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CLINICAL TRIALS AND OBSERVATIONS

Comment on Ji et al, page 1619

Targeting inflammation-induced Kasabach-Merritt phenomenon

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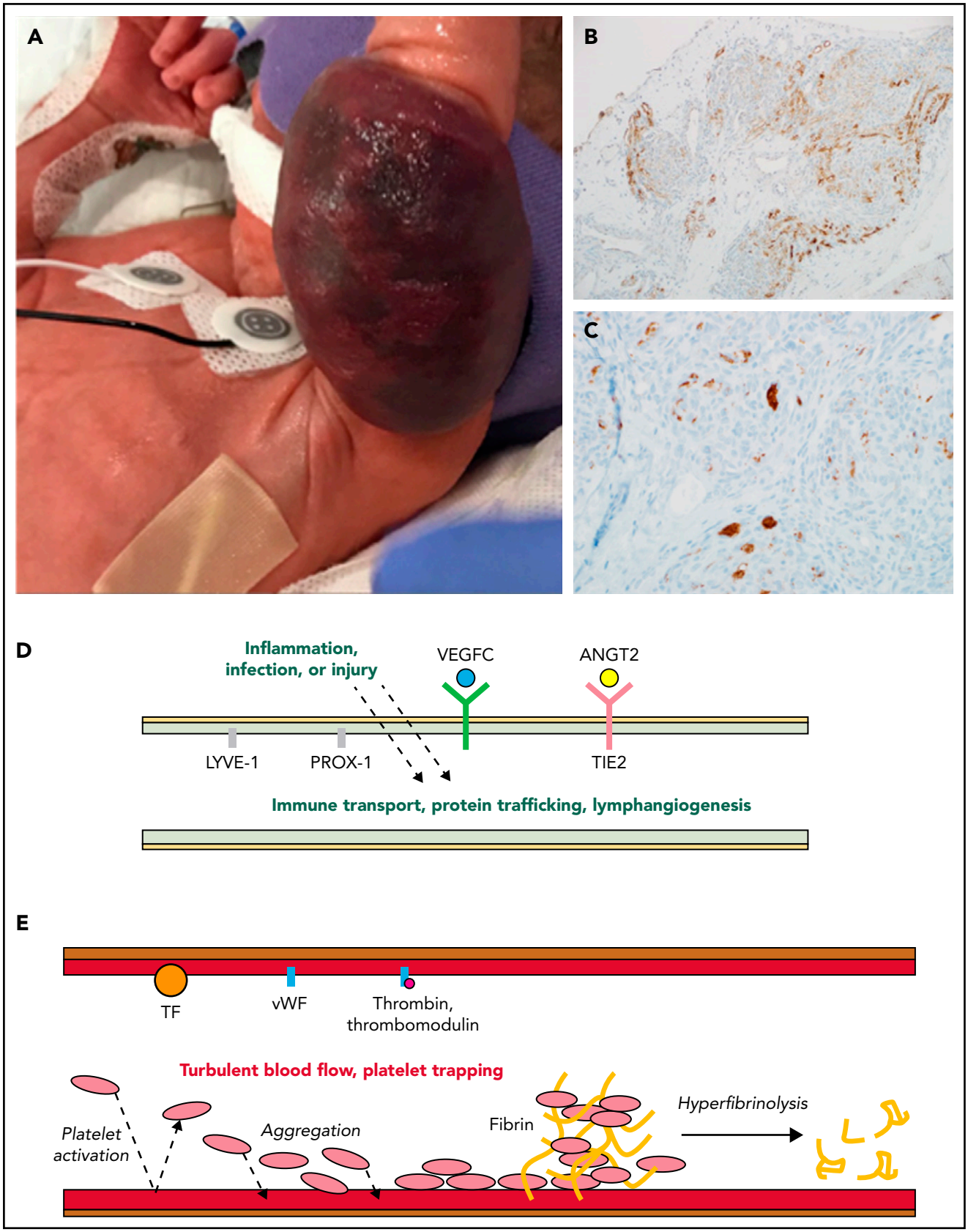
In this issue of *Blood*, Ji et al[1] identified that up-front dual therapy sirolimus plus prednisolone induced faster resolution of life-threatening Kasabach-Merritt phenomenon (KMP) in children with kaposiform hemangioendothelioma (KHE) compared with sirolimus monotherapy.

