

Communiqué

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Feature

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Metaplasia*

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Agnogenic Myeloid Metaplasia

Agnogenic myeloid metaplasia (AMM) is one of a group of rare diseases known as chronic myeloproliferative diseases (CMD) and is the most rare, having an incidence of less than 2 new cases/100,000 people diagnosed each year.¹ As with the other CMDs, AMM is most commonly seen in people between the ages of 50-70, but can occur in all age groups. The disease occurs equally in men and women and while there is no cure, treatments are available that can significantly reduce the symptoms of AMM.

Chronic Myeloproliferative Diseases (CMD)

- Chronic myelogenous leukemia (CML)
- Polycythemia vera (PV)
- Essential thrombocytosis (ET)
- Agnogenic myeloid metaplasia (AMM)
- Myelodysplastic syndromes
- Atypical CMD

Clinical Features

Like other CMDs, AMM frequently is identified as a result of incidental findings during a routine examination. Also like other CMDs, patients with AMM are at risk for thrombosis and/or bleeding and a small percentage (10%) of patients develop leukemic transformation.² All patients with AMM also are at increased risk of death from heart failure or infection.

Most patients are initially identified as a result of anemia and/or splenomegaly.¹ While patients may be asymptomatic in the early stages of the disease, nearly all will eventually experience symptoms of profound fatigue, weight loss, night sweats, and low-grade fevers or other signs of infection.² Extramedullary hematopoiesis, in which immature blood cells proliferate in organs other than the bone

marrow, is a feature of AMM and results in splenomegaly. Approximately 40% of patients present with only mild to moderate anemia; 20% with asymptomatic splenomegaly.¹ Approximately 40% of patients present with severe anemia and marked splenomegaly.¹ Massive hepatosplenomegaly causes a tender, enlarged abdomen² and may cause a constant feeling of fullness that frequently results in reduced food intake and weight loss. Portal hypertension also is a frequent finding. Additionally, patients with AMM may experience weight loss because of hypercatabolism (excessive metabolic breakdown of body tissue). Extramedullary hematopoiesis that involves the spinal cord can result in cord compression, pain, numbness, tingling, or paralysis. In addition, 25% of patients exhibit thrombocytopenia, thrombocytosis, or leukocytosis.²

Diagnosis

AMM is defined by the presence of significant bone marrow fibrosis, which occurs as a result of abnormally secreted growth factors by megakaryocytes. However, fibrosis also may be found in the fibrotic stages of both polycythemia vera (PV) and essential thrombocytosis (ET), other myeloid disorders, lymphoid disorders, and nonhematologic disorders.^{1,2} To reach a diagnosis of AMM, additional features of AMM must be present. These features include anemia, extramedullary hematopoiesis (see figure 1), leukoerythroblastosis, teardrop-shaped red cells (see figure 2), chromosome abnormalities, and hepatosplenomegaly.

Approximately 30% of patients with AMM demonstrate a chromosomal abnormality. The various CMDs may involve similar abnormalities, including deletion 20q and deletion 13q. The only disease-specific CMD

abnormality is the Philadelphia (Ph) chromosome, characterized by a 9;22 translocation, which is diagnostic for chronic myelogenous leukemia (CML) (see figure 3). Because of the similarity of presentation, cytogenetic studies are utilized to rule out CML in the differential diagnosis, in addition to identifying any other abnormality present. In all cases, it is also important to obtain a complete patient history to help rule out other diseases.



Figure 1. Radiographic imaging demonstrating extramedullary hematopoiesis in the liver and spleen of an AMM patient.
Figure 2. Teardrop-shaped red cells.

Laboratory Testing

Complete Blood Count

Initial evaluation should include a complete blood count (CBC) with differential and peripheral blood smear review. Anemia and evidence of leukoerythroblastosis (eg, nucleated red blood cells, immature granulocytes, and teardrop-shaped red blood cells) support further investigation.

