targeted therapies for ped AML will come not only from international collaboration and collaborative clinical studies but also from a better understanding of specific disease mechanisms and characteristics. Preclinical testing, as in the paper of Willier et al, is therefore a valuable and indispensable step in this challenging journey.

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PLATELETS AND THROMBOPOIESIS

Comment on Althaus et al, page 1061

Another front in COVID-19's perfect storm

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In this issue of *Blood*, Althaus et al identify circulating procoagulant platelets as a novel biomarker of COVID-19 disease severity and present provocative in vitro findings demonstrating that antibodies induced in response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can initiate procoagulant platelet formation.[1]

The movie "A Perfect Storm" dramatizes the terrifying and deadly travails of the fishermen of the *Andrea Gail* as they are captured within the confluence of a hurricane and 2 weather fronts off the shore of Massachusetts. By way of analogy, it is becoming increasingly evident that the vasculature in severe COVID-19 is enveloped by a perfect thromboinflammatory storm. Pulmonary micro- and macrothromboses are increased in autopsy studies of patients with COVID-19; D-dimer elevation has been identified as one of the more reliable predictors of disease severity, and anticoagulant therapy is under investigation as a promising therapy in COVID-19. How SARS-CoV-2 induces such an overly exuberant thrombotic response in some patients remains unclear. Multiple prothrombotic events have been proposed as contributing to this thromboinflammatory storm[2]: von Willebrand factor (VWF) is markedly elevated in patients with COVID-19 presumably because of endothelial damage; complement activation is evident in the tissues of patients with COVID-19; platelet activation is increased; fibrinolytic activity is decreased; and neutrophil activation and neutrophil extracellular trap (NET) formation are increased.

Althaus et al investigate the phenotype of circulating platelets in patients with COVID-19. Phenotypic markers of procoagulant platelet formation were increased, including phosphatidylserine externalization, calcium elevation, and mitochondrial depolarization. In linear regression analyses, these markers of procoagulant platelet formation were correlated with D-dimer elevation and thrombocytopenia, sequential organ failure assessment score, thromboembolic complications, and mortality. Heat-inactivated sera and immunoglobulin G (IgG) fractions from patients with severe COVID-19, but not plasma from other patients without COVID in the intensive care unit or healthy subjects, induced procoagulant platelet formation as measured by phosphatidylserine externalization, calcium elevation, caspase activation, and mitochondrial depolarization, all of which were blocked by the inhibitor of FcγRIIA, IV.[3] Antibody-induced procoagulant platelet formation was completely abrogated by the inhibitor of platelet necrosis cyclosporine and partially abrogated by caspase inhibition, indicating potential roles for both apoptotic and necrotic pathways of cell death in the antibody-mediated initiation of procoagulant platelet formation in COVID-19.

Although correlated with disease severity, only a small percentage of circulating platelets in severely ill COVID-19 patients were procoagulant. However, what can be seen in the systemic venous circulation presents only a porthole from which to view the vascular storm swirling within the microvasculature of affected organs, particularly those occurring with the pulmonary circulation. The procoagulant platelet is a potent catalyst for coagulation and driver of neutrophil activation and macroaggregate formation.[3] In murine models of ischemic stroke and organ injury with reperfusion, both local reocclusion and distal vasoocclusive events are propagated via procoagulant platelet formation and the procoagulant platelet's effects on neutrophil activation and NET formation.[4,5] Engagement of platelet FcγRIIA by antibody substantially potentiates procoagulant platelet formation in the presence of thrombin (ie, coagulation).[6] Thus, in COVID-19, one can envision that, within the COVID-19 patient's vasculature, antibody-mediated

procoagulant platelet formation intensifies coagulation; VWF multimers released by damaged endothelium further recruit platelets, and engagement of the innate immune system by virus and by the host's response initiate and intensify the terrifying "perfect storm" of COVID-19.

Intriguingly, the authors find that the quantity of IgG to the spike-protein of SARS-CoV-2 significantly correlates with the patient serum's ability to induce procoagulant platelet formation. In a seeming paradox, stronger antibody response to SARS-CoV-2 and its spike protein has been associated with increased disease severity following SARS-CoV-2 infection.[7] Higher viral load may elicit both more severe disease and a stronger antibody response. Alternatively, the current study suggests that the specific and productive anti–SARS-CoV-2 antibody response may overlap with a dysfunctional antibody response in severe COVID-19. Similar prothrombotic and autoreactive antibodies, including antiphospholipid antibodies and anti-heparin/PF4 antibodies akin to those occurring in heparin-induced thrombocytopenia, have also been associated with severe COVID-19.[8] A robust extrafollicular B-cell response occurs in severe COVID-19, possessing cellular, repertoire, and serological characteristics resembling processes mediating pathogenic autoantibody development in systemic lupus erythematous.[9] In the current study, the precise origin and nature of the procoagulant platelet initiating antibodies are not defined. However, an intriguing hypothesis is that, in severe COVID-19, a dysfunctional and overly robust extrafollicular anti–SARS-CoV-2 B-cell response generates autoreactive and prothrombotic antibodies that, in the context of the local immune response, drive a dysfunctional and autodestructive response within the vasculature. Understanding how these different prothrombotic antibodies are elicited, the association between such antibodies and antiviral immunity, and the distinction between these prothrombotic antibodies and their contribution to disease severity will impact COVID-19 diagnosis and treatment by guiding risk stratification and educating vaccine development based on the nature of the B-cell response produced.

Excitingly, the studies presented here encourage the development of therapeutic approaches in COVID-19 targeting FcγRIIA-mediated–platelet activation and procoagulant platelet formation. Fostamatinib and ibrutinib, US Food and Drug Administration–approved inhibitors of spleen tyrosine kinase and Bruton tyrosine kinase, respectively, limit both FcγRIIA-mediated platelet and B-cell activation and are currently in phase 2/3 studies in COVID-19. How these agents impact the local and systemic thrombotic manifestations of COVID-19 and their impact on bleeding risk in this setting will be of interest. In the setting of increased bleeding risk, targeting procoagulant platelet formation may be particularly beneficial, as procoagulant platelet formation can be specifically abrogated, without inhibiting the platelet aggregatory response or increasing bleeding risk. In this regard, inhibitors of mitochondrial calcium entry and of the mitochondrial permeability transition, among these, cyclosporine, specifically abrogate procoagulant platelet formation without limiting other aspects of platelet activation, including aggregation and granule release.[10] The impact of anticoagulation and classical antiplatelet therapies is the subject of ongoing trials, and the results of these studies are eagerly awaited. Encouragingly, the studies presented here by Althaus et al offer a new beachhead in the scientific community's efforts to mitigate and defeat the thromboinflammatory storm induced by SARS-CoV-2.

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THROMBOSIS AND HEMOSTASIS

Comment on Vollack-Hesse et al, page 1072

Getting under the skin: a new route for factor VIII?

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In this issue of *Blood*, Vollack-Hesse et al present an elegant study demonstrating a possible new path for administering factor VIII (FVIII) via subcutaneous injection.[1]

The past few decades have seen major advances in the treatment of hemophilia, perhaps most notably the advent of gene therapy approaches that have led to sustained expression of both FVIII and FXI in patients with hemophilia A and B, respectively.[2] But the mainstay of hemophilia treatment is still repeated with IV administration of recombinant protein concentrates. Although repeated IV injections are clinically effective, they are not pleasant, they can be particularly challenging in patients with poor vein access, and they are especially difficult for parents who have to inject small children.