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Developmemt of Pulmonary Edema Related to Heparin Administration

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Abstract: Bleeding, thrombocytopenia, and osteopenia are recognized as the side effects of heparin administration. We recently noted occurrence of pulmonary edema in a patient with myelofibrosis with myeloid metaplasia being treated with heparin for pulmonary embolism. The hypertensive episodes preceding left ventricular failure were considered related to serotonin released from the immunologically mediated lowering of platelets.

HEPARIN is widely used in clinical practice as an effective agent in the prevention and treatment of thromboembolic disease.[1] Significant side effects of continuous heparin therapy mentioned in the literature include bleeding, thrombocytopenia, and osteopenia. Several recent comprehensive reviews on the use of heparin do not mention pulmonary edema as a complication.[2] We recently noted this occurrence in a patient with myelofibrosis with myeloid metaplasia who was being treated with heparin for pulmonary embolism.

Case Report

A 60-year-old black woman was admitted to the orthopedic service with fracture of the right midfemur. Approximately 24 hours after her placement in traction, she developed moderate respiratory distress and infiltrates in both lung bases. Swelling and tenderness appeared in the right calf, and she was then transferred to the medical service with a presumptive diagnosis of pulmonary embolism.

The past medical history was essentially unremarkable for serious illnesses. She denied cigarette or alcohol abuse. Physical examination revealed a well-developed, well-nourished black female of stated age in moderate respiratory distress breathing at 32/min. The pulse was 120 beats/min and regular, temperature was 99°F orally, and the blood pressure measured 130/180 mm Hg in both arms. No abnormal arterial or venous pulsations were noted, and the carotid upstroke was brisk. There were few scattered rales over both bases. The heart sounds were normal; P2 was mildly increased in intensity. No murmurs or gallops were heard. The abdomen was soft and nontender, without hepatmegaly. The spleen was palpable 6 cm below the left costal margin and was soft and nontender. The right leg was in traction with superficial varicosities, the calf was tender and swollen. The left leg was also tender, with a palpable cord. The Homan sign was positive bilaterally.

A routine hemogram revealed a hematocrit of 30%, a hemoglobin of 10.2 Gm/dl, and a WBC count of 11,800, with normal differential. The platelet count was repeatedly around 690,000 to 846,000. Except for the blood sugar, SGOT, LDH, and CPK, which were substantially elevated, blood chemistry was within normal limits. Arterial blood gases revealed a pattern of respiratory alkalosis. The PO_2 was decreased to 60 mm Hg, PCO_2 to 18 mm Hg; the pH was elevated to 7.52. A chest x-ray revealed

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normal heart size with question of platelike atelectasis in the right lower lobe. A small area of infiltrate was also seen in the left lower lobe. An electrocardiogram revealed sinus tachycardia, with no evidence of right ventricular strain or changes consistent with pulmonary embolism. A right heart study using a blood flow-directed catheter (Swan-Ganz) revealed moderate degree of pulmonary hypertension. The pulmonary artery pressure measured 55/20, with a mean of 35 mm Hg. The pulmonary capillary wedge pressure was normal at 8 mm Hg. The cardiac output was normal at 5 liters/min. As the patient was in traction, lung scans and pulmonary arteriograms could not be obtained. Since the clinical picture, arterial blood gases, and right heart catheterization data were consistent with pulmonary embolization, intravenous heparin was administered as a continuous drip. Despite an average 24-hour dose of 36,000 units, the plasma thromboplastin time (PTT) could not be increased to a therapeutic level. This was considered possibly a result of thrombocytosis from recently discovered myelofibrosis (splenomegaly, low hematocrit, and high ferritin level of 974 μg/ml with normal serum iron and iron-binding capacity). A bone marrow biopsy was postponed at the request of the patient. During this period, the patient also required parenteral insulin to control persistent hyperglycemia.

