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### When Cancer Looks Like Something Else: How Does Mutational Profiling Inform the Diagnosis of Myelodysplasia?

Announcer:

Welcome to CME on ReachMD. The following CME activity is provided by TOPEC and the Roswell Park Comprehensive Cancer Center through the generous support of BlueCross BlueShield of Western New York.

Dr. Griffiths:

Hi, my name is Elizabeth Griffiths, and I'm one of the leukemia faculty at the Roswell Park Comprehensive Cancer Center in Buffalo, New York. Today I want to talk to you about "When Cancer Looks Like Something Else. How Does Mutational Profiling Inform the Diagnosis of Myelodysplasia?" This first slide is my disclosures and you can review them here.

At the end of today's program, I hope you'll be able to describe what is MDS and why you should care about it, what mutations are associated with myelodysplasia versus those associated with normal aging and be able to distinguish mutations alone from disease myelodysplasia.

What is myelodysplastic syndrome and why should you care? Myelodysplasia is fundamentally a clonal bone marrow failure disorder associated with aging that presents largely with cytopenias, either symptomatic or asymptomatic; low blood counts involving red cells, the white cells, or the platelets. This disease adversely affects quality of life, largely as a result of fatigue, and is associated with decreased overall survival. Therapy, given appropriately, can substantially improve survival for such patients.

So what is clonality? Clonality means that we can in the peripheral blood identify mutations. And these mutations can be in a variety of different genes. So in this slide, we have data from two large cohort studies published back-to-back in the *New England Journal of Medicine* in 2014. In the top two panels, you can see the number of patients presenting with mutations in the peripheral blood in each cohort of age. And what you can appreciate here is that in these people, who did not have a hematologic malignancy, a large percentage of them in their 60s, 70s, 80s, and 90s, had identifiable mutations. Fascinatingly, the spectrum of mutations observed in these older people was the same as those observed in patients with MDS, and involved mutations in genes: DNMT3A, TET2, and ASXL1. So fundamentally, what that means is that mutations alone are not diagnostic of myelodysplastic syndrome.

So historically, we assess clonality in patients with myelodysplasia using cytogenetics. On the top left-hand panel, you can see a metaphase spread from a patient who underwent a bone marrow biopsy. Bone marrow cells are cultured in vitro and then lined up to show us in the karyotype. About 50% of myelodysplastic syndrome patients will have a normal karyotype, and you can see this in the top left-hand corner. A subset of patients will have a readily established clonality, as evidenced by an abnormality of a particular chromosome, such as deletion 5q, or a complex karyotype, as you can see in the bottom left-hand corner.

So, what about symptoms? Unfortunately, the symptoms of these patients are actually very nonspecific. These data, presented here and published by my colleague, Dr. David Steensma, surveyed 359 patients with myelodysplastic syndrome and asked them about what their most frequent symptoms were. And as you can see here, most patients complained of fatigue, some people complained of easy bruising or bleeding, and others complained of night sweats, but these are very nonspecific symptoms and can be seen in a large percentage of patients in clinical practice. The most important risk factor for the diagnosis of myelodysplasia is actually age. Age is the

largest risk factor for the development of myelodysplastic syndrome. And as you can see here, with each increasing decile of age, the frequency of the diagnosis increases.

In order to make the diagnosis of myelodysplastic syndrome, you have to reach some minimal criteria. These include the presence of low blood counts over a period of at least 3 months. Low blood counts in the sense of low hemoglobin, low platelets, or low neutrophils, and these have to be stable for at least 3 months. Simultaneously, you have to have an MDS decisive characteristic and that includes an increase in dysplasia in the bone marrow of greater than 10% of one of the lineages, the presence of a typical karyotypic event, or the presence of increased blasts. These days, we can also use an alternative such as the presence of a FISH abnormality on cytogenetic profiling, or a molecular abnormality, or flow cytometry evidence of the disease. Simultaneously, one must exclude other features which can mimic the diagnosis. Typical things that one might see in practice that mimic the diagnosis of myelodysplasia include a vitamin deficiency such as B12 or folate deficiency. Also, copper deficiency can occur, especially in people who are heavily supplemented with zinc. We can also see dysplasia and low blood counts associated with heavy alcohol use, coexisting infections like HIV or hepatitis, autoimmune conditions, Felty's syndrome is a great example, and other congenital abnormalities or hematologic malignancies which can also mimic myelodysplasia.

