

Agnogenic Myeloid Metaplasia

I. Definition: One of the myeloproliferative group of disorders, characterized by abnormal proliferation of the hematopoietic elements, presence of marrow fibrosis, and myeloid metaplasia.

A. To be distinguished from

1. Spent-phase polycythemia vera
 - a. Hematocrit fairly stable
 - b. Marked splenomegaly
 - c. Not much marrow fibrosis
2. Post-polycythemic myeloid metaplasia closely resembles AMM except for the history. The distinction is arbitrary.

II. Etiology

A. May be caused by radiation - high incidence in atomic bomb survivors

B. Benzene compounds

C. Clonal, stem cell

1. First demonstrated using G6PD analysis in women heterozygous for G6PD subtype.
2. Mutation of the *ras* oncogene and cytogenetic lesions also support this conclusion

D. Origin of marrow fibrosis

1. Proliferation of fibroblasts is polyclonal
2. Affected megakaryocytes, monocytes, and histiocytes secrete excessive amounts of platelet-derived growth factor, basic fibroblast growth factor, and transforming growth factor- β . All of these stimulate fibroblast growth.

III. Clinical aspects

A. Onset in late middle life. Incidence is about 1/100,000.

B. Insidious presentation, dominated by symptoms of anemia or splenomegaly

1. Weight loss
2. Bone pain

C. Signs

1. Splenomegaly - almost always present, often massive
2. Hepatomegaly - 75% of cases

D. Sites of extramedullary hematopoiesis

1. Spleen
2. Liver
3. Lungs
4. Kidneys
5. GI tract

E. Prognosis

1. Median survival is 40 to 65 months from diagnosis
2. Scoring system (Dupriez, et al) considers Hgb < 10 g/dL and WBC < 4 or $> 30 \times 10^9/L$ to be adverse risk factors.
 - a. Those with no risk factors have median survival of 93 months
 - b. Those with 1 risk factor have median survival of 26 months
 - c. Those with 2 risk factors have median survival of 13 months
3. Fever, night sweats, weight loss, and abnormal karyotype also confer poor prognosis
4. Increased blood vessel formation (angiogenesis) in the bone marrow correlates with the presence of a splenomegaly and shorter survival (Tefferi, 2000). It occurs in up to 70% of cases (Mesa).

IV. Laboratory aspects

A. Normochromic, normocytic anemia which may be severe

1. Tear drop cells, ovalocytes
2. Polychromasia, anisocytosis, poikilocytosis
3. Nucleated RBCs

B. Leukocytosis common, usually $\leq 20,000$ and left-shifted

C. Platelets

1. Counts may be high or low

2. Aggregation is often abnormal
 3. Giant forms and mini-megakaryocytes seen
- D. Bone marrow
1. "Dry tap" on aspiration
 2. Marrow biopsy usually shows fibrosis
 3. Megakaryocytes often increased
 4. CFU-C in marrow decreased, although often increased in peripheral blood
 - E. Bone x-rays show osteoporosis but may show osteopetrosis
- F. Blood chemistry
1. Uric acid increased
 2. LDH increased
 3. LAP variable, but tendency is to decrease with time
- G. Chromosomes abnormal in 1/3 of cases
1. Ph¹ absent
 2. C group chromosomes often duplicated, especially trisomy 9. Trisomy 21 also seen.
 3. Deletions include 20q-, 13q-
 4. Abnormal karyotype confers a poor prognosis. In one study, median survival of patients with chromosomal abnormalities was 30 months, while for those with normal karyotypes it was over 6 years.
- V. Therapy
- A. Objective is palliation of symptoms - thus early therapy not usually necessary
- B. Anemia
1. Transfuse as needed
 2. Androgens improve anemia in fewer than 1/3 of cases, and the results are not long-lasting
 3. Role of growth factors?
 - a. Two patients in the literature developed increased splenomegaly when treated with EPO
 - b. One case at Buffalo VAMC developed jaundice repeatedly when treated with EPO.
- C. Thrombocytosis and leukocytosis may require control by means of alkylating agents or interferon
1. Alpha-interferon has some activity, especially in the cellular/proliferative phase, but is toxic
 2. Hydroxyurea is also useful in the cellular/proliferative phase, and cladribine has been used successfully post-splenectomy.
- D. Steroids occasionally helpful for cytopenias
- E. Splenectomy
1. Alternatives
 - a. Local radiation - does not produce sustained improvement
 - b. Chemotherapy
 2. Indications
 - a. Pain due to splenic infarction or large size
 - b. Anemia
 - i. Sequestration of red cells
 - ii. Plasma volume increases more than is accountable by splenic blood pool, resulting in a dilutional component
 - c. Thrombocytopenia due to hypersplenism
 - d. Portal hypertension
 3. Results (Tefferi 2000)
 - a. Perioperative mortality rate runs about 10%
 - b. Median survival post-splenectomy is about 27 months
 - c. Improvement in constitutional symptoms occurs in 67%, anemia in 23%, portal hypertension in 50%, and thrombocytopenia in 0%
 4. There is a suggestion that females do better post-splenectomy than males
- F. Autologous stem-cell transplantation would not be expected to be curative, but may slow the disease by

