White Clot Syndrome Associated With Renal Failure

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ABSTRACT

In a minority of patients, heparin administration is associated with thrombocytopenia and this thrombocytopenia may be associated with thromboembolic events. Heparin-associated thrombembolism is described as heparin-associated thrombocytopenia and thrombosis or white clot syndrome. White clot syndrome is caused by antibodies to a heparin-platelet membrane complex. The diagnosis carries a high mortality and morbidity from limb thrombo-

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embolism. Treatment includes discontinuation of heparin, use of alternate anticoagulants, and aggressive treatment of thromboses. A case in which acute renal failure occurred in the setting of heparin treatment and thrombocytopenia is described, and evidence that renal failure was a result of white clot syndrome is provided.

Key Words: Thrombocytopenia, acute renal failure, heparin, thrombosis

Heparin, although generally used as an anticoagulant, can occasionally cause thrombosis. Although heparin-induced thrombocytopenia is well recognized, the ability of heparin to cause platelet aggregation and thrombosis is less widely appreciated. Thrombocytopenia and thrombosis accompanying heparin administration is known as white clot syndrome, or heparin-associated thrombocytopenia and thrombosis (HATT). Previous reports have not mentioned renal failure accompanying this syndrome. We describe a case of renal failure associated with white clot syndrome, along with pathologic evidence that the renal failure was precipitated by heparin-induced thromboembolism.
V.L. was a 59-yr-old white woman with stage T3 N3 head and neck squamous cell carcinoma who was admitted for radical neck dissection. Her medicines included quinine sulfate (200 mg as needed), temazepam (30 mg each day), and acetaminophen (as needed).

On her initial examination, her vital signs were normal. Her oral examination disclosed a friable left tonsil and an exophytic neoplasm of the left lateral margin of the tongue. Her neck had a mobile 5.5 by 7 cm mass in the midjugular region.

Laboratory examination of her serum showed Na of 133 mEq/L, K of 4.2 mEq/L, Cl of 101 mEq/L, CO₂ of 21 mEq/L, urea of 3.6 mmol/L, creatinine of 70 µmol/L, hemoglobin of 118 g/L, white blood cell count of 6.3 × 10⁹/L, platelet count of 361 × 10⁹/L, prothrombin time of 11 s, and partial thromboplastin time of 28 s.

She was admitted to the hospital. The following day, the carcinoma was resected and a tracheostomy was performed. She was admitted to the Surgical Intensive Care Unit where she received antibiotics and narcotics as needed for pain relief. An iv line was flushed with heparin (10 U) three times per day. When she was transferred to the floor, she continued to receive heparin iv line flushes.

On the fifth hospital day, she became acutely dyspneic and complained of midsternal chest pain. An examination revealed her blood pressure was 180/100 mm Hg, her pulse was 140, her respiratory rate was 28, and she was afebrile. She was cyanotic and had bibasilar crackles on lung examination. A chest radiogram showed bibasilar infiltrates and pleural effusions. An arterial blood gas measurement showed a PO₂ of 26 mm Hg; this improved to 47 mm Hg when she was given 100% oxygen.

She was transferred to the intensive care unit and started on heparin at 3,000 U iv and then 1,000 U/h for presumed pulmonary embolism; a perfusion/venilation isotope scan was nondiagnostic. A pulmonary angiogram was attempted; this showed a clot in the proximal left common iliac vein and inferior vena cava. A Greenfield filter (Meditech, Boston, MA) was placed infrarenally, after which she became acutely dyspneic. On 100% oxygen, her PO₂ was 54. She was placed on a ventilator. Intravenous heparin was continued, and her partial thromboplastin time was kept in the therapeutic range.

Over the next several days, she remained febrile. On the seventh hospital day, a urine culture grew gram-negative bacteria which was later identified as *Enterobacter* species; treatment with gentamicin was begun on the 10th hospital day. The course of her platelet count, serum creatinine, and urine output are shown in Figure 1.

On the 12th hospital day, gentamicin levels were 4.2 µg/mL peak and 0.4 µg/mL trough. She became acutely anuric on the 13th hospital day. Coagulation studies showed the following values: prothrombin time, 20 s; partial thromboplastin time, >150 s; fibrinogen, 4.82 g/L; fibrin degradation products, >80; platelet count, 41 × 10⁹/L. An electrolyte panel was normal.

