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Mixed Phenotype Acute Leukemia

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In this issue, Marcondes, Fernandes, and Faulhaber comment on the case study interpretation (CSI) presented by Dr. Chen in the September/October 2013 issue of the journal (1) and raise interesting questions about the diagnostic criteria for mixed phenotype acute leukemia, as presented in the 2008 World Health Organization monograph on the Classification of Tumours of Haematopoietic and Lymphoid Tissues (2), and how those criteria are applied. In the monograph, criteria for T/Myeloid MPAL (mixed phenotype acute leukemia) can be met in one of two ways. The criterion most are familiar with requires the expression of the most specific markers for each lineage—in this case cytoplasmic CD3 and myeloperoxidase. However, less frequently recognized is the fact that expression of these specific markers only applies to the situation in which there is a single population of blasts; criteria for identifying a myeloid component are also met “. . . when there are two or more distinct populations of leukaemic cells, one of which would meet immunophenotypic criteria for acute myeloid leukaemia (with the exception that this population need not comprise 20% of all nucleated cells). . .”

Dr. Chen's case hinges on the interpretation of a small distinct population of cells with a phenotype different from the bulk of the leukemia, with clear-cut myeloid features including expression of CD33, CD34, and myeloperoxidase. Marcondes et al. object to the interpretation of this population for two reasons: (i) Myeloperoxidase (MPO) positive cells account for <10% of cells; and (ii) Dr. Chen has not definitively excluded the possibility that these myeloid cells could be a normal or reactive blast population unrelated to the leukemia. In our view, the first of these arguments is not relevant. Implicit in the second criterion for MPAL above is the fact that the diagnosis of MPAL does not specifically require MPO expression at all, provided that there is a distinct abnormal myeloblast population that can be recognized as part of the leukemia. The WHO specifically and deliberately does not put a lower limit on the number of myeloblasts that must be present to permit a diagnosis of MPAL. This is important, because many cases of MPAL show only a minor component of a second lineage, and following therapy this minor lineage may predominate, giving rise to many cases of what has been considered “lineage switch” in the literature; overlooking these minor leukemic populations may lead to an inappropriate choice of therapy. We are somewhat sympathetic to the point raised by Marcondes et al. that requiring 10% MPO positivity is a “safer” criterion for making a diagnosis of MPAL. When, unlike in this case, MPO is the sole myeloid feature in an otherwise typical acute lymphoblastic leukemia

(ALL), we view small populations of MPO positive cells skeptically, and do not consider them sufficient to establish a diagnosis of MPAL. However, we would reject the use of 10% as a definitive criterion. We do not believe that any percentage threshold is an accurate measure of biology. Nine percent MPO positive myeloblasts with an aberrant phenotype would clearly establish an MPAL diagnosis, while 15% MPO positive normal myeloblasts that could represent an unusual reaction to the lymphoid leukemia would not.

Clearly, however, the smaller the population of myelo-blasts, the more incumbent it is upon the interpreter to be certain that the myeloid blasts in question could not be explained as a non-neoplastic variant. This, essentially, is Marcondes's second concern. Looking at the analysis presented, it appears that the level of CD34 expression on the myeloperoxidase positive cells may be a little brighter than expected, but in the absence of supporting data showing that this is outside the range ever seen in normal in Dr. Chen's assay system, we would not consider this a definitive finding to prove that these are leukemic cells. Without a more convincing demonstration of an aberrant maturational pattern to these myeloblasts, we would have to conclude that while MPAL is a possibility, there are insufficient data presented to establish the diagnosis of MPAL with certainty.

It is worth discussing what this case might represent if not T/Myeloid MPAL. The expression of multiple T cell markers with specific lack of CD8, CD1a and only partial CD5, along with expression of markers such as CD34 and CD117 fit the diagnosis of Early T-precursor (ETP) ALL (3). This entity had not been described at the time of the WHO publication, but available evidence of both its unique biology and very poor outcome will likely justify its inclusion as an entity in forthcoming classifications. A unique feature of ETP ALL, in addition to its phenotype and poor outcome, is that it has many genetic features in common with myeloid leukemias (4). Thus, in the broadest sense, ETP ALL is a kind of "T/myeloid" leukemia. From a definitional perspective, however, MPO expression excludes ETP ALL, while the great majority of cases of MPAL are MPO positive. In addition, the T cell component of T/myeloid leukemia frequently would meet criteria for ETP ALL. Thus, these two leukemias appear more alike than different, although because of the central importance of MPO to labeling something as myeloid, and the way leukemia treatment protocols are structured, they are typically treated differently. Unfortunately, this may make it difficult ever to understand whether these do in fact constitute different leukemic entities. It will be interesting to see how this situation will be treated in the next iteration of the WHO classification.

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