Disseminated Intravascular Coagulation in a Patient with Metastatic Prostate Cancer: Fatal Outcome Following Strontium-89 Therapy

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A patient with metastatic prostate cancer was found to have low-grade disseminated intravascular coagulation (DIC). He had significant bone pain despite external-beam radiotherapy and was given ^{89}Sr with subsequent thrombocytopenia and epistaxis. The patient died from generalized hemorrhage 36 days postinjection. Although it is not possible to establish a causal relationship between the ^{89}Sr and DIC, practitioners should be alert to complications associated with the primary disorder which might occur at a time to raise concern about the intervention.

Key Words: prostatic neoplasms; disseminated intravascular coagulation; strontium; thrombocytopenia

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An association between metastatic prostate cancer and disseminated intravascular coagulation (DIC) has been reported in the past (*1–4*). We believe this is the first reported case of marked DIC progression following ^{89}Sr therapy for metastatic hormone-resistant prostate cancer.

CASE REPORT:

A 65-yr-old male presented with obstructive urinary symptoms and was found to have a clinical stage C prostate cancer. He underwent transurethral prostatic resection and a needle biopsy of the prostate gland which showed Gleason grade 3 + 5 = 8 adenocarcinoma with extracapsular extension and extensive perineural invasion. Baseline blood tests showed hemoglobin 165 g/liter, white blood cell count 5.7 × 10^9/liter, and platelet count 157 × 10^9/liter. A whole-body bone scan with ^{99m}Tc-MDP showed areas of increased uptake over the occiput, right proximal humeral metaphysis, left inferior glenoid, right tenth and eleventh ribs, multiple lower thoracic and lumbar vertebrae, both inferior SI-joints, left ischial tuberosity and left pubic bone anteriorly. A diagnosis of metastatic prostatic adenocarcinoma was made and the patient was started on 50 mg p.o. b.i.d. Cyproterone acetate and 0.1 mg p.o. diethylstilbestrol daily. Prostate-specific antigen (PSA) levels fell from a baseline of 26.8 μg/liter (normal <4 μg/liter) to 1.2 μg/liter after 1 mo of hormone therapy.

Five months after diagnosis, the patient underwent bilateral orchidectomy and stopped exogenous hormone therapy. Two months later, the patient presented with progressive bone pain in the right shoulder, lower lumbosacral area and right groin. PSA was measured to be 18 μg/liter. Plain x-rays confirmed multiple bony metastases. The patient was treated with a course of palliative external-beam irradiation directed towards the right shoulder, lumbosacral spine and right hip.

Ten months after diagnosis, the patient was admitted for pain control. Although the right shoulder pain had improved, the right groin and lumbosacral pain were not affected by the radiotherapy. In addition, the patient developed new left shoulder pain and tenderness over the right iliac crest. Admission blood tests showed hemoglobin 91 g/liter, white blood cell count 4.7 × 10^9/liter, and platelets 152 × 10^9/liter (Table 1). Electrolytes and creatinine were normal. Liver function tests were consistent with bony metastatic disease. PSA was elevated to 400 μg/liter. Plain x-rays showed diffuse sclerotic metastases. Repeat bone scan showed increased uptake throughout the entire axial skeleton, both humeri, both femora and the right tibia. The patient was treated with a course of palliative external-beam radiation directed towards the right shoulder, right hip and right iliac crest.

The patient's hemoglobin was 91 g/liter on admission but fell to 78 g/liter on Day 3. He was transfused with three units of packed red blood cells (PRBC). Subsequent studies failed to reveal a source of blood loss. Hematologic studies on Day 7 showed an elevated D-dimer assay 2.0–4.0 mg/liter (normal <0.25 mg/liter), normal fibrinogen level, slight elevation of prothrombin time (PT) 14.1 sec (normal, 10.0–13.0 sec), normal partial thromboplastin time (PTT) and mild microangiopathic red blood cell morphologic changes suggesting the presence of low grade DIC. Slight thrombocytopenia of 79 × 10^9/liter was documented but the platelet count spontaneously rose to 104 × 10^9/liter on Day 8. Because the patient continued to have diffuse bone pain despite narcotic analgesics, he was assessed for ^{89}Sr therapy in conjunction with the nuclear medicine department. A decision was made to administer 150 MBq of ^{89}Sr intravenously on Day 8. Although the platelet count initially began to fall, he appeared clinically stable and was discharged home under the care of his family physician on Day 10.

