associated with an increase in specific markers and subtypes of myeloid cells. Along the same line, Lyu et al analyzed data from a large cohort of T-ALL patient-derived samples and observed a worse outcome associated with high monocytes and macrophage signatures.

In light of the multiple challenges encountered in designing an efficient immunotherapy against T-ALL,[10] the work from Lyu et al opens a new chapter of investigation in the T-ALL immune niche, paving the way for mechanistic and clinical studies to further decipher the intimate relationship between T-ALL and the myeloid microenvironment and exploit it for therapeutic benefit.

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

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DOI 10.1182/blood.2020007970

MYELOID NEOPLASIA

Comment on Palomo et al, page 1851

Toward classifying the unclassifiable

Eric Padron | H. Lee Moffitt Cancer Center

For decades, the pathologic classification of myeloid neoplasms has provided the framework necessary to dissect and study a group of diseases that, in many ways, is far more similar than it is different. Myeloid neoplasms are not afforded the clear anatomic boundaries given to solid tumors, and their clinical manifestations overlap significantly. As such, the pathologic demarcations that have been historically set for the diagnosis of these malignancies have been critical to understand the pathophysiology and, more importantly, to identify effective therapies. However, although existing pathologic boxes capture the majority of cases, a significant minority of cases does not fall neatly into 1 category. To address this, the World Health Organization (WHO) includes an "unclassifiable" category to coalesce these entities when cases do not fully meet criteria for bona fide disease subtypes. Unfortunately, the unintended consequence of this is that patients with "unclassifiable" hematologic malignancies often have no approved therapeutic options and do not qualify for clinical trials that are designed for specific diseases. These issues are amplified in patients with so-called overlap syndromes, defined as myelodysplastic /myeloproliferative neoplasms (MDS/MPNs) by the WHO, because they lie at the interphase of pathologically defined myeloid neoplasms and are inherently difficult to classify. Furthermore, the "unclassifiable" subtype of MDS/MPNs, MDS/MPN-U, actually occurs more commonly than most other MDS/MPN diagnosis categories.[1] Given that clinical trials per capita for MDS/MPNs are among the lowest across adult cancers and no therapy has been approved that alters their natural history, strategies to understand and classify MDS/MPN-U are critically needed.

In this issue of *Blood*, Palomo and colleagues describe the use of whole-genome sequencing to establish the mutational spectrum and clonal architecture of MDS/MPNs with the goal of identifying genomic signatures that could reclassify cases pathologically designated as MDS/MPN-U.[2] They profiled a clinically annotated cohort of 367 MDS/MPN patients, including 106 MDS/MPN-U cases and 71 cases of atypical chronic myeloid leukemia (aCML) and MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T), respectively. Although the authors confirm known mutational frequencies and clonal architecture of MDS/MPNs as previously reported,[3-6] they importantly identify or validate genomic signatures that can be readily derived from existing clinical next-generation sequencing (NGS) assays. These signatures were then able to reclassify MDS/MPN-U cases into subtypes resembling other bona fide MDS/MPN entities. For example, cases with biallelic mutations of *TET2* and those with comutation of *SRSF2* with either *TET2* or *RUNX1* were deemed "CMML-like." These MDS/MPN-U cases were clinically similar to pathologically defined chronic myelomonocytic leukemia (CMML) to include a relative increase in monocytes. Clinical similarities were also seen between "MDS/MPN-RS-T-like" and "aCML-like" genomic signatures and their respective disease category. These findings were validated in an external cohort demonstrating reproducibility and applicability to more targeted and clinically relevant NGS. Ultimately, 61% of all MDS/MPN-U cases could be genomically reclassified as another MDS/MPN subtype, whereas the remaining cases were either classified as harboring a *TP53* mutation (13%), a rare event in MDS/MPN, or as genomically ambiguous (26%).

Although the lack of germline controls prohibited a more unbiased assessment of genomic signatures in MDS/MPN, several important observations were made from these data. First, this work adds to mounting evidence that, although genetic assessment cannot fully substitute pathologic diagnosis, clear genotype phenotype relationships exist across MDS/MPNs. Second, it highlights

the importance of evaluating coexisting mutational combinations as they provide unique phenotypic insights that can aid in diagnosis.[7,8] Finally, these data support the growing body of evidence that genomic signatures can reclassify pathologically ambiguous cases into known disease entities.[9] These and other data are giving pause to strict cutoffs for disease diagnosis as exemplified by the recently proposed entity known as "oligomonocytic" CMML.[10] The increasing number of studies establishing the utility of genomic signatures for diagnosis makes a future in which inclusion criteria for MDS/MPN clinical trials may not solely require a WHO-defined pathologic diagnosis but also include genomic signatures similar to those proposed in this paper.

Conflict-of-interest disclosure: E.P. has received research funding from Kura Oncology, Incyte, and Bristol Myers Squibb and an honorarium from Novartis. ■

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DOI 10.1182/blood.2020007157