In the United States, between 10 and 20,000 people are diagnosed with myelodysplasia every year. Based on statistical data, that means there are 60 to 170,000 people with MDS living in the United States. The median age for this diagnosis is 74 years.

So what causes myelodysplastic syndrome? In a small percentage of cases, the disease is the result of an inherited germline mutational event, that is to say, all the cells in the patient have the disease, or have a mutation, and this mutation is associated with an increased risk of developing hematologic cancer. In a majority of patients, we actually have no inciting risk factors. The only association here is age. Median age at presentation for these patients is 74 years, as I said before. These patients largely have a history of clonal hematopoiesis and, in fact, we have no explanation for why these people develop disease.

So, how do we make this diagnosis? I told you we need to establish clonality. I told you we need to look at dysplasia. How do we do that? In order to make the diagnosis of myelodysplastic syndrome a bone marrow aspirate and biopsy is required. This procedure is performed in the outpatient clinic, usually with local anesthetics. A bone marrow needle is inserted into the bone of the hip, a small amount of blood is aspirated and smeared on a glass slide, and a piece of bone marrow is obtained for further analysis. Looking under the microscope we can see the normal progression from the most primitive cell, which should be present in the bone marrow at a relatively low percentage, usually less than 2% of cells, and then an orderly progression from young myeloid cells, all the way through each of the differentiated myeloid compartments. We should see normal progression down the red cell lineage, normal megakaryocytes, and normal myelocytes and myeloblasts. So myelodysplastic syndrome can seem very intimidating as a word, but when we break it down, it's very simple. "Myelo" means bone marrow. "Dysplastic" means funny-looking. And "syndrome" just means group of symptoms.

One of the reasons I decided to specialize in myelodysplasia is because I love to look under the microscope at the bone marrow. In these slides, one can see typical features associated with the diagnosis of myelodysplastic syndrome on a variety of different bone marrow aspirate specimens. In the top left, you can see a normal neutrophil with hypersegmentation and normal differentiation. In the middle, you can see, by contrast, a neutrophil from a patient with myelodysplastic syndrome. This neutrophil is hypogranular, that is to say the cytoplasm of the cell is pale and the nucleus is dysplastic, that is to say it is bilobed instead of multilobed. On the top right you can see another myelodysplastic syndrome granulocyte, again, hypogranular and hypolobated. In the bottom portion of this slide, you can see a bone marrow aspirate that has been stained for iron. Both of these images demonstrate the presence of ringed sideroblasts. Ring sideroblasts are red blood cell precursors which have accumulation of stainable iron in the mitochondria, and these mitochondria are encircling more than two-thirds of the nucleus of this red cell precursor. This is a definitive feature of dysplasia. And if one sees more than 10% ring sideroblasts in the marrow, this can be strongly associated with the diagnosis of myelodysplastic syndrome. Dysplasia in the megakaryocyte lineage can also be observed in patients with MDS. On the left-hand side of this slide, you can see a relatively normal-looking megakaryocyte, or platelet parent. These cells usually have an even number of nuclei and a nice pink-purple cytoplasm. On the right-hand side, you can see a dysplastic megakaryocyte. This cell has a single nucleus and the cytoplasm is less consistently granulated. The symptoms in myelodysplasia stem from the abnormal clonal stem cells in myelodysplastic syndrome. These abnormal stem cells differentiate abnormally and cause the cytopenias in these patients, resulting in low blood counts and the symptoms of fatigue, easy bruising and bleeding, and an increased risk of infection. They cause the dysplasia we observe when we do a bone marrow aspirate, and these patients have a variable likelihood of progression to the deadly bone marrow disease of acute myeloid leukemia.

