-R radioImmune assay (Hybritech, Nottingham, UK).

Collection of samples

Venous blood was obtained from an anterior cubital vein using a 21G butterfly needle, taking care to achieve a clean puncture. If the venepuncture was difficult or the blood slow to flow, the sample was discarded and a fresh site on the contralateral arm sought with a new needle. The first 5 ml of blood was discarded and the sample promptly aliquoted into the appropriate tube for measurement of FpA, D-dimer and PSA.

Statistical methods

Data analysis was performed using the Statgraphics® statistical software system. FpA and PSA data were not normally distributed and summary statistics are therefore presented as medians and interquartile ranges (IQR). Differences between groups were assessed using the Mann–Whitney U test. Correlations between such data were determined with Spearman's rank correlation test. The results of the D-dimer assays were categorical in nature and were therefore analysed with the χ^2 test for observed and expected observations.

Results

The normal range for plasma levels of FpA in healthy individuals is 3 ng/ml (Manufacturer's data, 95% confidence level). The results from this study are illustrated in Table I. FpA levels were generally low in patients with BPH (median 0.45 ng/ml, IQR 0.1–1.7). Nevertheless, five patients (16%) had elevated levels by the manufacturer's criteria compared with 21/53 (40%) of patients with prostatic cancer ($P<0.02$, χ^2 test). Levels in those patients with cancer were significantly higher (1.9, 0.6–6.0) than those with BPH ($P<0.005$). When classified according to bone scan status, 6/25 (24%) of patients with bone scan negative cancer had elevated FpA (1.3, 0.4–2.9) compared with 5/32 (16%) patients with BPH ($P=$ NS, χ^2 test). Although the median value of patients with bone scan negative cancer was higher than the BPH group, overall levels were not significantly different ($P=0.1$). Levels of FpA were considerably higher in patients with bone scan positive disease ($n=18$; median 4.2, IQR 1.2–18.7) compared with patients with BPH ($P<0.0001$) and bone scan negative cancer ($P<0.05$). Because of the significant increase in plasma FpA in patients with bone scan positive prostate cancer, a correlation between FpA and serum PSA was sought in

Table I. Fibrinopeptide A levels (ng/ml) in patients with benign prostatic hypertrophy (BPH), patients with untreated prostate cancer and patients with prostate cancer classified according to bone scan status. Results are presented as median and interquartile range (IQR)

	Fibrinopeptide A (ng/ml)		
	n	*Median*	*IQR*
BPH	32	0.45	0.1–1.7
Untreated	53	1.90	0.6–6.0
Bone scan negative	25	1.30	2.9–2.5
Bone scan positive	18	4.20	1.2–18.7

Table II. D-dimer levels in patients with BPH and untreated prostate cancer. Results are given as the percentage of patients (number) at each D-dimer level

	D-dimer level (ng/ml)					
	0	*500*	*1000*	*2000*	*4000*	*8000*
BPH	100%	0%	0%	0%	0%	0%
($n=37$)	(37)	(0)	(0)	(0)	(0)	(0)
Cancer*	76%	16%	4%	0%	2%	2%
($n=55$)	(42)	(9)	(2)	(0)	(1)	(1)
Bone scan negative	96%	4%	0%	0%	0%	0%
($n=27$)	(26)	(1)	(0)	(0)	(0)	(0)
Bone scan positive	44%	33%	11%	0%	6%	6%
($n=18$)	(8)	(6)	(2)	(0)	(1)	(1)

* Untreated prostate cancer

cancer patients. However, none was demonstrable ($r=0.21$, $P=0.15$).

The normal level of D-dimer is < 500 ng/ml (manufacturer's data). None of the patients with BPH had detectable D-dimer in their plasma (Table II). This contrasted with those patients with prostate cancer where 13 (24%) had detectable levels ($P<0.005$, χ^2 test). Review of Table II reveals that most of this elevation is due to those individuals with bone scan positive prostate cancer. There was no significant difference in levels between those with BPH and bone scan negative cancer, but levels in bone scan positive patients were higher than those with BPH ($P<0.001$, χ^2 test) and negative bone scans ($P<0.001$, χ^2 test). D-dimer was detectable in 10/18 patients with bone scan positive cancer compared with only 1/27 with negative isotope scans. This gives this assay a sensitivity of 56%, a specificity of 96% and a positive predictive value of 91% for the detection of positive bone scan status. There was no significant correlation between D-dimer titre and PSA level ($P=0.4$).

Discussion

This study shows that activation of the haemostatic system in prostate cancer is common and appears to be related to disease stage as determined by bone scan status. Comparison of these findings with previous reports is difficult as many of the earlier investigations did not use comparable assays and patients groups were often mixed, containing treated individuals in addition to those presenting *de novo*.

However, two studies have measured D-dimer levels in similar patient groups. Henrickson *et al. (17)* found abnormal levels in 3/17 patients (18%) with prostatic cancer deemed suitable for hormonal manipulation, while in another, larger study, D-dimer levels were higher in prostatic cancer than BPH or healthy blood donors *(18)*. In contrast to the current findings, the latter study found no correlation between D-dimer levels and disease stage. However, patients in the latter study were staged clinically rather than by bone scan status.