The patient developed problems with massive epistaxis and his complete blood count revealed a hemoglobin of 78 g/liter and a platelet count of 56 × 10^9/liter on Day 18. He was managed with an overnight hospital admission and transfusion of two units of

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TABLE 1
Progress of Hematological Parameters before and after Strontium-89 Administration

Days after admission	3U PRBC ↓				^{89}Sr ↓									
	0	3	4	7	8	9	10	14	18	19	24	28		
Hb	91	78	106	114	118	113	102	98	78	101	85	73		(140–180 g/liter)
WBC	4.7	4.3	6.2	5.8	6.9	7.0	5.4	8.7	4.4	4.8	2.4	1.9		(4.5–11.0 × 10^9/liter)
Plt	152	110	122	79	104	82	53							(125–400 × 10^9/liter)
PT				14.1					15.2					(10.0–13.0 sec)
PTT				22.9					27.1					(22.0 × 34.0 sec)
D-Dimer				2.0–4.0										(<0.25 mg/liter)
Fibrinogen				3.84										(1.25–4.00 g/liter)

	2U PRBC ↓				4U PRBC ↓		6U Plt ↓			Death
29	30	31	32	33	↓ 36	
	89		101	103		(130–170 g/liter)
	1.4		1.2	1.5		(3.5–10.5 × 10^9/liter)
	15.6					(11.5–13.5 sec)
	25.3					(24.0–32.0 sec)
	>4.0					(<0.5 mg/liter)
	5.31					(1.7–3.8 g/liter)

PRBC = packed red blood cells and Plt = platelets.

PRBC. On Day 29, the patient developed further epistaxis that was not controlled with local pressure. He was readmitted to hospital, transfused with four units of PRBC, and treated with a topical 4% cocaine solution as well as a 48-hr balloon tamponade in the left nostril. Hematologic studies showed increased microangiopathy and a D-dimer level greater than 4.0 mg/liter (normal <0.25 mg/liter), which is consistent with marked DIC. Renal function
remained normal. The patient was transfused with six units of platelets because of persistent oozing and then given a trial of Decadron. Unfortunately the patient's condition deteriorated with massive generalized hemorrhage and bone marrow failure, and died on Day 36. No autopsy was performed.

DISCUSSION

Hypercoagulable states associated with malignancy resulting in thrombocytopenia and DIC are well recognized (*1*). Tissue thromboplastins derived from the tumor cells and exposed to the circulation are believed to be important in the pathophysiology. The manifestations of DIC associated with prostate cancer can range from being a subclinical marker of disease (*1,2*) to overt bleeding after minor to moderate trauma (*3,4*). DIC presenting as purpura after chemotherapy for lung cancer has been reported (*5*); however, this is the first report of a patient with mild prostate cancer associated DIC and thrombocytopenia which progressed to overt bleeding after ^{89}Sr therapy.

Therapy for metastatic prostate cancer often includes hormonal maneuvers to reduce or eliminate endogenous androgens and radiotherapy for symptomatic bony disease. Recently, randomized studies have demonstrated the efficacy of ^{89}Sr in the treatment of bony metastases either alone (*6*) or in an adjuvant setting with external-beam irradiation (*7*). Published reports of ^{89}Sr therapy have included patients with hormone refractory prostate cancer with characteristics similar to our patient (*7*). Authors have reported no symptomatic thrombocytopenia when pretreatment platelet counts were at least 200 × 10^9/liter (*6*) or a low (10.4%) incidence of grade IV thrombocytopenia with pretreatment platelet counts of 150 × 10^9/liter and white blood cell counts of 3.5 × 10^9/liter (*7*). Many patients have been treated with platelet counts as low as 60 × 10^9/liter without complications (*8*). Therefore, our patient's decline in the few weeks after ^{89}Sr administration was surprising to us. It was because of this that we felt the patient's pre-existing DIC may have played an important role, although this is difficult to prove.

The relative contribution of DIC versus treatment-induced myelosuppression is difficult to determine although both are probably implicated. The fibrinogen level remained normal or increased but this finding is not uncommon as an acute-phase response in patients with neoplasia. However, the elevated D-dimer assay which specifically measures cross-linked fibrin degradation products and is a sensitive indicator of DIC significantly increased following ^{89}Sr therapy. Also, the timing of complications is consistent with ^{89}Sr-induced thrombocytopenia which has a nadir of 4–8 wk after injection. Tumor destruction from ^{89}Sr therapy may have exacerbated the pre-existing low-grade DIC resulting in an even greater fall in platelet counts.

Unfortunately, the exact mechanism of death is not known since no autopsy was performed. However, this case highlights that cautious clinical judgment taking into account both risk and benefit must be employed when considering ^{89}Sr therapy for patients with impaired marrow reserve, especially if there is evidence of other confounding variables such as low-grade DIC.

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