Charting a course through the acute promyelocytic leukemia (APL)-like nebula: the enigmatic cousins of APL

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Acute promyelocytic leukemia (APL) is characterized by a constellation of well-established elements, including distinctive morphology, flow cytometry, and clinical presentation. Nowadays, the definitive diagnosis of APL requires the presence of a unique genetic feature, namely the t(15;17)(q24;q21), and/or the presence of the PML-RARα fusion protein.[1] The management of this special subtype of acute leukemia relies on a unique approach based on differentiation induction therapy using all-*trans* retinoic acid (ATRA) and arsenic trioxide (ATO).[2] This dual-targeted therapy has completely revolutionized outcomes in APL. Consequently, relapse or refractory disease in patients treated with ATRA/ATO is extremely unlikely, and practically nonexistent. The success of the ATRA/ATO approach has launched a search for similar types of acute myeloid leukemia (AML) that may benefit from this treatment.

Based on the distinctive morphological features of APL, this type of leukemia was categorized as M3 in the original French-American-British classification in 1976.[3] It was only 1 year later that Rowley and colleagues reported that most patients with M3 APL share similar abnormalities of chromosome 17, later shown to be t(15;17)(q24;q21).[4] For the last 45 years, the overlap between morphologically and genetically defined APL has been a topic of intense debate and scientific interest. The World Health Organization-mandated requirement for the presence of t(15;17)(q24;q21) or the *PML-RARα* fusion for the diagnosis and definition of APL paved the way for a disease entity called variant APL.[5] Variant APL, sometimes called APL-like disease, has all the morphological features of APL but lacks both t(15;17)(q23;q21) and *PML-RARα*. In most cases, alternative translocations that involve either *RARA* or *RARG* can be identified (Figure 1). The first APL variant was described in 1993 and is defined by the presence of t(11;17)(q23;q21), resulting in a novel fusion gene, *ZBTB16-RARA*.[6] The encoded fusion protein is involved in MLL-induced leukemogenesis and is the most common form of non *PML-RARα* APL. Patients harboring *ZBTB16-RARA* have an unfavorable prognosis and are resistant to ATRA/ATO therapy. In these cases, conventional AML chemotherapy with or without differentiation agents is the most appropriate management approach. Patients with variant APL are less likely to achieve complete remission and have a lower overall survival than those with typical APL.[7] Multiple translocations involving various retinoic acid receptors (RAR) have been frequently reported in variant APL. An extensive list was published by Sanz *et al.* in 2019.[2] The response of these variant APL to ATRA and/or ATO is variable and, to some extent, unpredictable based on the type of genetic event alone.

Lately, gene expression techniques have been used to characterize morphologically defined cases of APL that lack rearrangements involving any of the RAR. Such leukemias were also termed APL-like leukemias but distinctively selected to lack any abnormalities affecting RAR. It is currently unknown whether they represent a unitary type of AML with common molecular pathology, clinical presentation, and, most importantly, response to ATRA/ATO therapy. To date, six case reports have described non-RAR molecular aberrations, with the *MLL* rearrangement being the most cited fusion gene involved.[7] In the current issue of *Haematologica*, Su *et al.* report the gene expression profile of four cases of APL-like disease that lack the classical PML-RARα fusion protein as well as other RAR chimeric transcripts.[8] Using sophisticated genetic tools, including transcriptome sequencing, they identified novel non-RAR chimeric transcripts such as *KSR1-LGALS9*, *GPBP1L1-CCDC17*, *GLYCTK-DNAH1*, *NUP98-HOXD8*, and *CFD-GNA15*.[8] These genetic events are relatively abundant and non-overlapping, which begs the question of whether they are actually "driver" or "passenger" mutations. Some of the described partners, such as *NUP98* and *HOXD8*, have well-established roles in normal hematopoiesis, and it is conceptually possible that their dysregulation leads to abnormal differentiation and hematologic malignancies. Nevertheless, the impact of these molecular events on the pathogenesis of APL-like disease remains to be determined.

