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HEMATOPOIESIS AND STEM CELLS

Comment on Gutierrez-Rodrigues et al, page 244

VEXAS: walking on the edge of malignancy

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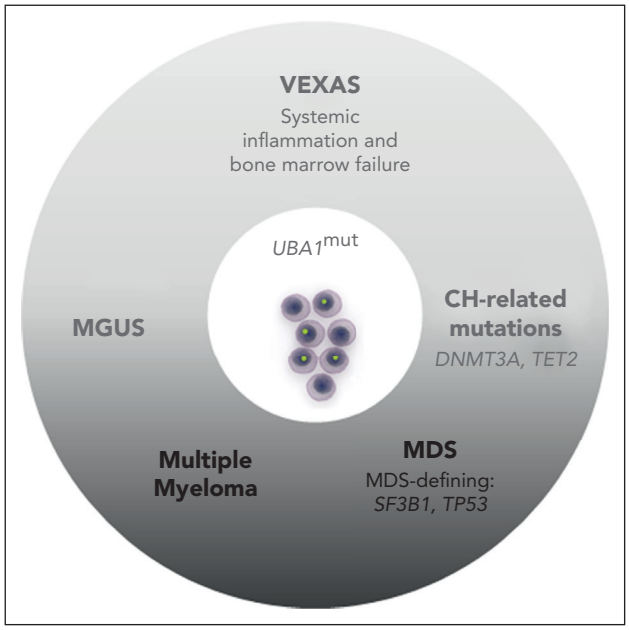
In this issue of *Blood*, Gutierrez-Rodrigues et al analyze a large cohort of 80 patients with VEXAS syndrome for additional somatic mutations. Based on these findings, they reconstruct major patterns of clonal hierarchy and correlate the findings with clinical outcomes.[1]

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a systemic autoinflammatory disease associated with acquired somatic mutations arising in hematopoietic stem/progenitor cells in the gene *UBA1*, an X-linked gene encoding an enzyme involved in ubiquitylation.[2] *UBA1* mutations are propagated in the myeloid lineage and trigger the activation of inflammatory pathways, resulting in severe systemic inflammatory symptoms.[3] Patients with the VEXAS syndrome have a predisposition for hematologic malignancies, including myelodysplastic syndrome (MDS) and plasma cell dyscrasias (see figure). Notably, although MDS has been reported at a high frequency in VEXAS syndrome, most cases are classified as relatively low-risk MDS, while increased blasts and progression to acute myeloid leukemia (AML) has been reported occasionally.

Concomitant somatic mutations in genes within the spectrum of myeloid drivers have been reported occurring with *UBA1* mutation in VEXAS syndrome. However, the true prevalence and the biological and clinical implications of these comutations have not been so far fully elucidated. The study by Gutierrez-Rodrigues et al found typical myeloid mutations cooccurring with *UBA1* mutations in 60% of patients. Notably, approximately half of these patients showed somatic mutations in 2 or more myeloid genes, consistent with an increased propensity to the emergence and expansion of mutant clones. The observed mutations largely involved *DNMT3A* and *TET2*, detectable in approximately 50% of patients, although somatic mutations in classical MDS-associated genes, including *TP53*, *KRAS* and *NRAS*, *SF3B1*, *STAG2*, and *IDH2*, were also observed.

Although the variant allele frequency (VAF) of *UBA1* mutations was almost invariably consistent with being the dominant hematopoietic clone, the VAF of other mutated myeloid genes ranged from 27% for *DNMT3A* to <10%, for *TET2* clearly delimiting divergent clonal hierarchies. Accordingly, single-cell DNA analysis revealed distinct patterns of clonality. *DNMT3A* mutations mainly preceded *UBA1* mutation, consistent with the occurrence of the latter on the background of a *DNMT3A*-driven clonal hematopoiesis. Conversely, *TET2* and other genes mainly occurred as *UBA1* mutation subclones or independent clones. Although hematologic phenotype apparently did not differ between patients with or without additional myeloid mutations, survival was significantly affected by co-occurring mutations and clone metrics. Surprisingly, whereas severe cytopenias (transfusion-dependent anemia and thrombocytopenia) strongly associated with a diagnosis of MDS, additional somatic mutations apparently did not.