Heparin was discontinued. High-dose iv diuretics were given without effect. A physical examination showed bibasilar rhonchi and cyanotic fingertips. Urinalysis showed 5 to 9 white blood cells per high-power field, 5 to 9 red blood cells per high-power field, 2+ blood, and 2+ leukocyte esterase reaction on dipstick examination. Gentamicin was discontinued. Renal ultrasonography showed no hydronephrosis. Venography of the inferior vena cava disclosed left renal vein thrombosis and a normal right renal vein (Figure 2). Another inferior vena caval filter was placed above the renal veins.

On the 15th hospital day, her corneal reflex was absent and she was comatose. She had become hypokalemic. Coagulation tests showed the following values: fibrinogen, 6.68 g/L; fibrin degradation products, >80 µg/dL; thrombin time, 29/91 (control) s; fibrin monomer, 100 µg/L; D-dimer, >4 µg/mL; antiplasmin, 112%. Tests of platelet aggregation in the presence of serum were not done. On the 16th hospital day, hemodialysis was initiated.

The following day, her extremities were more mottled than previously. On bronchoscopy, the trachea was almost occluded with white fibrotic clots, which were removed. Blood cultures from the previous day grew a gram-negative rod. On the 18th hospital day, the patient was febrile and hypotensive. She had no return of renal function. The following day, the patient developed asystole and died.

**PATHOLOGIC FINDINGS**

A postmortem examination disclosed left renal vein thrombosis and a patent right renal vein. Thrombus
involved the left iliac and extended up the inferior vena cava past the renal veins and involved both intravascular filters. The kidneys had a mottled appearance bilaterally, with multiple areas of acute infarction and hemorrhagic rimming, consistent with acute bilateral cortical necrosis. A histologic examination of the kidneys revealed large areas of cortical infarction; some were wedge shaped, consistent with arteriolar embolization. Others were congested and did not conform to the end-artery distribution of intralobular arteries, suggesting venous infarction. Intraglomerular fibrin was seen in some glomeruli, consistent with disseminated intravascular coagulation (DIC). However, in other glomeruli, the afferent arterioles were occluded with pale material consistent with the fibrin-platelet aggregates of white clot syndrome (Figure 3). Electron microscopy was later done on paraffin-embedded tissue; it showed poor preservation. Fibrin was seen in some glomeruli, but platelets could not be identified in the poorly preserved tissue.

DISCUSSION

This is a complex case in which the patient had numerous potential causes of renal failure. We believe that the root cause of this patient’s renal failure was HATT, although no heparin-induced platelet aggregation test was done. Although she did have renal vein thrombosis, one renal vein was patent both during radiographic examination and at autopsy. Unilateral renal vein thrombosis should not cause anuria. Gentamicin toxicity is unlikely, because renal failure occurred only a few days after this antibiotic was started, levels were within normal range, and the renal failure presented as anuria. Evidence consistent with DIC was seen on histologic examination. DIC can be associated with malignancy, but DIC can be a complication of white clot syndrome as well (1). Although her serum fibrin degradation products were elevated, her serum fibrinogen was not decreased. Further, the fibrinous clots found obstructing the afferent arterioles of many glomeruli had an appearance consistent with heparin-associated thrombosis. White clots were also removed from her trachea. Finally, the onset of anuria was temporally associated with thrombocytopenia.

Heparin affects several factors in the clotting cascade. It acts as a cofactor of antithrombin III, which has a protease activity that inhibits kallikrein, XIIa, XIa, IXa, Xa, and thrombin by forming irreversible complexes. Heparin works by accelerating these reactions. Heparin is metabolized in the liver by heparinase enzymes; the inactive metabolites are excreted in the urine. Dosages need to be decreased in patients with hepatic or renal failure and increased in patients with pulmonary embolism because of increased plasma clearance. Complications of heparin therapy include hypersensitivity reactions and hemorrhage, as well as thrombocytopenia and thrombosis.

