AA·MDS
INTERNATIONAL FOUNDATION

MDS Update

Connecting Patients and Families with News and Expert Opinion

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INTERVIEWS WITH THE EXPERTS

Meet the Hematopathologist: A behind-the-scenes consultant in an MDS diagnosis

What are some of the tests used on bone marrow samples that help diagnose MDS? Does each test have a different role in determining a diagnosis?

The diagnosis of MDS typically involves a complex integration of multiple sources of information obtained from the clinical history, blood counts, peripheral blood smear, bone marrow aspirate (liquid) and core biopsy (solid), immunohistochemistry, flow cytometry, cytogenetic analysis, molecular testing and additional ancillary testing. The role of the hematopathologist is to evaluate the bone marrow and peripheral blood specimens, to make sure all of the required tests for diagnosis are performed, to obtain relevant clinical history, and to ideally integrate the information into a final diagnosis.

There are many other conditions that can mimic MDS, and the hematopathologist must make sure that all of the other possible disorders are excluded before a diagnosis of MDS is rendered. Direct communication between the hematopathologist and the hematologist or oncologist is critical in this process.

When we look at the bone marrow preparations under the microscope, we usually review the blood counts in the peripheral blood first to determine which cell lines (e.g. red cells, neutrophils, platelets) are reduced. This guides our examination of the bone marrow. Microscopically, we assess:

- **Cellularity** – Bone marrow cellularity is assessed on the core biopsy, and is a measure of the overall number of cells being produced by the bone marrow. In most forms of MDS, the marrow appears hypercellular, meaning that too many cells are being produced. However, their production is ineffective in MDS, as the cell counts are not adequate in the peripheral blood. Some forms of MDS are hypocellular, reflecting marked underproduction of blood cells.

- **Trilineage hematopoiesis** – We determine the level of production of each of the three major cell lineages in the bone marrow. For example, we determine whether red cell precursors [the cells that make red blood cells (RBCs)], myeloid precursors (the cells that make neutrophils), and megakaryocytes (the cells that make platelets) are over-produced (hyperplasia) or under-produced (hypoplasia).

Katherine R. Calvo, MD, PhD

Dr. Katherine Calvo is a hematopathologist at the National Institutes of Health Clinical Center in Bethesda, Maryland. She attended medical school at the University of California, San Diego where she earned MD and PhD degrees. In 2003, she began residency training at the National Cancer Institute at NIH in anatomic pathology, with subsequent subspecialty training in hematopathology. Dr. Calvo joined the Hematology Laboratory in the Department of Laboratory Medicine in the Clinical Center in 2008 where she plays an active role in diagnosis of hematologic diseases, teaching hematology and hematopathology fellows, and conducts research related to bone marrow failure.

In this two-part interview, Dr. Calvo speaks about the laboratory tests and evaluation of bone marrow biopsies used to make a diagnosis of MDS, and further determine its subtype and possible prognosis.

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- **Cell morphology and lineage maturation** – For each major cell lineage, the early immature or precursor cells divide and undergo maturation in the bone marrow, giving rise to mature cells (neutrophils, RBCs, and platelets) that are released into the peripheral blood. Each cell lineage has a normal appearance or morphology for the stages of maturation that can be visually assessed by the hematopathologist or hematologist on the bone marrow aspirate smear seen under the microscope. In MDS, cells become "dysplastic" and have abnormal features in the nucleus and in the cytoplasm in comparison to normal healthy cells.

- **Blast count** – Blasts are very immature cells that normally differentiate or mature, that is, give rise to precursors that generate normal blood cells. Blasts are often thought of as the "bad" cells in MDS if they become too numerous. We count the number of blasts on the aspirate smear to determine if they are elevated. We can also use immunohistochemistry on the core biopsy to help assess the number of blasts present.

Ancillary testing is often critical to confirm an MDS diagnosis, including the following types of tests:

- **Immunohistochemistry** – allows us to stain bone marrow tissue with antibodies against specific cell markers to help determine their representation in the marrow.

- **Flow Cytometry** – Flow cytometry (FC) is a technology that allows us to analyze all of the different cells in bone marrow aspirate or peripheral blood simultaneously. By using antibodies that recognize specific proteins on the surface of different cell types, we can determine the number of each cell type, and often whether or not the cells are abnormal or malignant. Flow cytometry can be helpful in MDS for determining if cells are dysplastic.

- **Cytogenetic analysis** – Normal cells have 46 chromosomes that can be evaluated by the cytogeneticist. In over 50% of MDS cases there are recurrent cytogenetic abnormalities that can be detected and are very helpful in MDS diagnosis, prognosis, and monitoring of disease over time. Presence of specific cytogenetic abnormalities can support or confirm the diagnosis of MDS.