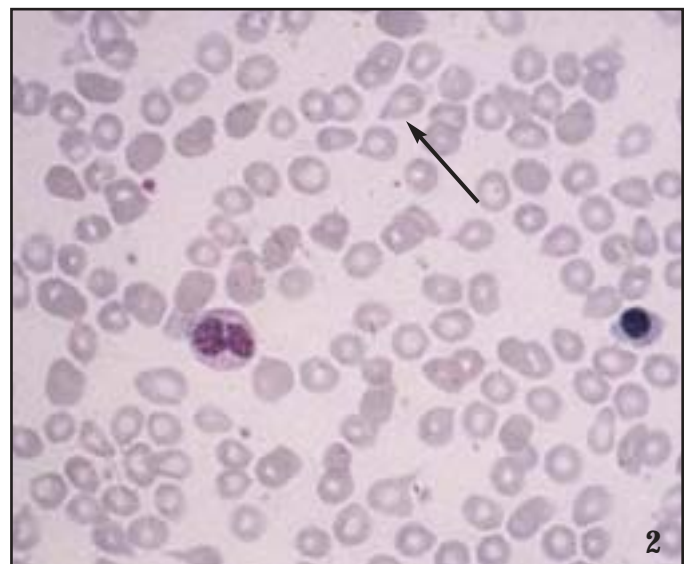
Bone Marrow Analysis

A bone marrow biopsy should be performed for general morphology and to demonstrate fibrosis: [#5434 Hematopathology Consultation](#) or [#9172 Bone Marrow Biopsy](#).

Chromosome Analysis

Cytogenetic studies are strongly recommended to identify any chromosome abnormalities and detect any abnormalities associated with other disorders (eg, Ph, +8, +9, and deletion 20q have been associated with PV). Because deletion 20q may occur in both AMM and PV, cytogenetic analysis will not necessarily differentiate between these 2 CMDs.

While conventional hematologic chromosome studies, [#8506 Chromosome Analysis, For Hematologic Disorders, Bone Marrow](#), are recommended to detect a wide range of chromosome abnormalities that may be present, fluorescence in situ hybridization with DNA probes that detect double fusion products (D-FISH) also



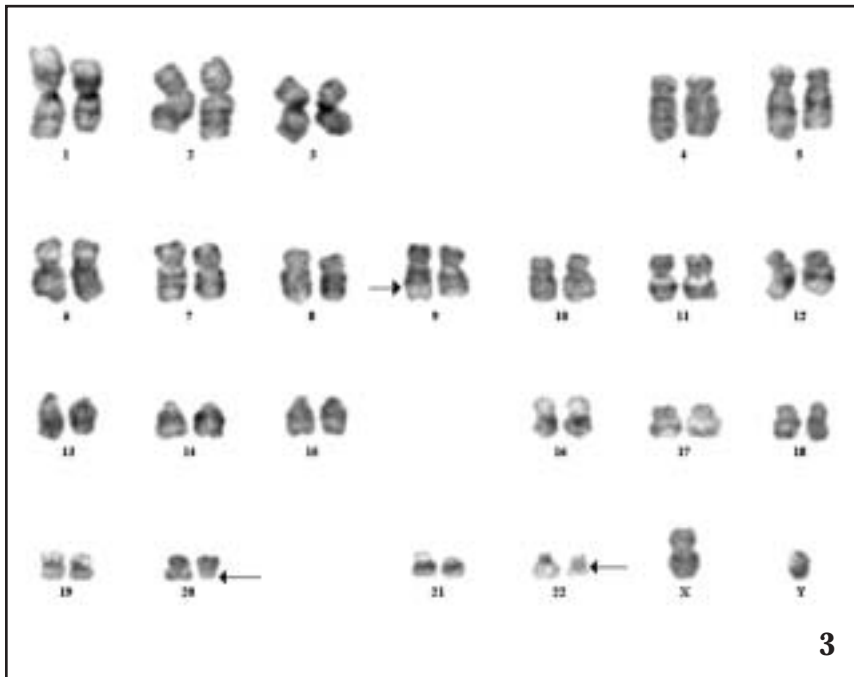
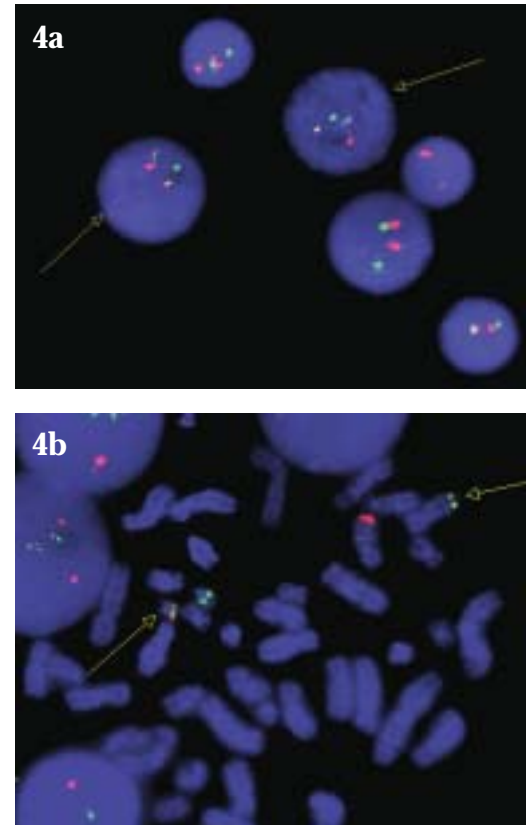


Figure 3. Karyotype of 9;22 translocation, with an additional abnormality (chromosome 20).