As the PTT failed to rise significantly even after five days of continuous heparin therapy, an additional heparin dose of 5000 units was administered as a bolus. This was followed 20 minutes later by the abrupt onset of dyspnea, tachycardia, and a blood pressure of 200/100 mm Hg. Physical examination revealed bronchial wheezing, few rales, and an increase in the intensity of P2. No rash developed. An electrocardiogram was essentially unchanged. Arterial blood gases at this time were normal; the PO_2, PCO_2, and pH while breathing room air were in the normal range. A repeat right heart catheterization revealed normal pressures and cardiac output. Urine and sputum were again negative for fat bodies. A lung scan and pulmonary arteriogram were not obtained. Heparin hypersensitivity was considered a possible explanation for this abrupt change in clinical picture, but continuous intravenous heparin was not discontinued. Platelets had dropped to 212,000 during this episode. The patient recovered spontaneously in an hour without any medical therapy. After three days of intravenous drip, a bolus of 7500 units of heparin was administered through a fresh drip. Twenty minutes later, the patient again developed abrupt onset of dyspnea and tachycardia and the blood pressure measured 200/120 mm Hg. A loud S3 was heard; the P2 was normal. There were moist rales at both bases, but no wheezing or rhonchi were heard and no rash was observed. An electrocardiogram and arterial blood gases were unchanged. A chest x-ray showed pulmonary edema and venous engorgement in the upper lobes. Repeat right heart catheterization revealed a pulmonary wedge pressure of 20 mm Hg with normal pulmonary artery pressures and normal cardiac output. A pulmonary arteriogram done at this time revealed no evidence of recent or chronic pulmonary embolization. Platelet count, which had returned to normal levels two days before, declined to 112,000 during this episode. Blood sample drawn for serotonin during this episode was unfortunately lost; a urine sample starting with the onset of symptoms and collected over the next 24 hours disclosed 8.2 mg of hydroxytryptamine (normal valve for the laboratory less than 8). Platelet antibodies were positive, with a signficantly elevated titer. The patient responded to a single bolus of intravenous Lasix, and heparin was henceforth discontinued.

The platelets returned over the next 48 hours to the usual count of around 800,000. A repeat urine collection at this time showed a decrease in the 5-hydroxyindoleacetic acid (to 5 mg), and serotonin was less than 25 mg/dl (normal 50 to 2000 mg/dl).

The femoral fracture at this time was pinned, and anticoagulation was resumed with oral warfarin sodium (Coumadin).

Discussion

These clinical episodes of abrupt onset of tachycardia, tachypnea, and systemic hypertension are obviously not related to recurrent pulmonary embolization. Hypersensitivity reactions consisting of bronchospasm, tachypnea, and dyspnea are reported in patients receiving intravenous heparin.[3] Hypotension is usually the integral part of an anaphylactic reaction; acute left ventricular failure due to hypertension and pulmonary edema have not been reported.[4]

The following explanation for this short-lasting hypertensive crisis with resultant pulmonary edema was considered most likely: Sudden boluses of heparin resulted in immunologically mediated lowering of platelets[5] and significant release of serotonin,[6,7] with subsequent hypertension and pulmonary edema. Elevated platelet-associated IgG levels are supportive. Serotonin levels drawn during the episode might have provided the direct proof. The 5-HIAA levels, although at the upper limits of normal, may have been diluted over the next 23 hours. Substantial amounts of 5-hydroxytryptamine (serotonin) are reportedly released from disintegrated platelets.[6,7] This amine usually causes hypotension[8]; both sustained and paroxysmal elevations of blood pressure, however, have been reported.[9] Serotonin also causes pulmonary venous hypertension.[10] Anaphylaxis appears unlikely, as there was no hypotension; furthermore, the patient did not develop such symptoms while receiving continuous drip of heparin or insulin both from the same animal source.

In this patient, pulmonary edema appears to have been related to heparin administration. Development of tachypnea and tachycardia in a patient receiving heparin with no other evidence of recurrent pulmonary embolization should raise one's suspicion to the possibility of this complication.

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