The investigators successfully completed a large prospective randomized trial on this rare vascular tumor that has captivated hematologists for its vicious infiltrative response to inflammation and its catastrophic intratumoral coagulopathy[2,3] (see figure panel A). Their work highlights an impressive collaboration to standardize and coordinate care for a rare disease among 5 institutions throughout western China. It may help us to better understand the unique relationship between inflammation and KHE tumor pathophysiology, ultimately serving to guide optimal medical therapy.

KHEs are histologically composed of blood vessels and lymphatic channels (characteristically staining D2-40$^+$ or lymphatic vessel endothelial receptor-1 (LYVE-1, and CD34$^+$), and disrupted angiogenesis and lymphangiogenesis are key to the tumor's pathophysiology[2,3] (see figure panels B and D). The lymphatic system is exquisitely sensitive to local and systemic inflammatory triggers, making it interesting to hypothesize how these pathways adapt when lymphatic channels are incorporated throughout a vascular tumor. The vascular endothelial growth factor C (VEGFC)/VEGFR3 and angiopoietin-2/TIE2 endothelial specific receptor tyrosine kinase (TIE2) signaling pathways within lymphatic endothelial cells are critical for regulating angiogenesis, lymphangiogenesis, and vascular stability.[3,4] These endothelial cell signaling pathways are likely to be key in promoting tumor inflammation, invasiveness, and growth.[3] Supporting the evidence for the role of these pathways in KHE pathogenesis are studies showing that prospero homeobox protein 1 (Prox1) overexpression can induce an invasive vascular tumor phenotype in mice, there is increased VEGFR3 expression in KHEs compared with other benign vascular tumors , and high serum levels of angiopoietin-2 are seen in patients with KHE and a decrease in response to therapy.[3]

In response to inflammation, trauma, or infection, KHEs uniquely erupt to aggressively infiltrate into surrounding tissues and entrap the elements of primary hemostasis in a cycle of consumptive hyperfibrinolysis called KMP. Clinically, KMP presents itself as a profound and sustained thrombocytopenia and a consumptive coagulopathy associated with a significant bleeding risk and a high risk for mortality.[2] Platelet trapping within the tumor is known to occur in tumors, both with and without KMP[3] (see figure panel C). Podoplanin expressed on lymphatic endothelial cells may interact with C-type lectin receptors on platelets, contributing to platelet aggregation in the tumor.[3] Endothelial cell damage within abnormal vessels of the tumor, via the exposure of the extracellular matrix, release von Willebrand factor and activated tissue factor.[5] Together, inflammation-induced release of these factors promotes rapid platelet and fibrinogen consumption and an increase in fibrin-split products (D-dimer), tumor expansion, and clinical bleeding (see figure panel E).[5] Intratumoral hemorrhage is certainly part of tumor expansion in patients with severe KMP, but there is also evidence from the oncology literature that platelet-released factors contribute to angiogenesis within the tumor.[6] The primary objective when initiating therapy is rapid resolution of life-threatening KMP and clinical bleeding.

Ji et al take on the problem that determination of optimal first-line therapy has been limited by the lack of prospective randomized trials for this rare tumor. Initial consensus-derived standards of practice were adapted from historic oncologic practices and consisted of dual-therapy vincristine and steroids as first-line therapy for KHE with KMP.[7] However, the first prospective trial on the use of sirolimus in patients with vascular anomalies, including KHE, was published 3 years later and generated much excitement about the efficacy of mTOR inhibition in KHE.[8] Since that time, the use of sirolimus in KHE has been reported in several case series and retrospective studies. Faced with life-threatening hemorrhage, many use a combination of medical therapies, including sirolimus, steroids, vincristine, and antiplatelet agents. The impact of steroids continues to be debated, because they are often thought of as the best and worst immunosuppressive agents in our armamentarium. Wide availability and rapid onset of action make steroids a reliable up-front agent. However, the requirement for steroids as part of therapy for longer-term outcomes has not