Figure 4. D-FISH of 9;22 translocation: a) arrows indicate nuclei with fusion of BCR/ABL signal; b) arrows indicate fusion of BCR/ABL signal.



is recommended specifically to rule out CML.² More than 90% of patients with CML will have the well-known Philadelphia (Ph) chromosome, and detection of the abnormality is considered diagnostic for CML. (See figure 4.) This test, ([#80578 Fluorescence In Situ Hybridization DNA Probes \(D-FISH\) with BCR/ABL](#)), is capable of detecting even so-called “masked” Ph chromosomes that are not detectable with conventional cytogenetics. Additionally, the FISH test can be performed on either blood or bone marrow, providing more flexibility for testing.

Treatment

Once diagnosed, patients should proactively reduce exposures that increase their risk of bleeding, bruising, and infection. As the disease progresses, most patients require frequent red blood cell transfusions, the primary supportive therapy in AMM.

Drug therapy also is an option. Patients may be given a combination of an androgen preparation and a corticosteroid to combat the anemia and increase red blood cell production. The drug combination is effective

in treating anemia in about 30% of patients.² Androgen therapy requires monitoring liver function and female patients should be aware of the virilizing side effects of such treatment. In addition, male patients should be screened for prostate cancer prior to initiating androgen therapy.

While androgen therapy is the preferred pharmacologic approach in AMM, other drugs may be prescribed. Hydroxyurea is an oral chemotherapeutic agent that reduces the numbers of specific types of blood cells. Thalidomide, an immunomodulator medication, has also been used to alter the blood count. Women who are capable of becoming pregnant cannot use thalidomide.

For those patients with symptomatic splenomegaly, splenectomy may provide relief on several levels. Splenectomy removes the physical discomfort associated with an enlarged spleen. In addition, in approximately 50% of patients, splenectomy reduces refractory thrombocytopenia, hypercatabolic symptoms, and portal hypertension. However, surgical procedures carry significant risk for patients with AMM. Postsurgical complications include:¹

- intra-abdominal bleeding
- subphrenic abscess
- sepsis
- large vessel thrombosis
- extreme thrombocytosis
- accelerated hepatomegaly

For patients who are poor surgical candidates, splenic irradiation has been utilized to gain short-term (3-6 months) benefit.¹ In addition, low-dose radiation therapy has been successfully utilized to treat extramedullary hematopoiesis.^{1,2}

Bone marrow transplantation is a rarely utilized option, as most patients with AMM are poor candidates for transplant. It is most frequently utilized in young patients, because of the slow clinical course of the disease and lack of other effective, long-term treatments.² Success rates are low, with only an estimated 30% of patients exhibiting long-term improvement.¹

Conclusions

Patients with AMM are identified by the presence of bone marrow fibrosis, anemia, massive hepatosplenomegaly, and/or wasting. Early asymptomatic stages of the disease may require no more than watchful waiting. However, as the disease progresses, palliative treatments can be undertaken to make patients more comfortable and optimize their quality of life. Close monitoring by their physician can help avoid medical crises.

References

1. Tefferi A, Silverstein MN: Myeloproliferative Diseases. In Cecil Textbook of Medicine, 21st edition. Edited by L Goldman. WB Saunders 2000, pp 935-941
2. Tefferi A: Chronic Myeloproliferative Diseases. In Primary Hematology. Edited by A Tefferi. Totowa, NJ, Humana Press, 2001, pp 119-148

17-Ketosteroid Fractionation Urine Test Changes and Additions

The method for [#8567 17-Ketosteroid Fractionation, Urine](#) (preferred) has been changed from gas chromatography flame ionization detection (GC-FID) to gas chromatography mass spectrometry (GC-MS). The new GC-MS method is free from the interferences observed with the GC-FID method. In addition, the GC-MS method uses deuterium-labeled internal standards that allow correction for variable recoveries during sample extraction and processing. This method change also has generated a change in reference value units from mg/24 hours to µg/24 hours.