The study by Gutierrez-Rodrigues et al sheds light on the spectrum of mutations and their clonal trajectories in patients with VEXAS syndrome. The results further corroborate the association



Spectrum of clonal trajectories of *UBA1* mutant clones. Patients with the VEXAS syndrome have increased risk of MDS and plasma cell dyscrasias (monoclonal gammopathy of undetermined significance [MGUS] and multiple myeloma). Additional somatic mutations in typical drivers of clonal hematopoiesis (*DNMT3A* and *TET2*) and/or other genes enriched/specific for MDS contribute to clonal progression toward overt malignancy. A staging based on conventional clinical parameters (cytopenia and bone marrow dysplasia) is complicated by the inflammatory environment. CH, clonal hematopoiesis.

between inflammatory environment and somatic mutations in myeloid genes, confirming previous findings.[4] Mutations in *TET2* and other myeloid genes appear to occur relatively more frequently than in *DNMT3A* in VEXAS syndrome compared with the clonal hematopoiesis observed in the general population. This finding, together with the analysis of clonal hierarchy, strongly suggests that these mutations occur as second hits preferentially selected in the highly inflammatory environment triggered by *UBA1* mutation. The present study also indicates that there are relevant clinical effects of additional somatic mutations in VEXAS syndrome, although a limited time to follow up and the retrospective design warrant confirmation of the clinical outcomes analysis in larger data sets and prospective studies.

Although this study confirmed the previously reported high prevalence of the evolution of VEXAS syndrome in MDS, the relationship between incidence of additional myeloid mutations, clonal patterns, and diagnosis of MDS still requires both further study and consistent definitions. Establishing a diagnosis of MDS in the context of VEXAS syndrome is extremely challenging using standard diagnostic criteria.[5] In fact, in addition to the characteristic vacuolated myeloid and erythroid cells,[6] *UBA1* mutation and its related inflammatory milieu are associated with changes in bone marrow cells that overlap with dysplastic features, as well as causing cytopenias, thus complicating the diagnosis of MDS. Similar challenges are usually faced when diagnosing MDS in the setting of bone marrow failure syndromes. Indeed, previous studies showed that discriminating between aplastic anemia and hypoplastic MDS relying only on conventional morphologic criteria may not be sufficiently accurate,[7] and the same applies to making a diagnosis of MDS in the setting of a germline predisposition.[5] In these contexts, the pattern of somatic genetic lesions, either cytogenetic abnormalities or gene mutations, has the potential to significantly improve this process. Emergence of del(5q), −7/del(7q), complex karyotype, multihit *TP53* mutations or *SF3B1* mutation are currently considered MDS defining, whereas additional mutation patterns have been reported associated with high positive predictive value and specificity for MDS in the context of unexplained cytopenia.[8] Although additional studies are required to correctly interpret acquired genetic changes in distinct contexts, moving toward a diagnosis of MDS based on specific genetic signatures will be critical to solve these diagnostic challenges and inconsistencies.

VEXAS syndrome is part of the spectrum of clonal diseases without overt malignant features, which also includes paroxysmal nocturnal hemoglobinuria and aplastic anemia with clonal hematopoiesis.[9] The landscape of somatic mutations, recently uncovered in these conditions and ranging from drivers of typical clonal hematopoiesis to mutations enriched in myeloid malignancies,[10] is making the borders between nonmalignant, premalignant, and early malignant conditions extremely subtle. Indeed, a subset of patients with VEXAS syndrome have ineffective hematopoiesis and many have dysplasia in 1 or more marrow lineages, thus meeting some of the minimum criteria for MDS. However, the relative lack of progression to increased blasts or AML appears at this stage as an unmet key criterion for a classification within the spectrum of MDS, although the severe systemic inflammation and complications related to immunosuppressive therapies may represent competing risks for early mortality, thus complicating the use of progression to AML as an endpoint. The study by Gutierrez-Rodrigues et al lays the groundwork for a better understanding of the role of mutations in *DNMT3A*, *TET2*, and other myeloid drivers in the drift of *UBA1* mutant clones toward myeloid malignancy.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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LYMPHOID NEOPLASIA

Comment on Tremblay et al, page 274

Targeting STAT5B in T-cell acute lymphoblastic leukemia

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In this issue of *Blood*, Tremblay et al demonstrate that STAT5B activation drives proliferation, self-renewal, and chemoresistance of leukemia stem cells (LSCs) in an early T-cell precursor acute lymphoblastic leukemia mouse model and explore STAT5B as a direct therapeutic target (see figure).[1]