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CLINICAL VIGNETTE

A Double HIT: Anaphylactoid Reactions in the Setting of Heparin-Induced Thrombocytopenia

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Introduction

Severe, life-threatening episodes of heparin-induced anaphylactoid reactions in the setting of heparin-induced thrombocytopenia have been recognized for years. Milder forms of anaphylactoid reactions are likely underreported and may go unrecognized, leading to a delay in diagnosis.

Case Presentation

A 63-year old woman with type 2 diabetes mellitus, hypertension and hyperlipidemia presented to the emergency department for one day of shortness of breath following several weeks of abdominal discomfort, poor appetite, nausea, and vomiting. The patient's home medications included metformin, propranolol, olmesartan, hydrochlorothiazide, and simvastatin. Her initial physical exam was notable for sinus tachycardia to 130 beats per minute, respiratory rate 30 breaths per minute, and mild distress. Initial laboratory studies were notable for platelets 306 $x10^3$/uL, glucose 36 mg/dL, creatinine 10.3 mg/dL, bicarbonate 4 mmol/L, and pH 6.93. She was admitted to the ICU and underwent emergent hemodialysis for acute renal failure and lactic acidosis attributed to metformin use in the setting of dehydration. She was placed on subcutaneous heparin for DVT prophylaxis. She underwent two sessions of hemodialysis with improvement in renal function. On hospital day 3 (HD3) she transferred out of the ICU. On HD5 her temporary dialysis catheter was removed, which was complicated by local bleeding. On HD6 through HD10 she refused most doses of heparin. On HD8 through HD10, she developed worsening short of breath while walking in the hallway.

On HD11 while ambulating she became severely dyspneic with tachycardia to 130 beats per minute, SpO2 in the high 80s, and reported paresthesias in the left leg concerning for pulmonary embolism. She received heparin bolus 60 units/kg IV, and within fifteen minutes developed nausea, flushing, and dry cough with tachycardia to 120 beats per minute, blood pressure 154/101 mmHg, tachypnea to the 30s, and desaturation to 91% on 2L nasal cannula. The heparin drip was stopped and her vitals improved over the next several hours. A CBC drawn several hours after the event was notable for platelet count 60 $x10^3$/uL (**Figure 1)**, an approximately 50% decrease from level that morning of 110 $x10^3$/uL. On HD 12 she underwent VQ scan demonstrating large mismatch defects in the bilateral upper lobes with high probability for pulmonary embolism and was placed on an argatroban drip for anticoagulation. On HD 13 her anti-platelet antibody returned positive with absorbance >3.0 OD. On HD 23 her platelets had improved to 155 $x10^3$/uL and she started warfarin for ongoing anticoagulation.

Discussion

Heparin-induced thrombocytopenia (HIT) occurs due to a humoral immune reaction to the complexes formed between platelet-factor 4 and heparin products.[1] The prevalence of HIT varies depending on patient population and type of heparin used, but is reported as 0.2 – 5%,[2] with risk reported at 2.6% for hospitalized patients receiving unfractionated heparin.[3]

The occurrence of anaphylactoid-type reactions to heparin in association with HIT has been reported in the literature for decades.[3] These reactions are characterized by their rapid onset in the setting of heparin administration with subsequent decrease in platelet count. Patients may experience a variety of symptoms classified as inflammatory, cardiorespiratory, gastrointestinal, and neurologic. Interestingly, hypertension is more characteristic of these reactions than hypotension, as is classically seen with anaphylaxis.[1]

The development of the anaphylactoid-response appears directly related to the IgG antibodies formed against PF4/heparin antibodies. One patient with HIT-associated anaphylactoid reaction had anti-PF4/heparin antibodies detected all of the IgG subclass.[4] Other studies have implicated IgG antibodies in allergic reactions to hirudin,[5]

protamine,[6] dextran, and thiamine.[7] Causal mechanisms have not been definitively demonstrated, though in some cases immune-complex activation of complement through the classical pathway has been theorized.[6,7]

The prevalence of HIT-associated anaphylactoid reactions is unclear, but patients on hemodialysis appear to be at increased risk and presenations have emphasized this danger. In some cases, the prominent symptoms of respiratory distress may mimic pulmonary embolism,[8] in which case ongoing treatment with intravenous heparin may prove devastating. In other reports, the anaphylactoid reaction may lead to cardiopulmonary arrest requiring resuscitation, intubation, ICU admission, and may prove to be fatal.[9,10] Underreporting of less morbid presentations of HIT-associated anaphylactoid reactions makes determination of prevalence inaccurate. More worrisome, in cases such as ours, characterized by milder symptoms of flushing, nausea, and cough, failure to recognize the association between anaphylactoid reaction and HIT could lead to a delay in diagnosis.

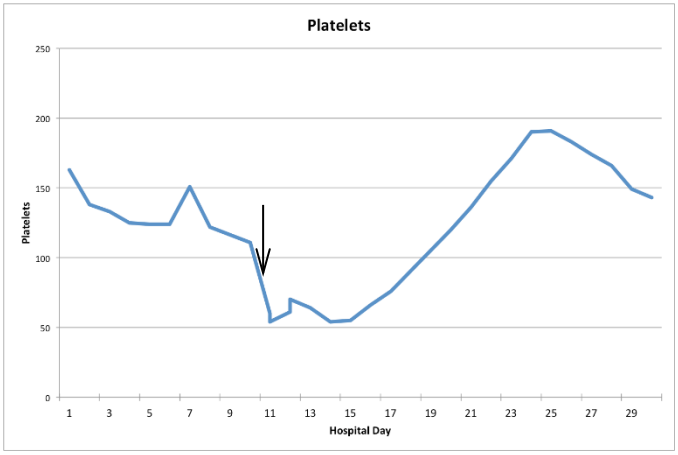

Figure 1. Arrow denotes administration of IV heparin

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