New Reference Values

Androsterone

≤12 years: 6.0-725 µg /24 Hr

>12 years

Males: 234-2703 µg /24 Hr

Females: 55-1589 µg /24 Hr

Etiocholanolone

≤12 years: 7.0-515 µg /24 Hr

>12 years: 151-3198 µg /24 Hr

11-Hydroxyandrosterone

≤12 years: 13-382 µg /24 Hr

>12 years: 66-1032 µg /24 Hr

11-Hydroxyetiocholanolone

≤12 years: 6.0-198 µg /24 Hr

>12 years: 17-1006 µg /24 Hr

11-Ketoandrosterone

≤12 years: 1.0-27 µg /24 Hr

>12 years: 4.0-55 µg /24 Hr

11-Ketoetiocholanolone

≤12 years: 20-477 µg /24 Hr

>12 years: 51-1016 µg /24 Hr

Pregnanetriol

≤12 years: 9-410 µg /24hr

>12 years

Males: 245-1701 µg /24 Hr

Females: 59-1391 µg /24 Hr

(Previous reference values omitted)

In all cases, a 24-hour collection is the preferred specimen type. However, when a 24-hour collection is not possible, or is incomplete, a random profile has been implemented to allow the specimen to be analyzed; [#84349 17-Ketosteroid Fractionation, Random, Urine](#). This new profile, which includes analysis of creatinine, also utilizes the new GC-MS method.

Cyclosporine Method and Reference Value Changes

A change in method from high-performance liquid chromatography (HPLC) to high-performance liquid chromatography/tandem mass spectrometry (HPLC-MS/MS) also has resulted in reference value changes for [#8931 Cyclosporine, Blood](#). In addition, the change in reference values brings the reference values in better alignment with recent literature.

New Reference Values

100-400 ng/mL

Previous Reference Values

100-300 ng/mL

DNA Ploidy by DIA for Paraffin Block Billing Changes

The technical performance for [#80948 DNA Ploidy by Digital Image Analysis \(DIA\), Paraffin Block](#) has not changed. However, to properly charge for the test, 2 new billing codes have been added. Charges will no longer be associated with the test code [#80948](#); the price of the test has not changed.

New Billing Codes

83348 **DNA Ploidy and Proliferation by DIA**
CPT Code 88358

82230 **MIB-1, Immunostain**
CPT Code 88342

Immunoglobulin Gene Rearrangement Test Changes

A method change for [#83123 Immunoglobulin Gene Rearrangement](#) also has generated changes in the billing and reporting codes. In the Southern blot component of this test, genomic DNA is digested and the fragments are now detected utilizing a chemiluminescent-based system, rather than radioactive labels.

The billing code for the Southern blot component has changed as follows.

New Billing Code

83042 Immunoglobulin Gene Rearrangement, Southern Blot (if appropriate)
CPT Codes 83892/x2 enzyme digestion
 83894/x2 electrophoresis
 83896/x2 nucleic acid probe, each
 83897/x2 nucleic acid transfer

Coagulation Reference Value Changes Affect Multiple Coagulation Tests

A change by the manufacturer in formulation of reagents for [#81967 Activated Protein C Resistance V](#) has resulted in a change to the normal ranges for the screening baseline activated partial thromboplastin time (APTT) mix, the activated partial thromboplastin time (APTT) after the addition of APC and the APC-R Ratio.

New Reference Values

Baseline APTT V: 35-44 seconds

APTT V with APC: 100-130 seconds

APC-R Ratio: ≥ 2.3

Previous Reference Values

Baseline APTT V: 31-39 seconds

APTT V with APC: 80-113 seconds

APC-R Ratio: ≥ 2.1

Pediatric reference values: Pediatric normal values have neither been established nor are available in scientific literature. The adult reference values likely would be applicable to children older than age 6 months.

The reference value change for the free protein S component of [#83049 Protein S Antigen, Plasma](#) also was implemented.

New Reference Value

Males: 65-130%

Females: 55-130%

Previous Reference Value

Males: 60-130%

Females: 50-120%

These changes also affect [#550 Coagulation Consultation, Thrombosis/Hypercoagulability, Blood and Plasma](#).