- **Fluorescence in situ hybridization (FISH)** – This is similar to cytogenetic analysis in that it is designed to detect cytogenetic abnormalities including translocations, or loss or gains of whole or portions of chromosomes with use of specific probes. The advantage of FISH is that the cells do not have to be dividing although it only detects predetermined targets.

- **Molecular testing** – One of the newest tests being performed in MDS involves next generation sequencing using targeted sequencing panels to evaluate for mutations in genes commonly mutated in MDS. As time goes on, gene sequencing is anticipated to play a greater role in MDS diagnostics and classification. One of the confounding issues regarding the interpretation of targeted sequencing results involves the presence of the same mutations in normal healthy aging population. Typically, the frequency of mutations is higher in MDS than in the normal aging population, but more data are needed to better define the role of gene sequencing in MDS for diagnosis.

In the next issue of MDS Update, Dr. Calvo speaks about examination of liquid and solid bone marrow samples, and how subtypes of MDS are determined.

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STORY OF HOPE

San Diego Family Takes **Action for Awareness**

Amy Ohton speaks about her husband's MDS and her son's initiative to hold a swabbing drive

My husband David's journey with MDS began in April 2014, when it was discovered almost by chance while we were on vacation. David was bitten by a brown recluse spider and had a very severe reaction to it. He had to be hospitalized, which is when he got his first blood test in years. The doctor noted that his blood counts were low and, while he didn't rule out that the spider bite might have affected the counts, there was a possibility of myelodysplasia.

It was a ten-day hospitalization, during which he was also under the care of a rheumatologist because his joints were severely affected by the spider venom. When David's blood counts did not improve, the doctor was certain there were other factors involved so she referred us to a hematologist at the Moores Cancer Center at University of California, San Diego. They did a bone marrow biopsy, which led to the official diagnosis of intermediate MDS, as defined by the revised International Prognostic Scoring System, also known as IPSS-R. David was only 52 at the time, younger than the average age of newly diagnosed patients.

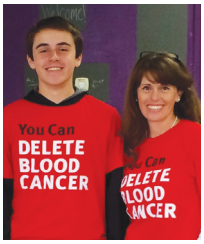
Next, the hematologist explained the three FDA approved drugs, azacitidine, decitabine, and lenalidomide – noting of course that the latter was on for the 5q deletion category of MDS, which David did not have – and he was put on azacitidine. We also learned a clinical study of oral azacitidine – taken by mouth, in pill form. We were interested in this but it meant another biopsy to see if prospective patients are qualified for the trial. However, because he remained in high-risk status he wasn't qualified, as his blast count had actually increased. We thought things over for a month or two, but knew we had to get started.

In October of 2014 David began the treatment, getting the subcutaneous shots instead of intravenous administration – he was on the treatment cycle of seven days of 2 shots per day, and then three weeks of no shots. But he responded well to the treatment, and after about three months on azacitidine, he no longer needed transfusions.

A search for a stem cell donor had been started prior to this treatment. Because David is multiethnic, no matches were immediately found, so he was to have a stem cell transplant from cord blood {ADD statement about difference of cord blood and matched donor). Then right at this point a matched donor was found although was not available until August. Still we decided to wait for this matched donor transplant.

But then the donor fell through, and this was a disappointment. So we decided to go ahead the with cord blood transplant as we originally had planned. In September 2015, my husband had the stem cell transplant from cord blood, which was of course preceded by 3 days of preparation by chemotherapy, and then followed by radiation treatment. The actual transplant occurred at UCSD on September 25.

David was discharged and came home on October 20, and although it took a while for him to recover some significant side effects of treatment that began in the hospital and during his recuperation at home. We are watching things closely with subsequent biopsies and while results are encouraging, we're being cautious as results still show what they are calling 'residual disease'.



Son Steps Up

Right from the start of David's diagnosis, we found AAMDSIF and have been getting information from the Foundation ever since. We saw an announcement that AAMDSIF was connecting with the National Council of Churches (NCC) to promote swabbing drives to tie in with Aplastic Anemia and MDS Awareness Week.

So I discussed it with our son Connor, who is 14, and he liked the idea of doing a swabbing drive through our church. He understands the importance of helping build the pool of potential donors, particularly because bone marrow failure has struck our family before. My husband's mother passed away from aplastic anemia while waiting for a match that never came, so we are committed to doing what we can to help the community of patients like us.

The swab drive was held at Connor's church school. He passed out flyers, spoke at church about it, and publicized it at school. He worked with the school administration so that not only students, but also the students' families are aware of his drive. Connor is now ensuring that the entire congregation and local school community knows that he's standing up to make a difference for bone marrow patients everywhere. "It was my decision to hold the drive," says Connor. "I'm speaking about it in school and church about it."

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