AA·MDS
INTERNATIONAL FOUNDATION

MDS Update

Connecting Patients and Families with News and Expert Opinion

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Inherited Genetic Mutations and Myeloid Diseases

Q What is known about the relationship of genetic mutations with MDS and related myeloid diseases?

A There is increasing recognition that some cases of myeloid malignancies are caused by inherited or familial mutations (changes in the DNA sequence). The inherited mutations that can predispose to MDS are a large group – and within this group are those that can lead to aplastic anemia as well as others. MDS is a very heterogeneous disease with many subtypes, including hypoplastic MDS which mimics aplastic anemia.

A particular genetic mutation can present in different ways in the same family. As we study more cases of inherited MDS and other myeloid malignancies in families, we are seeing a broader spectrum of conditions resulting from the exact same mutation. The inherited mutation within a family does not define, at a molecular level, the malignancy that may develop in the future—that is to say, that individuals who have the same inherited mutation can develop different types of bone marrow malignancies. It's easy to think that if everyone in the same family inherits the same mutation they will all get the exact same disease, but it doesn't always happen this way.

Equally important, we want to know if there is a way to figure out who is likely to develop a malignancy over time. We want to learn if we can detect in advance if they are on a path to developing one of these diseases before it actually happens. Very little is understood now about additional genetic factors that alter the presentation of the diseases—affecting which diseases may occur, when they occur, and whether environmental factors also play a part. It's truly an open question—what makes a person with a particular genetic mutation go on to get MDS or acute leukemia—or sometimes nothing at all? We're very interested the progression of events from the inheritance of a mutation to the point where a myeloid disease is certain to occur.

These inherited conditions often show what we call 'anticipation', meaning that as the mutation is passed from generation to generation, the disease presents earlier with each generation. As the mutation is passed along, younger and younger family members are affected. It's harder to identify in the grandparent generation because the disease presents later.

Q What should hematologists and oncologists keep in mind about inherited mutations when evaluating a patient for MDS and related diseases?

A It can be difficult for doctors to think about inherited mutations for a few reasons:

- First, there is a bias that if someone has a familial mutation, s/he will present with MDS earlier in life than the average—which is 71 years old. But we have many examples of people who develop MDS in their 60's or 70's who have an inherited mutation.

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Dr. Godley earned her Ph.D. at the University of California, San Francisco, and her M.D. at Northwestern University School of Medicine. She conducted her internal Medicine residency and Hematology/Oncology fellowship at the University of Chicago, where she has remained on the faculty.

She is an active researcher on the molecular basis of bone marrow malignancies.

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When the patient knows of hematologic diseases that have occurred in present or past family members, they should be sure their doctor is aware of this. Sometimes doctors won't think to ask about the family history. We're always trying to bring attention to the need for patients to bring up family history with their doctor.

- Second, acute myeloid leukemia (AML) is different from other diseases because it can present in a very dramatic and life-threatening way that can't be ignored. Even for younger patients, doctors have to focus so much on treating the immediate AML, that there won't be any time spent on trying to determine whether the disease is an inherited or acquired form. Initially, the treatment is the same regardless of how the disease originated. However, while a clinical team provides the treatment, there can be a separate team that works with the patient to obtain information on the family history. So the treatment and information gathering duties can be divided in this fashion, and a more complete family history is obtained this way. Sometimes, this approach reveals information that suggests that the disease is an inherited one.
- Third, depending on the genetic mutation, some effects can be observed prior to a definitive diagnosis. For example, some of the predisposition syndromes that confer an increased risk for myeloid malignancies can first present with a low platelet count, but it's often quite mild –even close to normal and thus be overlooked. It's important for hematologists and oncologists to keep this in mind.

  It is important for doctors to recognize an inherited basis of diseases, since we use allogeneic stem cell transplants as an important tool in the treatment plans for our patients. The preferred donor is usually a relative, but a relative could have the same mutation as the patient, and using such stem cells could nullify the advantages of treatment by transplantation.

  But awareness isn't enough. Patients need access to testing for inherited mutations and only recently are recommendations being set by major cancer research and policy groups, including NCCN, that include testing for inherited mutations. Also, we need this testing to be covered by insurance.

Q What should patients remember about inherited MDS?

A They need to know first that, although rare, genetic mutations can cause malignancies of the bone marrow.

These patients need to be identified through increased screening, especially when allogeneic stem cell transplant is being considered as a potentially curative therapy. If someone has MDS with an inherited basis, simply going into remission with chemotherapy may not be sufficient for control of the disease, since the gene mutation is still present. Allogeneic stem cell transplant can be curative, but the donor should be chosen carefully, using a donor who lacks the family mutation.

