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Don’t forget about thrombosis in acute promyelocytic leukemia

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Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML) with an excellent prognosis when treated with all-trans retinoic acid (ATRA) plus arsenic trioxide (ATO)-based therapy. (1) Hower, the disease is notoriously associated with a relatively high early (</= first 30 days after presentation) death rate, particularly in population-based reports where every patient is accounted for. This high early death rate is usually attributable to bleeding, most often intracranial hemorrhage. Bleeding in APL reflects a unique and complex coagulopathy composed of disseminated intravascular coagulation (DIC), fibrinolysis, and proteolysis. (2) Thrombocytopenia accompanying the disease itself as well as its treatment further contributes to the bleeding diathesis. Although much less frequent than bleeding and often unrecognized and overlooked, thromboembolic disease is also a manifestation of the coagulopathy. (3) To provide insights into thrombosis in APL, Rodriguez-Veiga and colleagues examined the incidence, outcome and risk factors for thromboembolic events and developed a scoring system to predict for the occurrence of such episodes. (4)

Using data from the Programa Espanol de Tratamientos en Hematologia (PETHEMA) cooperative group protocols LPA2005 and LPA2012 for patients with newly diagnosed APL, 195 of 1,210 (16%) patients developed thromboembolic disease. The incidences varied by phase of treatment: at diagnosis before ATRA began, during induction and during consolidation when in complete remission. Most events occurred either at diagnosis (4.0%) or during induction (9.3%),

with less frequent occurrences during consolidation therapy (3.2%). Most frequent locations during induction included superficial vein or central catheter in 6.9%, central nervous system in 2.2%, deep vein thrombosis in 2.1%, pulmonary embolism in 2.1%, acute myocardial infarction in 1.6% and in other locations in 1.2%. Importantly, thromboembolic episodes were associated with a high early death rate of 31% compared to 12% among patients who did not develop thromboembolic events. Independent risk factors for the development of life-threatening thromboembolic events included prolonged aPTT, age >40 years, ECOG performance >1, platelet count >25,000/uL, and absence of bleeding at presentation. These investigators then developed the Thrombo-On score to identify patients at high risk of life-threatening thrombosis. The score system assigned 1 point for each risk factor including age older than 40 years, platelet count >25,000/uL, absence of hemorrhage at diagnosis, prolonger aPTT and ECOG performance status >/=2. Risk groups were distributed as follows: low-risk 0 points, intermediate- risk 1-2 points or high-risk 3-5 points with a risk of 1.4%, 4.9% and 23.2%, respectively. Validation was carried out in a cohort of 585 patients treated with either ATRA plus chemotherapy (for high-risk patients) or ATRA plus ATO (for low-risk patients). The early death rate considering all patients was 13.7%. Early death among patients with thromboembolic events was most often caused by thrombosis (18%) followed by hemorrhagic transformation of the thrombosis (4%) then other hemorrhages (2%). The findings of Rodriguez-Veiga and colleagues lead to several questions.

Why examine the role of thromboembolic disease in APL when serious bleeding is essentially universal? Thromboembolic episodes are more common than may be appreciated in this setting. The 16% incidence of thromboembolic events observed by Rodriguez-Viega and coworkers is higher than that found in patients with AML of 12%. (5) Furthermore, the major cause of treatment failure in APL is early death and the development of clotting is associated with early death. Early death in APL occurs most frequently during the first 24-48 hours after presentation. Understandably, very few if any of such patients are enrolled on clinical trials. Enrollment on a trial would facilitate further insights into thromboembolic events and may pave the way for prevention and therapeutic intervention.

Why are patients with APL predisposed to develop thrombosis? Afterall, the disease is infamous for its life-threatening and potentially catastrophic bleeding. This prominent characteristic was recognized by Dr. Leif Hillstad who is credited with the first description of APL as a distinct clinical entity in 1957. (6) Acute promyelocytic leukemia cells are associated with the release of plasminogen activator inhibitor-1, tissue factor and TNFα. These proteins, together with a decrease in thrombomodulin which functions as an anticoagulant by binding to thrombin, favor the balance towards thromboembolic events.[7] (Figure 1) Alternatively, with the generation of annexin II, plasminogen activators, and podoplanin, a transmembrane protein which interacts with (cell lectin superfamily 2) CLEC-2 on platelets to induce platelet aggregation and adhesion to lymphatic vessels, (8) bleeding is much more commonly present. Furthermore, direct

proteolysis of fibrinogen and von Willebrand factor contributes to bleeding. This compilation of processes explains why some patients with APL have bleeding while others have thromboembolic episodes and some have both depending on the balance of procoagulant and anticoagulant proteins. However, bleeding, usually clinically manifested by large ecchymoses on the trunk and extremities, is the major hallmark of the disease.

