Determining Risk: What Testing and Genetic Mutations Reveal About Your MPN

Naval G. Daver, MD
Assistant Professor, Department of Leukemia
The University of Texas MD Anderson Cancer Center

Andrew Schorr:
Dr. Daver, let's talk about diagnosis and monitoring for a little bit. So, I mentioned earlier, when I was diagnosed, they looked at my blood. And they could see certain mutations or changes that shouldn't be there. And that led to a diagnosis of myelofibrosis. But you also have bone marrow biopsies. So, could you help us understand how do you know when somebody comes to you whether they have one of these conditions and which condition and how advanced it may be?

Dr. Daver:
Sure. Yeah. So, I think each one of those present little bit differently. So, in patients who have ET or p. vera, they will usually be referred to us because they have elevation in either hemoglobin and/or platelets. And it's important to note that it's not always a uni-model meaning that ET patients may not always have just high platelets. They may also have high platelets and high hemoglobin. And the same is true for P Vera where they may present with a high hemoglobin hematocrit but also may have elevated platelets. So, the most common referral we will get is a person who is seen by his community doctor.

Maybe he started having fatigue, weakness, abdominal distension, or maybe it was just a routine bloodwork for work related, insurance related things. And they say, "Well, the hemoglobin came out at 17. We're concerned about this. Let's go to a tertiary center." And they will come to Colorado or MD Anderson. Same thing with ET. They will say, "Platelets are at seven, eight hundred. We don't find any clear reason why that should happen. So, let's refer you.

So, the first thing we do in these patients is rule out what we call secondary erythrocytosis which means a secondary elevation of your hemoglobin. So, there are conditions that we know for example, people who have COPD, lung diseases, heavy smokers, marathon runners who have a physiological increase in hemoglobin to keep up with the decreased oxygen diffusion from the underlaying lung condition or because they're doing marathons, etcetera. And we will rule that out by a good history. So, you talk to them, you get that idea. If you don't find that clear association, then we will say the next thing to do is look at two things. One is molecular mutations.

And the three most common mutations that we look for either on blood or bone marrow are JAK2 which is the most common mutation seen in 97 percent of PV and about 50 percent of ET. And the second one is CALR called calreticulin which is seen in about 20 percent of ET and very uncommon in PV. So, with these mutations, in the PV cases, we almost 100 percent can diagnose in 97 percent plus two percent MPL or other mutations. And in ET, about 70 percent will have that.

Andrew Schorr:
All right. Let me just explain. Okay. You be the professor. So, a mutation. So, okay. So, we have genes that we're born with. Do we have blue eyes or brown eyes or dark skin or light skin or eventually no hair? And then we have other kinds of cancer genes that develop where the cells go a little haywire. And that's what you're talking about is is there the JAK2 gene

that starts showing up where it shouldn't or the—you even mentioned a new one that many people have here, MPL or calreticulin. And does that then correlate with one of these diagnoses?

Dr. Daver:
Right. So, normally, we should not have mutations in those genes. So we have the genes, but there's actually a point in the gene that is looking abnormal from how it should look in a normal person. So, that's the mutation where your gene is now abnormal. And we can pick those up…

Andrew Schorr:
…from the blood test?

Dr. Daver:
Quite easily now from blood tests, right. So if we find those mutations in the right clinical scenario—and that's important because rarely, these mutations can be seen in people without disease. This is something that's new emerging. But if we have a clinical patient with high hemoglobin, with high platelets, with the mutation, that helps you confirm the diagnosis.

Andrew Schorr:
Why, Dr. Daver, do you ask sometimes for a bone marrow biopsy? What's the point?

Dr. Daver:
So, usually, the reason we do a bone marrow biopsy is because in spite of having clinical symptoms and being able to check the mutations on blood, one is really to confirm the diagnosis and then to know which of these conditions it is, PV, ET, myelofibrosis. Only a pathologist looking at a bone marrow can tell you that. So, you could have a patient with myelofibrosis, PV, ET who could have high platelets, high hemoglobin. But the treatment is quite different for these conditions. So, to confirm and differentiate between these three very accurately, you need a bone marrow.

The second thing is in some cases, we see that even at presentation, patients are already progressing to what we would consider high risk myelofibrosis or progressive myelofibrosis. And those are people who need more early and more aggressive treatment either with Jakafi or even with combinations of Jakafi with other agents. And so, we don't wanna miss that and delay treatment. And so, those are two main reasons we do a bone marrow biopsy.

Andrew Schorr:
Okay. And also, we talked about scarring in the bone marrow. So, the bone marrow biopsy can also tell you the percentage of scarring.

Dr. Daver:
Correct. The percentage of scarring. Yes.