To summarize, we want to find out when a person presents with a myeloid disease, how often it is because of an inherited mutation. With MDS diagnosed usually in the early 70s, we want to know why a 40 year old person gets the disease at all. When young people get MDS, it's logical to suspect a genetic connection. This is not to say genetics aren't involved in older people, but it is really obvious that younger people shouldn't be getting MDS! There's a large research effort trying to answer this and related questions.

Greetings to our MarrowStrong Community!

Throughout the summer, we have had numerous neighborhood walks, runs, barbeques and other activities to raise awareness and funds for bone marrow failure disease.

Thank you for your generous support of all of our community events!

Did you know that individual gifts like yours help more than 10,000 patients and families annually, including almost 5,000 newly diagnosed patients?

Please support AAMDSIF today and throughout the year as generously as you can.

We envision a day when bone marrow failure is a benign diagnosis and manageable disease.

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PATIENT STORY

Alaska Resident Returns to North Carolina for Treatment, Family, and a New Career

Shauna McMillan

I am 40 years old and have recently been diagnosed with a rare type of MDS having an unusual deletion 12q cytogenetic abnormality, known MDS 12q (-), or MDS 12q minus. I was diagnosed in February of 2015 at age 38, however, my health struggles began several years before that.

I had been living in Alaska for nearly twenty-five years. In 2008, I was diagnosed with lymphocytic colitis (also a rare disease for someone of my age). I was referred to a hematologist for the first of many visits because of low blood counts. After multiple visits and many tests, no cause was identified.

In January of 2014, I began having issues with my gallbladder. One night I went to the emergency room. There, a CBC was ordered along with many other tests and to the amazement of the ER staff, it showed a hemoglobin of 4.3. Before I could leave the ER, I received two units of blood. They refused to treat my gallbladder (even though I was in great pain) until I received an approval from a hematologist. From that referral, I was required to have multiple weekly tests, blood transfusions and had my first bone marrow biopsy (BMB).

By July of 2014, my hematologist could not figure out what was happening and finally agreed to sign off on the gallbladder removal surgery with certain precautions to be taken. After the operation, he wanted me to continue having blood transfusions every 6 to 12 weeks depending on my numbers. A month later, my gallbladder was removed. However, I was not satisfied with being told I was going to need the transfusions for the rest of my life without an explanation of why. This simply was not acceptable to me because I knew something was wrong.

In October of 2014, I decided I wanted a second opinion. I began seeing a physician's assistant (PA) and she referred me to a gastroenterologist. I had tests that were looking for internal bleeding. By January of 2015, again nothing had been found.

My PA gathered all of my medical records for the last 10 years and sent them to the best oncologist in Alaska for review. After this review, it was recommended that I have another BMB. Again, the preliminary findings from this found nothing wrong in my bone marrow. The samples from the biopsy were then sent for additional evaluation sent to the Fred Hutchinson Cancer Center in Seattle.

In the meantime, I made the difficult decision to relocate to North Carolina. A week before leaving Alaska, I got a phone call from the oncologist. It had been determined I had a rare form of MDS and they wanted to send me to Fred Hutchinson for treatment. I told them that I preferred a referral to a doctor in North Carolina because I had a support system there.

Shauna with (left to right)her parents Roy and Melvin, daughter Jolynda, granddaughter Anastasia and son-in-law Ben.

My first appointment with my new doctor in North Carolina took place March of 2015. This first appointment was also when my treatments began. I was placed on lenalidomide (Revlimid®) injections for 12 weeks at which point it was determined this treatment was not working. In August of 2015, I was put on cyclosporine, which helped improve my blood counts. A year later in August of 2016, the cyclosporine had become less effective and I was taken off this drug to see how I would respond. Two months later, I took a turn for the worse and was placed back on the cyclosporine.

In February of 2017, I was admitted to the hospital and given ATG treatment along with cyclosporine. Unfortunately the ATG treatment has been ineffective as of this time, and I am still receiving blood transfusions about every 6 weeks.

As therapy for myself and to help my self-esteem, I became a fashion model, something I have been passionate about for several years. I am pleased to announce that I was selected to run for Ms. Full-Figured North Carolina 2017 this October. I knew upon my selection there was no doubt that my platform would be to bring awareness to MDS.

My advice to those with MDS is never give up. When you stop fighting, that's when you allow this disease to win. My faith in God has given me the strength to live every day to the fullest.

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Connecting is Strength

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