Previously, I told you that 50% of patients with myelodysplastic syndrome will have a normal karyotype, historically, our gold standard for documentation of clonality. If we profile patients with a normal karyotype, what we can find is that a majority of these patients will actually have bone marrow mutational events, and the spectrum of mutational events that we observe in these patients with normal

karyotype is actually similar to those observed with normal aging. The most frequently observed mutation in this particular cohort of patients with normal karyotype, was in the gene TET2, followed by the gene SF3B1, ASXL1 and DNMT3A, as observed in normal aging. As a result of the recognition that mutations are associated with the diagnosis of myelodysplasia, but also associated with normal aging, we have changed the way we think about myelodysplastic syndrome, and many of use who treat these diseases regularly have started to look at patients with and without mutations as a spectrum of disease. Historically, when people presented with a low blood count, we would do a bone marrow aspirate and biopsy and if we couldn't identify an obvious mutational event using karyotype, we would follow those patients regularly. And this meant that a percentage of patients who actually did not have myelodysplastic syndrome, and did not have substantial risk of developing myelodysplasia, were followed extensively. Using mutational profilings, what we can now distinguish is a group of patients who actually do not have clonality in the bone marrow, and we call these patients "nonclonal idiopathic cytopenias of undetermined significance." These patients have a relatively low risk of developing any kind of disease process in terms of hematologic malignancy. By contrast now, we can identify a group of patients who have no evidence of dysplasia, who would have clear evidence of a mutational event when we do a bone marrow biopsy. We now think of these patients as being CHIP patients, "clonal hematopoiesis of indeterminate potential." These patients have evidence of clonality without evidence of substantial dysplasia. They have a relatively low risk of developing MDS, but they're certainly at higher risk than those people without clonality.

Moving along, we then have a group of patients who have clonal cytopenias of undetermined significance, associated with a mutational event. These patients, again, have a relatively low risk of disease progression, but we need to follow them a little bit more carefully because their risk of developing MDS is substantially higher.

In the final category, we have people who meet the diagnostic criteria for myelodysplasia in whom we can identify a molecular event. Critically, some of these molecular events can actually help modify disease prognosis and are going to be likely incorporated into new prognostic scoring systems when we think about the diagnosis and the treatment of this disease.

Historically, cytogenetics were used to identify clonality. In 2012, a paper was published documenting cytogenetic abnormalities in more than 2000 people with myelodysplastic syndrome who did not receive any disease-modifying therapy. This cohort of patients identified 5 different risk categorizations for patients with myelodysplasia and clonal cytogenetic events. Using cytogenetics as evidence of clonality, a clinical prognostic scoring system has been developed to identify likelihood of prognosis in newly presenting patients with myelodysplastic syndrome. This revised international prognostic scoring system was published in 2012 and has become the gold standard for prognostication in patients with myelodysplastic syndrome. This score includes: cytogenetic risk category, bone marrow blast percentage, and cytopenias, in order to predict how patients will do. In addition to our clinical prognostic scoring system, mutational events may actually help to predict outcome in our patients. In this publication in 2011, Rafael Bejar published in the *New England Journal of Medicine* that 5 different mutational events involving the gene p53, EZH2, RUNX1, ASXL1 and ETV6 could have a contribution to outcome that was additive when added to the IPSS. Although our clinical scoring system does not currently include mutational profiling for patients with myelodysplasia in order to predict prognosis, our best means of prognostication for an individual patient with myelodysplastic syndrome is the revised International Prognostic Scoring System, but mutational profiling might be able to give us additional information. On the left panel here, you can see a group of patients studied by Rafael Bejar. These patients were distinguished into 5 different risk groups based on clinical features of the IPSS-R. In the left-hand panel, you can see that the mutational profile, described by him in the previous slide, was able to add additional information on top of the IPSS-R to determine prognosis. Mutational profiling can help us to predict clinical outcome. Some mutations, such as SF3B1, can be associated with a better prognosis, while other mutations, or the number of mutations in a particular patient sample, are associated with worse prognosis.

Finally, at the end of this presentation, I hope that I've convinced you that gene mutations and cytogenetic abnormalities are frequent in normal aging. Up to 20% of aging adults will have mutations, but these mutations don't mean that the patient has myelodysplastic syndrome. By contrast, more than 90% of patients with an MDS diagnosis will have a mutation, and these mutations are frequently present at higher numbers and at higher variant allele frequency than patients without MDS. Patients with MDS will usually have 2 to 3 mutations per patient, although the range is quite broad, and the allelic burden of these mutations is usually more than 20% of the total cells. A large number of different genes are mutated in MDS.

Now that we know that mutations are a frequent event in patients with MDS, these mutational events are likely to be used in the future to help inform our clinical prognostic scoring of these patients, and to help determine what therapies are the most appropriate for each patient category.

Thank you for your attention. If you have additional questions, please contact me at [RoswellPark.org](mailto:RoswellPark.org).

Announcer:

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