Activated lymphatic and capillary vessels in KHE with KMP. (A) Rapid expansion and infiltration of KHE in response to inflammation, infection, or injury. (B) D2-40^{+} histologic stain ×20 view reveals abnormal lymphatic vessels. (C) CD61^{+} histologic stain ×40 view reveals platelet trapping within abnormal capillary vessels. (D) Upregulated and overexpressed signaling from activated abnormal lymphatic endothelium results in increased vessel immune transport, protein trafficking, and lymphangiogenesis. (E) Turbulent blood flow within abnormal capillary vessels results in activated endothelium, consumptive platelet trapping, and hyperfibrinolysis causing KMP. ANGT2, angiopoietin-2; TF, tissue factor; vWF, von Willebrand factor.

been known. In this study, Ji et al demonstrate that up-front steroid therapy improves time to resolution of KMP, as well as durability of platelet response. Overall lesion response was also improved in the group receiving up-front steroids with sirolimus. This effect was seen as far out as 12 months following the initiation of therapy. Importantly, this benefit was seen without an increase in infectious complications, which is 1 of the arguments against steroid use in infants and young children.

Ji et al speculate that the combined neoplastic and inflammatory nature of KHE is best treated with pharmacotherapy that targets both key pathologic features of this vascular tumor. Indeed, there are data from the literature on infantile hemangiomas that corticosteroids suppress VEGF signaling and may suppress other proangiogenic factors.[9] Corticosteroids have also been found to have inhibitory effect on angiopoietin-2 expression in endothelial cells and in other tumor types.[10] It is possible that early blunting of lymphangiogenesis within the tumor prevents rapid tumor expansion and the cycle of inflammation, activation of coagulation, and tumor growth, thus improving near-term and longer-term outcomes.

Inflammation, disrupted vasculogenesis, and severe consumptive coagulopathy are all key to the dangerous pathophysiology and aggressive presentation of KHE. Prospective treatment and risk-stratification studies, such as performed by Ji et al, are needed to better understand this rare tumor and improve patient outcomes, but the lessons learned from such endeavors are not unique to KHE. Identification of the complex mechanisms regulating angiogenesis, lymphangiogenesis, and disrupted coagulation and inflammation at the endothelial cell level are key to improving our understanding of many disease processes and malignancies. As novel therapeutic agents are identified that target these pathways, treatment options for patient with rare tumors like KHE will expand.

Conflict-of-interest disclosure: The authors declare no competing financial interest. ■

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Comment on Min et al, page 1646

Toward consensus on geriatric assessment in AML

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In this issue of *Blood*, Min et al[1] report on the use of geriatric assessment tools to predict toxicity and survival among older adults receiving intensive induction therapy for acute myelogenous leukemia (AML).

Despite the expanding treatment options for AML, outcomes for older adults remain poor.[2] As a group, older adults derive less benefit and experience more toxicity from therapy. As individuals, however, older adults vary greatly in their resilience to the stresses of treatment. Chronologic age alone is insufficient to characterize "fitness" for potentially curative intensive treatment. Reliable criteria that enhance prediction of treatment tolerance and benefit are needed to inform treatment decisions and guide "precision medicine" trial design.

Geriatric assessment is a promising strategy to help define "fitness" and predict resilience.[3] It consistently identifies unrecognized vulnerabilities among older adults with hematologic malignancies and can be performed at the time of AML diagnosis.[4-6] Which specific domains or measures are most important in the context of AML therapy has remained an open question. Answering this question would help with clinical trial design at a global level and at an individual level would help select treatments that optimize benefits and risks for an older adult patient. To date, there is evidence that specific geriatric measures evaluating objective physical functioning (short physical performance battery [SPPB]), cognition, and mood are predictive of survival among older adults receiving intensive AML therapy.[5,7] These observations, however, have not yet been independently validated.[8]

Min et al sought to validate prior observations and provide a standardized set of geriatric assessment measures for use in clinical trials and practice. The authors also extended prior work by evaluating these measures for the prediction of toxicity. Their results validate the importance