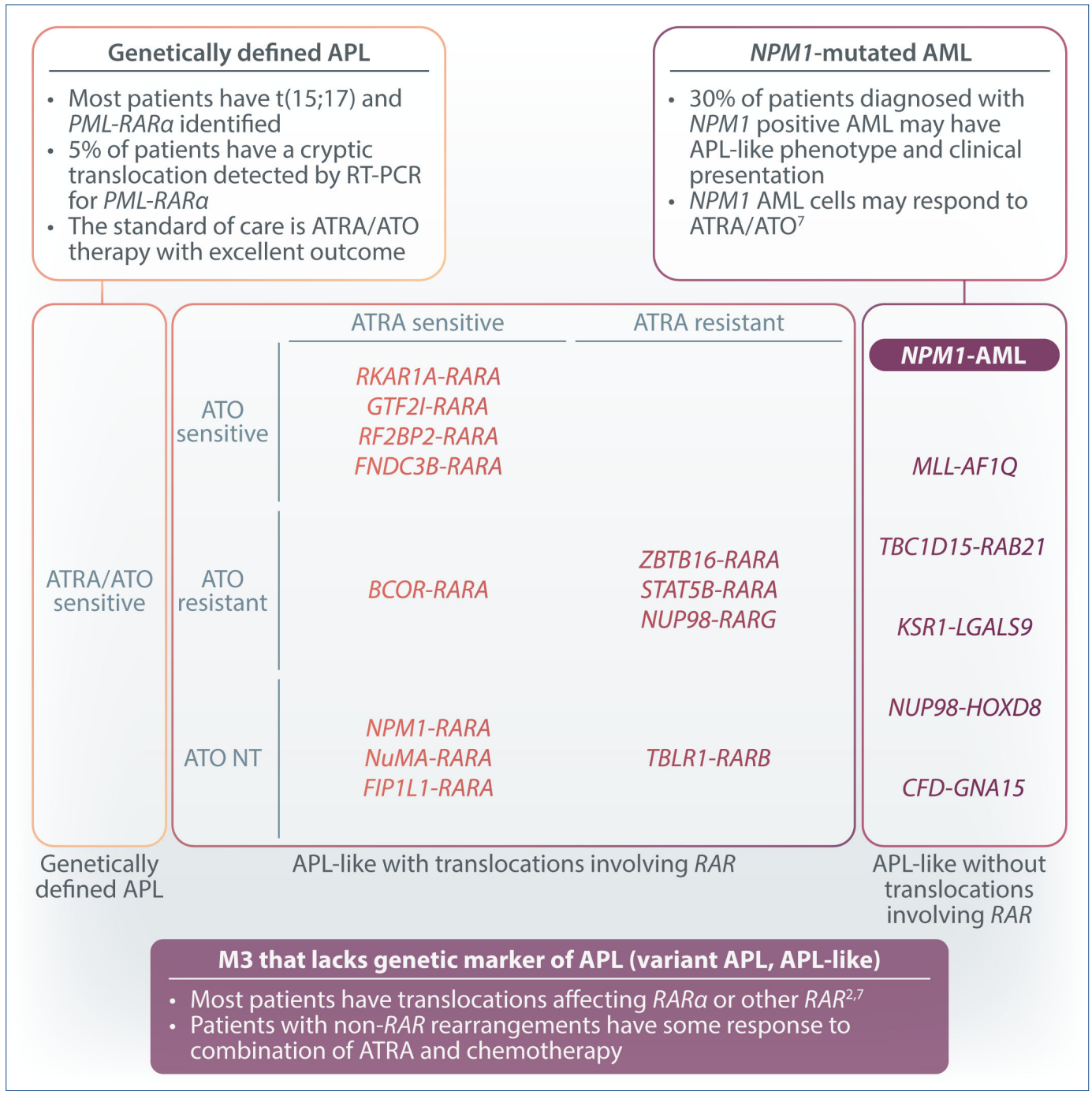

Figure 1. Schematic representation of the genetic features and therapeutic implications of acute promyelocytic leukemia (APL) and APL-like disease. PML: promyelocytic leukemia; RARα: retinoic acid receptor alpha; RT-PCR: reverse transcriptase polymerase chain reaction; ATRA: all-*trans* retinoic acid; ATO: arsenic trioxide; NPM1: nucleophosmin 1; AML: acute myeloid leukemia.

In a previous investigation, five pediatric patients with non-RAR APL-like disease were managed with a combination of ATRA/ATO and standard chemotherapy, and the outcomes were favorable.[9] In the investigation by Su *et al.*, one pediatric patient and three adults were treated with ATRA/ATO plus chemotherapy, with a considerably wide range of survival from 5 weeks to 44 months.[8] Thus, the utility of ATRA/ATO in the treatment of non-RARα APL variants remains unclear.

While the current report by Su *et al.* is a step forward towards a better understanding of the molecular landscape of APL-like disease,[8] further studies are warranted to establish the role of each fusion gene in variant APL development. Studies such as this one represent an opportunity for more precise stratification of APL-like AML and, at the same time, a more appropriate treatment approach.

Gene expression signatures, rather than the presence of discrete molecular events, are more likely to predict clinical behavior in acute leukemia. The best-known data come from the use of gene expression signatures in pre-B-cell acute lymphoblastic leukemia to identify a group of patients who have Philadelphia chromosome-like disease even though they lack the t(9;22).[10] Similar approaches in AML may one day, not too distant, lead to the identification of an APL-like signature that predicts response to ATRA/ATO regardless of the genetic category of the disease. Until then, it is important to clearly define our goals and terminology as we chart our course through future studies of this disease entity.

Disclosures

No conflicts of interest to disclose.

Contributions

AG and GG wrote and edited the manuscript.

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