How can thromboembolic events in APL be prevented? Most important is to maintain a high level of suspicion. The report by Rodriguez-Veiga and coworkers reminds us to be vigilant for the possibility of thromboembolic events in patients with APL. The risk of thrombosis was 1.4% among low-risk patients (presenting WBC</=10,000/uL and platelet count>40,000/uL), 4.9% for intermediate-risk patients (WBC<10,000/uL and platelet count <40,000/uL) and 23.2% among high-risk (presenting WBC>10,000/uL and platelet count<10,000/uL). In contemporary practice low- and intermediate-risk groups are combined since outcomes among these patients proved to be similar. The data presented by Rodriguez-Veiga and colleagues suggest that the Thrombo-On score will identify high-risk patients. In their study, central venous catheter (CVC) together with superficial vein thrombosis were the most common locations during induction. Placement of CVCs disrupts the vessel endothelium and may precipitate thrombosis. Therefore, they should be avoided if possible. Thrombogenic medications such as oral contraceptives and hormone replacement therapy, corticosteroids, sulfa drugs such as Bactrim, and some antiseizure medications should be avoided. Hopefully, future studies of the coagulopathy in APL will contribute to further reduction in bleeding, thrombosis and early death.

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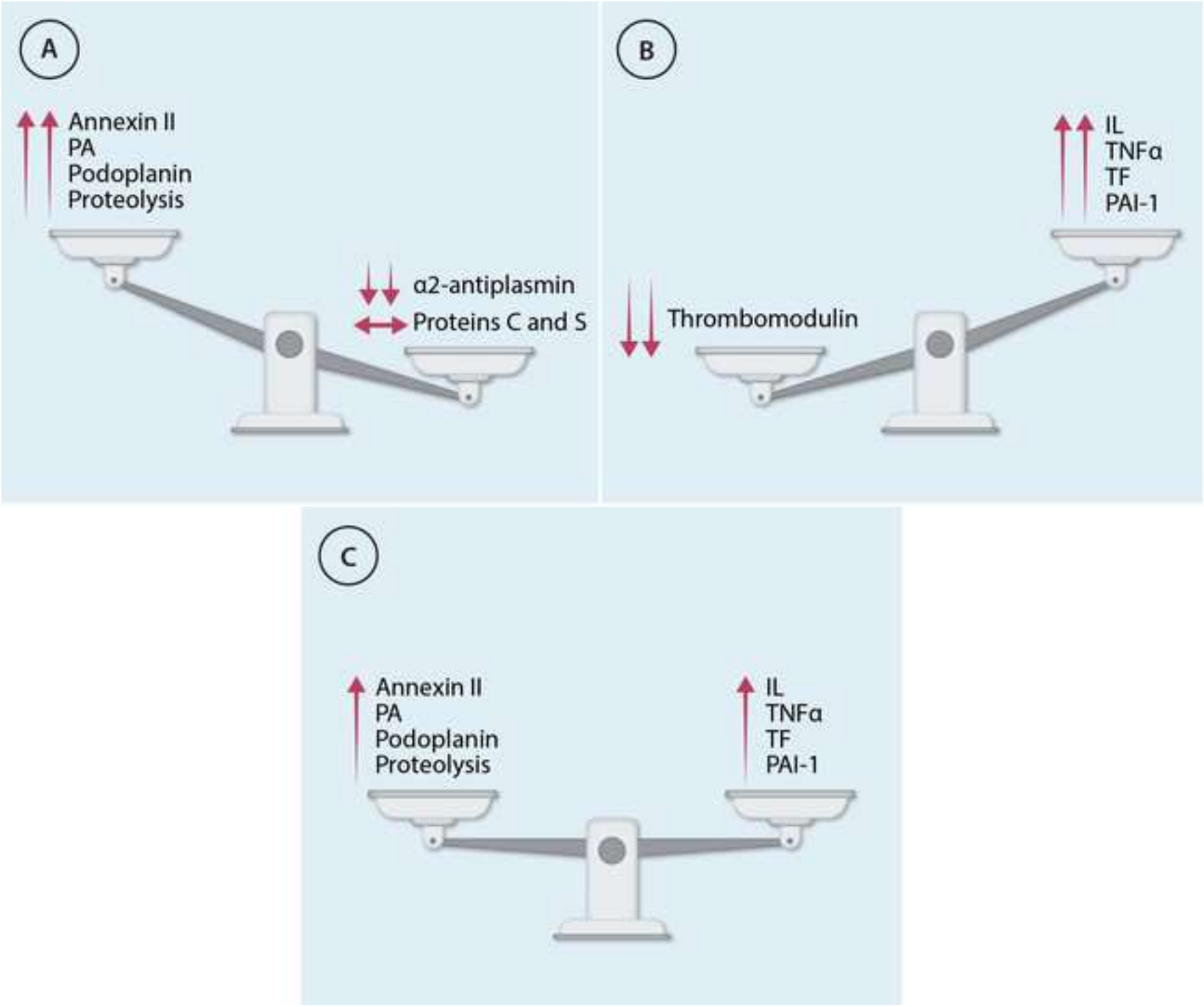
Figure 1 Legend

The dynamic interplay of procoagulant and anticoagulant agents/mechanisms resulting in (A) Hemorrhage, (B) Thrombosis, and (C) Concomitant hemorrhage and thrombosis. IL, Interleukin; PAI-1, Plasminogen Activator Inhibitor-1; TF, Tissue Factor; TNFα, Tissue Necrosis Factor α. From Odetola and Tallman. (7)

Figure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