Severe Thrombocytopenia in a Man with Prostatic Cancer

Pages with reference to book, From 252 To 254

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A 66 year old gentleman was diagnosed to have metastatic adenocarcinoma of the prostate in 1990, following a CT scan of the abdomen and trans-uretheral resection of prostate (TLJRP). He was started on estrogen therapy (Fosfesterol sodium). Two years later he presented to the emergency room with breathlessness and edema of the left ann of a week's duration. He admitted to persistence of symptoms of pmstatism and was found to have bilateral axillary lymphadenopathy and pitting edema of the left arm. A doppler scan revealed left subclavian vein thrombosis. The patient was started on i.v. heparin and was maintained on it until the resolution of arm edema and was subsequently switched to oral anticoagulation. The serum Prostate Specific Antigen (PSA) level was found to be 1460 ng/ml. Fosfesterol was discontinued and the patient was started on antiandrogen therapy (Cyproterone acetate). The patient was sent home on anticoagulation, but had to be readmitted shortly thereafter because of the sudden onset of shortness of breath. This time he was found to have bilateral pitting pedal edema and :tenderness in the right calf. Intravenous heparin was reinstituted. An infçrior venacavagram revealed extensive thrombosis of the right popliteal vein and the left common iliac vein. A clinical diagnosis of pulmonary embolism was made. Despite continuous i.v. heparin in adequate doses, the patient experienced recurrent episodes of shortness of breath. A greenfield filter was placed in the inferior vena cava to prevent further episodes of pulmonary embolism. The patient remained heparinized for more than two weeks, until complete resolutionofsyniptoms had occured. Subsequently oral anticoagulation was started and the dose of coumarin was adjusted to maintain an international normalized ratio (INR) between 1.8 and2.0.

Over the next several months, the patient was followed up in the oncology clinic with serial measurements of PSA. Despite being on maximum doses of cyproterone acetate, the PSA level. did not normalize. Cyproterone was discontinued and the patient was started on the non-progestational anti-androgen flutamide. However, the PSA values continued to fluctuate and subsequently started to increase. The serum testosterone level was found to be high (235 ng/dl). The corresponding PSA level was 936 ng/ml. The patient was advised to have a subcapsularorchidectomy. He was admitted to the hospital, where the following laboratory values were obtained: Hb 10.1 gm/dl; TLC $5.7x10^9$/l; platelets $147x10^9$/L; PT 19/12 seconds (INR 1.9); and APTF 34/3 2 seconds. Coumann was stopped and heparin was started. On the 4th day, the platelet count was found to be $16x10^9$/L. This was rechecked and was found to be the same. The PT, APT!' and FDP were all found to be within normal !imits. At this time, them was no purpura. The next day, ecchymoses had appeared and the platelet count had dropped to $7x10^9$/L and subsequently to $146x10^9$/L after another two days. The plan for subcapsular orchidectomy was cancelled and the LHRH analogue (Buserelin) was injected subcutaneously. Because of the relationship of the onset of thrombocytopenia and its resolution, to the start and discontinuation of heparin, a diagnosis of heparin-induced thrombocytopenia was entertained. Two weeks later, the patient was readmitted with calf tenderness and left leg edema. He was again found to have deep venous thrombosis, extending from the popliteal to the external iliac vein. Since the patient was already taking coumarin, which proved ineffective in preventing thrombus formation, the patient was started on low molecular weight heparm (LMWH) and aspirin. Presently, the patient is doing well, the symptoms have largely resolved and the platelet counts, repeated on several occasions, have remained within normal limits.

Discussion

Thrombocytopenia is one of the most common and important immunological complications of heparin therapy'. The attendant morbidity and mortality is significant[2,3]. The incidence of the complication is 1-5%; higher with bovine than with porcine heparin[4]. Two clinical types have been described; a mild, early onset type and a severe, delayed onset type[5]. In the former type, the platelet count does not fall below $100x10^9$/L and the patient is usually asymptomatic. The situation is easily reversible without any specific therapy; the mechanism of thrombocytopenia is unknown. The second type is characterized by a reduction 'in the platelet count to usually less than 50x109/L, and it occurs 4-9 days after the onset of heparin therapy. This type is associated with an increased risk of thrombo-embolic complications and an immune mechanism is implicated in the pathogenesis[6,7,8]. Of the various drug-induced thrombocytopenias, that caused by heparin is different as it is associated with relatively little risk of bleeding, but a high risk of paradoxical thrombosis involving majorvessels. The thrombo-embolic complications may manifest as cerebral thrombosis, acute myocardial infarction, recurrent pulmonaiy emboli, orarterial thrombosis resulting in limb gangrene with a 20% risk of amputation[9]. The proposed mechanism of heparin induced thrombocytopema is as follows: IgG antibody forms after several days of exposure to heparin. The antibodies are not specific for heparin and interact with heparin only in the presence of platelet factor 4 (PF4)10. The IgG/hepann PF4 immune complexes are formed on the platelet surface and activate platelets by binding to Fc receptors[1,11,12,13]. Thrombosis is secondaiy to platelet activation and endothelial cell injuiy[4,13]. Although the diagnosis of heparin induced thrombocytopenia is usually clinical, different laboratory tests can be employed, not only for the confirmation of the diagnosis, but also for screening agents which could be used as alternatives to heFarin. In-vitro platelet aggregation is a rapid and simple test[9,14,15] ^{14}C- serotonin release test is more sensitive and specific[4,16]. Other assays have been developed but have little practical value for routine diagnosis[4]. Recognition of the condition requires immediate discontinuation of heparin. Platelet transfusion should be avoided, as these may precipitate arterial thrombosis. As alternatives to i.v. heparin for anticoagulation, different agents have been tried. Low molecular weight heparin (LMWH) has been used frequently, generally with a favourable clinical course. Although there may be 25-60% cross reactivity between unfractionated heparin and LMWH[17], the incidence of heparin induced thrombocytopenia is significantly low[18,19,20]. An in-vitro platelet aggregation test may help in selecting the type of LMWH. Besides LMWH, other treatment options include the use of Heparinoid[21], Heparan sulphateand dermatan sulphate[22],. Ancrod, and the placement of inferior vena caval filters[23]. For established thrombosis, aspirin, dipyridamole, prostacyclin analogues, fibrinolytic therapy and plasmapharesis all have been tried[4,24] with variable success. Our patient developed severe thrombocytopenia on the fourth day of heparin therapy and this reversed four days after cessation of the drug without any specific intervention. The diagnosis was established clinically. The patient had been heparinized on two previous occasions, and retrospective analysis of records revealed that on one occasion the platelet count had dropped to $84xl0^9$fL, but reverted spontaneously. With as high an incidence of HIT as that reported in the literature(l-5%), together with the frequency of heparin use in clinical practice, physicians need to be aware of this important and potentially life-threatening complication of heparin therapy. LMWH could be usefully employed instead of unfractionated heparin and in such cases the probability of cross-reactivity could be decreased by performing a simple in-vitro platelet aggregation test.

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