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LETTER TO THE EDITOR

Response to The challenges of diagnosing heparin-induced thrombocytopenia in patients with COVID-19

We thank May et al[1] for their comments, expanding the number of reported cases of suspected and confirmed heparin-induced thrombocytopenia (HIT) associated with coronavirus disease 2019 (COVID-19), and reemphasizing the complexity of the prothrombotic state observed. We agree that false-positive enzyme immunoassay (EIA) detection of anti–platelet factor 4 (PF4)/heparin antibodies could explain the results we observed in patients 2 and 3,[2] and this has been the conventional interpretation when functional testing (such as the serotonin-release assay [SRA]) returns negative. We suggested that a false-negative SRA result *could* have explained our findings, as opposed to the contention by May et al that we concluded they *were* falsely positive, to broaden our discussion about SRA-negative HIT, a relatively new and evolving clinical condition.[3-6]

Though not yet standardized, SRA-negative HIT may be considered when clinical suspicion for HIT is high (4Ts score ≥ 6) with an EIA optical density > 1.00, or intermediate (4Ts score 4 or 5) with an optical density ≥ 2.00,[3,6] especially if the clinical course is highly suggestive of HIT (eg, an appropriate rise in platelet count after stopping heparin or thromboses occurring while receiving heparin). Neither our patient 3 nor the seven patients presented by May et al met these definitions, and we did not perform any of the proposed adaptations of functional testing to confirm SRA-negative HIT, so our contention remains possible, but not confirmed. Testing to confirm SRA-negative HIT might include adding exogenous human PF4,[4] or using a flow cytometry PF4-dependent P-selectin expression assay.[6]

May et al also cite the review by Connors and Levy,[7] which does not mention HIT as a potential contributor to the prothrombotic state associated with COVID-19; we would highlight two additional concerns regarding this otherwise comprehensive review. They propose that inflammation, rather than any specific property of the virus, explains the coagulation abnormalities seen with severe acute respiratory syndrome coronavirus 2.[7] Although inflammation undoubtedly contributes, additional mechanisms must be considered. Cross-reactivity of specific antiviral antibodies with PF4, leading to a catastrophic thrombotic environment, has been proposed (Hillen H, personal communication, June 5, 2020 [hhillens@icloud.com]). This was previously documented during clinical trials with a humanized monoclonal IgG1 antibody for Alzheimer disease (ABT-736), halting its development.[8] If this mechanism is confirmed, supplementing antiviral antibodies with convalescent plasma may have unexpected adverse consequences. Additionally, Connors and Levy propose empiric escalation of heparin to treatment levels when sudden respiratory decompensation, right ventricular strain, or peripheral thrombosis is noted and imaging to test for pulmonary embolism cannot be obtained.[7] If HIT is not considered and excluded in this situation, continuing heparin may have life-threatening consequences.

We agree with May et al that functional platelet assays should be included when assessing for HIT and would modify their proposal with two additional recommendations:

1. HIT must be considered and assessed in patients treated with prophylactic or therapeutic doses of heparin or low-molecular-weight heparin when thrombocytopenia or new thromboses occur.
2. SRA-negative HIT is an uncommon but real entity that should be considered in patients with high clinical suspicion and a negative standard functional assay for HIT.

RELATIONSHIP DISCLOSURE

The authors declare nothing to report.

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