Rubella Test Changes

A change to the method for [#8172 Rubella Antibodies Only, Serum](#) has generated changes to the test title and reference values as well. The name of the test was changed to remove the word “only” from the title: [#8172 Rubella Antibodies, Serum](#). The method change also generated the need to change the reference value from “immune or non-immune” to “positive.”

New Method

Enzyme-linked fluorescent immunoassay (ELFA)

Previous Method

Microparticle enzyme immunoassay (MEIA)

New Bone Marrow Container Available as Supply Item

Protecting specimens from sudden and/or extreme temperature changes during shipment to MML is an essential element to maintaining specimen quality and integrity. To improve transport of bone marrow specimens, MML has introduced a new bone marrow container, supply item T517, which should be utilized throughout the year to protect specimens from both hot and cold temperature changes.

To use the new container, roll the specimen tube in a paper towel and secure it with tape or a rubber band before placing it in the container. When sending 2 tubes under the same accession number, wrap the individual tubes in paper towels and secure the tubes to each other with a rubber band before placing them in the container. Then place the container and accompanying paperwork into a MML ambient transportation bag (supply item T027) for appropriate shipping. Use of the new bone marrow container will ensure that your specimens reach MML without experiencing temperature fluctuations.

Sirolimus Reference Value Changes

A reference value change for [#81768 Sirolimus, Blood](#), was implemented to bring the values into alignment with recent literature. No other aspect of the assay was affected.

[New Reference Values](#)

4.0-20.0 ng/mL

[Previous Reference Values](#)

3.0-20.0 ng/mL

Tacrolimus Reference Value Changes

A reference value change for [#80783 Tacrolimus, Blood](#), was implemented to bring the values into alignment with recent literature. No other aspect of the assay was affected.

[New Reference Values](#)

5.0-15.0 ng/mL

[Previous Reference Values](#)

3.0-20.0 ng/mL

2004 Education Calendar

Interactive Satellite Programs . . .

Herbal Therapy 2004: Snakes in the Grass (Herb-Drug Interactions Clinicians Need to Know)

September 16, 2004

Presenter: Brent Bauer, MD

Moderator: Robert M. Kisabeth, MD

Markers of Inflammatory Bowel Disease

October 19, 2004

Presenter(s): Henry Homburger, MD and
Edward Loftus, MD

Moderator: Robert M. Kisabeth, MD

The Use of Diagnostic Tests in the Pediatric Age Group

November 2, 2004

Presenter: Robert Jacobson, MD

Moderator: Robert M. Kisabeth, MD

Thyroid Disease – Laboratory Support For Diagnosis and Management

December 7, 2004

Presenter: George Klee, MD, PhD

Moderator: Robert M. Kisabeth, MD

Upcoming Education Conferences . . .

Integration Through Community Laboratory Insourcing: Implementing a Successful Laboratory Outreach Program

June 17-19, 2004

Mayo Clinic, Siebens Building
Rochester, Minnesota

Bleeding and Thrombosing Diseases: The Basics and Beyond

Coagulation Conference and Wet Workshop
August 5-7, 2004

Mayo Clinic, Siebens Building
Rochester, Minnesota

Practical Surgical Pathology

September 16-18, 2004

Mayo Clinic, Siebens Building
Rochester, Minnesota

Practical Spirometry

November 2-3, 2004

Mayo Clinic, Siebens Building
Rochester, Minnesota

Introductory Clinical Mycology

November 18-19, 2004

Mayo Clinic, Siebens Building
Rochester, Minnesota

For additional information, contact

Mayo Reference Services Education Department at 800-533-1710. Visit us under "Education" at www.mayoreferenceservices.org.

Ask



US

Please e-mail your questions to mml@mayo.edu.

Q: MML offers many allergy test options. How do I select the right group of allergens for testing my adult patients?

A: When patients present with severe asthma, they should be referred to an allergist for evaluation. In other cases of possible respiratory allergies, it is first necessary to determine whether the presentation is seasonal or nonseasonal.

For seasonal allergies, you can select the appropriate allergens by identifying the exposures in your patients' geographic region. In many cases, a seasonal multiallergen panel is available or can be designed to fit your region. In this manner, testing can be optimized for your region.

When allergies are not seasonal, they are often caused by exposure to year-round allergens such as indoor molds, pet dander, etc. For nonseasonal allergies, a nonseasonal panel(s) is appropriate regardless of geographic location.

Note: In adults, food allergies are not commonly associated with respiratory signs and symptoms, and IgE antibodies to food allergens should only be tested for in patients who have exhibited signs of anaphylaxis on ingestion of a particular food.

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