The hematopathologist's role in the diagnosis of AML

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Welcome to *Managing AML*, I am Dr. Joseph Khoury. I will be discussing acute myeloid leukemia (AML) and diagnostic approaches by hematopathologists in routine practice.

AML is a complex disease and the diagnosis of AML is equally complex. It involves multiple lines of investigation including morphology, flow cytometry, cytogenetics, and molecular diagnostics. The foundation of the diagnosis is based on morphology. Morphology allows us to raise suspicion for acute promyelocytic leukemia or a core-binding factor leukemia, both of which require treatment approaches that are different from other types of acute myeloid leukemias. In addition, we can do special stains to assist morphology. These include cytochemistry, such as myeloperoxidase cytochemistry, which can help further confirm a diagnosis of AML. We can also use morphology to look for signs of myelodysplasia in background hematopoietic elements; and also to look for ring sideroblasts, another feature of myelodysplasia that could be part of an AML picture. Flow cytometry is a very important tool in the assessment of acute myeloid leukemia patients. It allows us to determine the lineage and to determine the expression profile of the leukemic cells, which we also call blasts. Flow cytometry increasingly is also allowing us to identify targets of therapy such as CD33 and CD123. In addition, because minimal residual disease (MRD) assessment at the end of induction is becoming increasingly important in AML, having a baseline immunoprofile with flow cytometry becomes invaluable as we assess for potential MRD at the end of induction. Cytogenetics remains a mainstay of risk-stratifying patients with AML. It is with cytogenetics that we can determine whether the patient has a diploid karyotype or a complex karyotype, or abnormalities that are typically associated with or seen in myelodysplastic syndrome. In addition, cytogenetics is one of the key tools that allows us to detect current cytogenetic abnormalities, such as t(15;17) or t(8;21), which define acute promyelocytic leukemia or one of the core-binding factor leukemias, in addition to inv(16), that again require a different line of management. Of course, there has been an expansion of the use of molecular diagnostics in AML. We have long used molecular diagnostics to assess for *FLT3* and *NPM1* mutations, among a few others, for the past decade or two; but with the advent of next-generation sequencing and the advent of mutation profiling panels, our knowledge of the molecular features of AML and the use of the molecular aspect of AML biology has been increasing. As we look at AML as hematopathologists, we also assess the disease within the appropriate context of the bone marrow microenvironment. We typically assess for reticulin fibrosis and for other features that could raise the possibility of immune deregulation, potentially contributing to a diagnosis of AML. Last but not least, we consider a diagnosis of AML within the appropriate clinical context; and we are always mindful and should be always looking for relevant clinical information such as whether the patient had an antecedent hematologic malignancy like an MPN (myeloproliferative neoplasm) or a known MDS (myelodysplastic syndrome). In addition, it is important to know whether the patient had received

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cytotoxic therapy in the past (i.e., chemotherapy or radiation therapy) for another kind of malignancy, because in those instances, the presence of an acute myeloid leukemia would be regarded as a therapy-related AML; these patients typically have a higher risk of disease. Last but not least, certainly fueled by the advent of NGS (next-generation sequencing), we are increasingly recognizing the presence of some genetic mutations that predispose families to acute leukemia; and thus, a family history in a patient with AML is increasingly important.

In this slide, I would like to share with you the next-generation sequencing-based mutation profiling that we use at our institution to assess patients with myeloid malignancies. The panel includes 81 genes known to be relevant to myeloid malignancy biology. Information gleaned from this panel has multiple uses that include diagnostic, prognostic, and therapy-guiding indications. Mutations in genes such as *TET2*, *ASXL1*, *CALR,* and *CSF3R*, for example, provide valuable diagnostic information. Mutations in genes such as *NPM1*, *TP53*, and *RUNX1* provide valuable prognostic information. Information from mutations on genes such as *JAK2*, *FLT3*, *KIT*, *IDH1*, and *IDH2* increasingly provide very valuable information to guide treatment selection.

I want to thank you for your attention and for viewing this activity.

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