Similarly, there are few studies of fibrinopeptide A levels in patients with prostatic cancer. Drewinko *et al. (15)* evaluated 16 patients (mainly stage C and D) and found FpA levels to be similar to the control groups. Various investigators have been concerned about the effect of hormonal manipulation of prostatic cancer on coagulation factors. Two such studies have measured baseline FpA as part of a coagulation screen before androgen ablation (ie in advanced disease) and found them to be elevated compared with controls *(19,20)*.

Nanninga *et al. (21)* reported that the incidence of coagulopathy in patients with localised disease is low; a finding supported by the results of the current study. Although staging by bone scan will undoubtedly result in the inclusion of some patients with extraprostatic and nodal disease in the bone scan negative group, only one patient had detectable D-dimer levels. Similarly, there was no difference in FpA levels between patients with BPH and those with negative bone scans.

Determining the incidence of coagulopathy in patients with cancer has clinical significance. The clinical manifestations of the acute decompensation of chronic DIC may be catastrophic and indeed fatal. Approximately 75% of patients with cancer and chronic DIC will eventually develop clinical evidence of this syndrome, and up to 25% will develop some type of significant thromboembolic event *(22)*. Clearly the clinician should be aware of those patients who are potentially at high risk for the development of these complications. This will allow appropriate measures to be taken which may reduce the morbidity and mortality associated with treatment of such patients. If, as seems reasonable, those with evidence of subclinical coagulopathy are those at most risk, then the current study suggests that they can be identified by simple tests.

Review of the D-dimer data suggests that this test may have some predictive value in determining bone scan status in patients presenting with untreated prostate cancer. PSA may have a similar role *(23)* and a comparison of the performance of D-dimer with that of PSA, using a cut-off point of 20 ng/ml, is shown in Table III. Data on PSA (using an identical cut-off point) within the

Table III. Comparison of PSA (cut-off point = 20 ng/ml) with detectable D-dimer as a predictor of bone scan status

	n	*Prevalence BS+ve*	*Sens (%)*	*Spec (%)*	*PPV (%)*	*NPV (%)*
PSA (this work)	42	43%	94	58	63	93
PSA *(23)*	521	14%	99	68	33	99.7
D-dimer (this work)	45	40%	56	96	91	76

Key: *n*, number of patients. BS+ve, bone scan positive. Sens, sensitivity. Spec, specificity. PPV, positive predictive value. NPV, negative predictive value

current small study group has also been included to facilitate further comparison with PSA in a patient population with similar prevalence of bone scan positivity. Although the sensitivity and specificity of PSA in the two series are similar, there is a marked difference in the positive predictive value. This probably reflects the difference in prevalence of bone scan positivity between the two series. The American series is from a tertiary referral centre and therefore is probably highly selected in favour of those patients who are candidates for radical surgery. The high positive predictive value of D-dimer may mean that, in tandem with PSA (with its excellent negative predictive value), bone scanning could be avoided in certain patients. However, prospective studies would be required to test this hypothesis. Oesterling *(24)* has highlighted the marked financial savings that could be made if bone scans were performed more selectively and further evaluation of D-dimer in this role therefore seems appropriate. The use of a fully quantitative assay for D-dimer would improve the flexibility of the cut-off points and may enhance the performance of the assay.

The association of detectable coagulopathy and its apparent correlation with disease stage, as defined by bone scan status, in this study, may have further clinical significance. Fibrinopeptide A has been suggested as a possible tumour marker and in one study of 50 patients with cancer, which included four patients with disseminated prostatic tumours, an upward trend in FpA levels over a 3-year period paralleled the clinical progression of the disease *(25)*. Indeed, persistent elevation suggested treatment failure and ominous prognosis. FpA may also have prognostic value in leukaemia *(26)* and clinically localised breast cancer *(27)*. The latter study found FpA to be valuable in predicting those women likely to develop recurrent or progressive breast cancer.

The idea of using haemostatic parameters as tumour markers in prostate cancer is not new. For example, van Deijk *et al. (28)* found increased levels of activated factor VII in a small number of patients with metastatic prostate cancer compared with BPH or non-metastatic disease, and elevated plasma urokinase levels have been reported in metastatic prostate cancer *(8)*. Although PSA is an excellent tumour marker there are severe limitations in its application. Measurement of FpA at the time of presentation and serial determinations after treatment may be of clinical value and the present findings suggest that such prospective studies in prostate cancer are worthwhile. Of particular interest would be the further study and follow-up of those few bone scan negative individuals with elevated FpA levels.

In summary, this study has confirmed that up to 40% of patients with untreated prostate cancer have evidence of activation of their haemostatic system. Quite apart from providing further evidence of the association between malignant disease and haemostasis, this observation may have important practical applications. Further studies investigating the possible role of coagulation indices as putative tumour markers in prostate cancer are warranted.

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