CLINICAL VIGNETTE

Influenza B ARDS Masking New Onset HIT

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Case

A 37-year-old male with newly diagnosed DM and probable OSA presented to the ER with one week of progressive shortness of breath and "flu symptoms" with myalgias, nausea, vomiting and diarrhea. In the ER, the patient was afebrile and hemodynamically stable but found to have PaO2 of 49 mmHg on 8L via nasal cannula. Admission labs were significant for hyponatremia to 131 mmol/L, new AKI with Cr 2.8 mg/dL, WBC 8.2 g/dL, Hgb 15.7 g/dL, Plt 473k/uL, and transaminitis in a hepatocellular pattern (AST 432 ALT 146 ALP 75). His troponin peaked to 0.211 ng/mL and pro-BNP was 259 ng/L. A CXR showed bilateral infiltrates and his nasal swab returned positive for influenza A. Due to escalating oxygen requirements and altered mental status, the patient was admitted to the ICU and intubated. He also received sepsis dose fluids, Ceftriaxone and Azithromycin for CAP and extended duration Oseltamivir. The patient developed a morbiliform drug rash and a unilateral DVT for which he was started on therapeutic Enoxaparin.

The patient was transferred to telemetry status after extubation. He had slow recovery of respiratory function, initially thought to be from lung parenchymal healing after ARDS. However, he continued to have ongoing oxygen requirements, up to 45L/min and 45% FiO2 on high flow nasal cannula, labored dyspnea on exertion, as well as relative tachycardia to the 90-100's refractory to a trial of diuresis. Follow-up EKG showed sinus tachycardia without significant ST deviations, a CT chest showed peribronchovascular opacities and ill-defined solid nodules suggestive of atypical infection. Contrast was deferred due to resolving AKI. Transthoracic echocardiogram showed an EF 55-60% and an elevated right ventricular systolic pressure to 43mmHg, tricuspid regurgitation, and mild dilatation diminished function. Further chart review noted that patient was initially started on prophylactic heparin on admission, and therapeutic lovenox when he was diagnosed with a DVT. This coincided with a gradual dip in his platelets over the course of a week, from 470,000 on admission to 93,000 at its nadir. Hematology was consulted out of concern for heparin-induced thrombocytopenia causing a submassive pulmonary embolus. The patient was discontinued from all heparin products and started on argatroban drip with titration. His coagulation studies were within normal limits, however d-dimer returned positive at 9.83 mcg/mL (>8x ULN), fibrinogen high at 712 mg/dL, and haptoglobin 330 mg/dL, decreasing concern for smoldering DIC. Similarly, the patient was not receiving any clear culprit medications known to cause drug related thrombocytopenias. Ultimately, the patient's bloodwork resulted with a positive Anti-PF4Ab and serotonin release assays. Off heparin products, his platelets recovered to 376k/uL and the patient was weaned off supplemental oxygen. He was discharged in stable condition with Warfarin for an intended 3-month course with outpatient hematology follow-up.

Discussion

Both unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are commonly used for VTE prophylaxis in both medical and surgical hospitalized patients. Rarely, administration of these agents may lead to heparin induced thrombocytopenia (HIT), a syndrome that occurs when heparin-dependent IgG antibodies bind to heparin/platelet factor 4 complexes, leading to a platelet activation cascade and prothrombotic state. Recent literature reported a propensity to over-diagnose and empirically treat for this this condition,[1] with most thrombocytopenias alternatively explained by drug induced thrombocytopenias and other thrombotic states such as malignancies, antiphospholipid syndrome or DIC. HIT most consistently presents with thrombocytopenia 5-14 days after the first initiation of heparin products. However, it is also possible to have rapid onset within the first 24 hours of heparin exposure due to pre-existing HIT antibodies generated from prior heparin exposure. Clinical presentations vary, with some experiencing only thrombocytopenia, while others may have venous or arterial thromboembolic events including DVTs, PEs, strokes or myocardial infarctions. The laboratory diagnosis of this condition is nuanced: HIT antibodies are transient, obtained through heparin/platelet factor 4 particle gel immunoassay and have high false positive rates. One study found up to 50% of patients who had cardiovascular surgery produced HIT antibodies, but only 2% of them actually developed the clinical syndrome.[2] More reliable is the functional serotonin release assay that has both high sensitivity (>95%) and high specificity (>95%).[3] The 2018 clinical practice guidelines from the American Society of Hematology gave a strong recommendation to use the "4Ts score" rather a clinical gestalt approach to determine the pretest probability of HIT, particularly for more time sensitive decision making. The 4Ts score involves a points system with a score of 0-2 given for each of four categories: magnitude of Thrombocytopenia, Timing of onset of decrease in platelet count (or other sequelae of HIT), Thrombosis, and oTher explanation for the decrease in platelet count. A low score (0-3) indicates <1% probability of HIT, an intermediate score (4-5) approximately 10% probability of HIT, and a high

score (6-8) approximately 50% probability of HIT.[4] Patients with moderate-high 4T scores should have all sources of heparin discontinued (including heparin used in flushing lines) and transitioned to non-heparin anticoagulants, with options including direct thrombin inhibitors such as argatroban and bivalirudin. Once platelet levels have recovered, suggesting that ongoing thrombin generation has been halted, treatment should be switched to an alternative anticoagulant such as warfarin or subcutaneous fondaparinux. Patients should be continued on this medication for 1-3 months, depending on whether their HIT was with only laboratory derangements vs. complicated by thrombosis.

Conclusion

Our patient had been started on prophylactic heparin on admission, and transitioned to therapeutic lovenox after discovery of a DVT, presumed provoked and in retrospect an immediate manifestation of HIT. The diagnosis of his subsequent PE was delayed and complicated by recent concomitant influenza ARDS. He had a 4T score of 7, and a platelet nadir at 8 days. He was started on argatroban to replace heparin products, preferable given his renal insufficiency, and both his anti-PF4 antibody and SRA ultimately clinched the diagnosis.

REFERENCES

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