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CLINICAL TRIALS AND OBSERVATIONS

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Ventricular arrhythmias in sickle cell anemia

Ankit A. Desai | Indiana University School of Medicine

In this issue of *Blood*, d'Humières et al report on the frequency of ventricular arrhythmias in the largest prospective registry of patients with sickle cell anemia (SCA) undergoing 24-hour Holter monitoring along with same-day multimodality cardiopulmonary testing.[1] The authors observed 22% of their cohort experienced ventricular arrhythmias, as defined by European guidelines. Within this subset, 64% exhibited a moderate burden of premature ventricular complexes and 41% presented with nonsustained ventricular tachycardia (VT).

Sudden death is an increasingly reported cause of early death in patients with SCA.[2] It was historically attributed to narcotic overdosing.[3] Grossly reduced left ventricular (LV) systolic function, obstructive coronary artery disease, and cardiac iron deposition are rarely reported in patients and do not seem to contribute to their cardiovascular risk.[4,5] Little, however, is known about possible links between arrhythmic pathologic features to sudden death in SCA, highlighting a poorly characterized and potentially underrecognized health risk for these patients. Although recent work has confirmed increased vulnerability for the development of ventricular arrhythmias in "humanized" sickle mouse models,[6,7] their prevalence in patients with SCA remains unknown. The current work by d'Humières et al begins to close this knowledge gap as their data cumulatively suggest a high prevalence of ventricular arrhythmias in patients with SCA.

Over a series of articles, we with others have reported on the development of sickle cell cardiomyopathy (SCC), characterized by the development of increased cardiac mass and fibrosis,[5] diastolic dysfunction complicated by heart failure with preserved ejection fraction,[4] and prolonged repolarization,[8] characteristics similar to hypertrophic cardiomyopathy (HCM).[5,9] In contrast to HCM, where risk factors for VT and sudden cardiac death are well characterized,[10] origins and risk factors for arrhythmias in SCA remain elusive. More importantly, to begin to address this gap, the current work found that male sex, a low platelet count, and a less negative global longitudinal LV strain percentage significantly increased the risk for ventricular arrhythmias, with trends toward an elevated N-terminal pro-brain natriuretic peptide (NT-pro-BNP) ≥160 ng/L and a lower ratio of peak velocity blood flow from left ventricular relaxation in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave; E/A ratio) on echocardiography. These preliminary data underscore the potential pathologic importance of subtle LV systolic dysfunction and a novel sex disparity in SCA. They emphasize that, although ejection fraction is reportedly normal in most patients, mild forms of LV systolic dysfunction may be more prevalent and associated with proarrhythmic consequences. This implication is further supported by trends with NT-pro-BNP and E/A levels, both markers for cardiac dysfunction as well as for all-cause mortality in SCA. Although inflammation status was not evaluated in the current study, it is a key driver of SCA pathologic features and prior work has suggested interleukin-18, specifically, as a possible biomarker of SCC and VT.[6] Finally, although basic parameters of hemolysis were not associated with the presence of ventricular arrhythmias, the association with lower platelet counts raises questions about the need for additional, larger studies to understand sickle cell–specific determinants of cardiac arrhythmias.

Caution, however, needs to be emphasized when interpreting the results. The current work was limited in several important ways. First, the subjects reflect a biased population of patients, all referred for cardiopulmonary issues within a single institutional cohort. Given the absence of an independent cohort for validation, these data fuel the need for larger observational studies measuring the prevalence in all patients with SCA. They also raise the importance of detecting for arrhythmias across different settings, such as during a vaso-occlusive or hemolytic crisis. Although the average age of the cohort was older, these data remain relevant given the average life expectancy plateaus in the fifth decade. In addition, a significant proportion of patients were on β-blockers and antiarrhythmic drugs, which may confound the "true" prevalence of ventricular arrhythmias.

Critically, the current work was not designed for longitudinal assessment of outcomes, such as cardiovascular-specific mortality. Nonetheless, given the robust association of ventricular arrhythmias to mortality and sudden cardiac death in a spectrum of cardiomyopathies, these data, for the first time, implicate a new and potentially high-risk cardiovascular phenotype in patients with SCA. They also highlight potential deficiencies in our

current approach in management of SCA, suggesting the need for careful cardiac risk factor evaluation in patients.

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Comment on Salmerón-Villalobos et al, page 434

Evolving beyond morphology in pediatric PTLD

Nader Kim El-Mallawany and Kala Y. Kamdar | Baylor College of Medicine

In this issue of *Blood*, Salmerón-Villalobos et al have elucidated the molecular code of monomorphic posttransplant lymphoproliferative disorders (PTLDs) in the pediatric population.[1] Through an integrated molecular approach including fluorescence in situ hybridization, copy number arrays, and targeted gene sequencing, the study establishes the genetic landscape of monomorphic PTLD with diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma (BL) histology. By comparing pediatric cases of PTLD-DLBCL and PTLD-BL to their counterparts occurring as de novo lymphomas in immunocompetent children and PTLD-DLBCL in adults, this study seeks to better understand the translational biology of pediatric monomorphic B-cell PTLD. It addresses a critical gap in knowledge that may enhance our understanding of the classification of PTLD and expected patterns of treatment response.

Children with advanced-stage, monomorphic PTLD with DLBCL histology can present with clinically aggressive disease including multifocal lymphoid masses, diffuse extranodal involvement, and an alarming disease burden on imaging studies. Selection of the optimal treatment regimen for these patients, particularly those with stage III disease, remains a formidable challenge. Some patients like this are cured with gentle therapeutic approaches, such as reduction of immune suppression, rituximab monotherapy, or low-dose chemoimmunotherapy (as reaffirmed within this cohort). Others, though, resemble clinical scenarios akin to de novo pediatric mature B-cell lymphomas and require intensive multiagent chemoimmunotherapy. Such polarizing heterogeneity in pediatric monomorphic PTLD-DLBCL renders it a high-stakes clinical dilemma, especially considering the potential life-threatening and transplant-threatening complications of intensive chemotherapy.

PTLD includes a broad spectrum of lymphoproliferation (see figure) ranging from nondestructive, early lesion PTLD (characterized as polyclonal, reactive B-cell hyperplasia) to polymorphic PTLD (polymorphic, often monoclonal, neoplastic, destructive lesions) to monomorphic and classical Hodgkin lymphoma PTLD (demonstrating transformation to or toward malignant lymphoma).[2] It is challenging to unify such a heterogeneous category of disease processes that are characterized by drastically different clinical patterns, therapeutic approaches, and survival outcomes.

Nondestructive and polymorphic PTLDs are prototypical Epstein-Barr virus (EBV)-driven PTLDs. Such quintessential PTLD in children is conceptually built on a framework in which acquired immune suppression in patients that are often EBV immune-naive creates susceptibility to varying degrees of EBV-driven lymphoproliferation.[3] For such patients, restoration of the immune response and EBV-directed therapeutic strategies are often curative.

Monomorphic PTLD is a problematic category because it encompasses an expansive array of posttransplant lymphoid neoplasia that does not neatly fit this conceptual framework. Some patients with EBV$^+$ PTLD-DLBCL have a favorable response to less intensive therapy such as rituximab and thus belong in the spectrum of quintessential PTLD. In contrast, others have relapsing or refractory disease after standard or even novel EBV-directed or low-dose chemoimmunotherapy strategies. For these latter patients, EBV may represent only one of multiple pathogenic factors driving lymphomagenesis. Such patients, plus many with EBV-negative PTLD-DLBCL, are similar to patients with PTLD-BL—they typically require aggressive multiagent chemotherapy for curative