HATT is an uncommon syndrome. In one study, 46 of 3,438 patients (1.3%) who underwent open-heart surgery from 1981 to 1989 developed heparin-associated antibodies (2). It is caused by the development of immunoglobulin G antibodies (3) that bind to a platelet membrane-heparin complex; the binding induces platelet aggregation (4). This aggregation leads
to thrombocytopenia and major vascular thrombosis. The activity of the antibody can persist for weeks or months (5). Thrombocytopenia tends to occur 6 to 12 days after heparin therapy begins, and sooner in patients who are previously exposed to heparin. There is no apparent relationship between the development of the syndrome and sex, route of heparin administration, or amount of heparin given (6). Those patients in whom the diagnosis was unknown before surgery had a 37% mortality rate and 32% rate of thromboembolic events (2).

HATT most frequently presents as stroke and vascular occlusion, especially of the limbs, in a setting of heparin therapy with decreased platelets. The thrombotic sequelae of this disease result in a high morbidity and mortality. In one study, 47 thromboembolic events occurred in 25 patients, requiring 43 vascular surgical procedures, causing 16 limbs lost and the death of 9 patients (6). HATT is fatal in 29% of cases and leads to limb amputation in 21% (5).

Acute renal failure has, to the best of our knowledge, not been described in association with white clot syndrome. This is somewhat surprising, given the frequency with which the syndrome results in loss of limbs due to thromboembolism. In a review of several series of cases, renal failure is not mentioned as a complication of HATT (6–11). Heparin-associated thrombocytopenia has been described in association with continuous arterial hemodialysis (12) and with hemodialysis (for which low-molecular-weight heparinoids were successfully used) (13).

Patients on heparin therapy should have platelet counts checked frequently after the start of therapy. If the platelet count begins to decrease, especially below counts of 100,000 or 50% of baseline, heparin should be stopped if at all possible and consideration should be given to alternate means of anticoagulation. Similarly, recurrent thromboses with the patient on heparin should also lead to suspicion of HATT. The early administration of warfarin in clinically appropriate situations can permit discontinuation of heparin therapy before thrombocytopenia begins.

Once the platelet count has decreased, the diagnosis can be confirmed by nephelometric measurement of the aggregation of normal platelets in the patient’s serum. Other hemostatic parameters can be affected in this disease. Fibrinogen and prothrombin time are usually normal, but fibrin split products can be elevated (7). HATT can occur in conjunction with or be complicated by DIC (1).

Many pharmaceutical agents have been used either to anticoagulate patients who have developed HATT or to deal with the complications of this disease (Table 1). Among these are the heparinoids and low-molecular-weight heparins. Org 10172 is a heparinoid that did not induce platelet aggregation in any of 13 plasma samples from patients with HATT (6), although the clinical use of heparinoids has been associated with thrombocytopenia and thrombosis (14).

Low-molecular-weight heparins were found to be useful in eight patients with thrombocytopenia (15) but, in other studies, have been found to induce platelet aggregation in vitro (6). In vitro, some low-molecular-weight heparins and heparinoids have been found to cause platelet aggregation in conjunction with serum samples from patients with heparin-associated thrombosis (16). Heparin-associated antibodies occur in only a fraction of cases receiving heparin. It is possible that low-molecular-weight heparin will be found to give rise to similar antibodies once sufficient experience has been accumulated.

Dextran can be used if the patient does not become fluid overloaded. Dextran has been shown to decrease platelet adhesiveness (17) and reduce heparin-mediated platelet aggregation (18).

The action of heparin antiplatelet antibody on platelets causes a release of thromboxane, which mediates aggregation (16). For this reason, the use of aspirin has been investigated in an attempt to decrease thrombus formation. In 9 of 16 patients, aspirin abolished in vitro platelet aggregation induced by the patient’s plasma. In the remaining seven cases, the extent of platelet aggregation was decreased (6).

Thromboses should be aggressively treated. Thrombolytics such as streptokinase (19) and urokinase (20) have been used to treat the thromboses associated with HATT. Surgical thrombectomy has also been successful.

HATT is associated with a grave prognosis. Effective therapy requires prompt recognition and treatment. White clot syndrome should be included in the differential diagnosis of acute renal failure in patients who have received heparin.

TABLE 1. Therapy for white clot syndrome

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<td>For Continued Anticoagulation</td>
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<td>Coumadin</td>
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REFERENCES