permitting aggressive cytotoxic therapy aimed at the neoplastic clones. Based on limited experience to date, this approach is at least feasible.

1. European study followed 55 patients (Guardiola)
 - a. This was a young group with median age 42
 - b. Five year survival was 47% post transplant, however 27% of patients died within 1 year from complications of the procedure
 - c. Severe GVHD affected 33% of cases
 - d. At 5 years, 36% of patients had failed treatment. Adverse prognostic factors were older age, presence of a cytogenetic abnormality, or absence of significant GVHD.

G. Experimental approaches

1. Anagrelide, an inhibitor of platelet proliferation, has no beneficial effects.
2. Inhibitors of fibroblast activity are under study, with nothing positive to report yet (mid-2000)
3. Thalidomide
 - a. Has some positive effect, but often not tolerated at usual dose of 100mg/d or higher.
 - b. Promising results when given at 50 mg/day with prednisone 0.5 mg/kg/d tapered over 3 months (Mesa). Regimen tolerated by 95% of cases.
 - i. 70% of transfusion-dependent cases improve
 - ii. Platelet count improves in 75% of thrombocytopenic individuals
 - iii. Shrinkage of spleen by half in 19%.

VI. Acute myelofibrosis

- A. A much more acute, severe syndrome not to be confused with agnogenic myeloid metaplasia
- B. Clinical aspects
 1. Fever, wasting, infection
 2. Absence of splenomegaly
- C. Laboratory aspects
 1. Often cytopenias
 2. RBC morphology characteristic of myelofibrosis often not present
 3. Increase in myeloblasts in marrow and peripheral blood
 4. Marrow fibrosis
- D. This entity probably represents an exuberant fibroblastic reaction to acute leukemia.

References:

- Cazzola M, et al. *Subcutaneous erythropoietin for treatment of refractory anemia in hematologic disorders. Results of a phase I/II clinical trial.* Blood 1992;79:29.
- Demory J, et al. *Cytogenetic studies and their prognostic significance in agnogenic myeloid metaplasia: A report on 47 cases.* Blood 1988;72:855.
- Dupriez B, et al. *Prognostic factors in agnogenic myeloid metaplasia: A report on 195 cases with a new scoring system.* Blood 1996;88:1013.
- Guardiola P, et al. *Allogeneic stem cell transplantation for agnogenic myeloid metaplasia: A European Group for Blood and Marrow Transplantation, Société Française de Greffe de Moelle, Gruppo Italiano per il Trapianto del Midollo Osseo, and Fred Hutchinson Cancer Research Center collaborative study.* Blood 1999;93:2831-8.
- Jacobsen R, et al. *Agnogenic myeloid metaplasia: A clonal proliferation of hematopoietic stem cells with secondary myelofibrosis.* Blood 1978;51:189.
- Mesa R, et al. *A phase 2 trial of combination low-dose thalidomide and prednisone for the treatment of myelofibrosis with myeloid metaplasia.* Blood 2003;101:2534.
- Mesa R, et al. *Evaluation and clinical correlations of bone marrow angiogenesis in myelofibrosis with myeloid metaplasia.* Blood 2000;96:3374-80.
- Milner G, et al. *Erythrokinetic studies as a guide to the value of splenectomy in primary myeloid metaplasia.* Br J Haematol 1973;25:467.
- Mulder H, et al. *Clinical course and survival after elective splenectomy in 19 patients with primary myelofibrosis.* Br J Haematol 1977;35:419.
- Silver R. *Interferon in the treatment of myeloproliferative diseases.* Semin Hematol 1990;27(Suppl 3):6.
- Silverstein M, et al. *Splenectomy in myeloid metaplasia.* Blood 1979;53:515.
- Tefferi A. *Myelofibrosis with myeloid metaplasia.* N Engl J Med 2000;342:1255-64.
- Tefferi A, et al. *Splenectomy in myelofibrosis with myeloid metaplasia: a single-institution experience with 223 patients.* Blood 2000;95:2226-33.

Yan X-Q, et al. *A model of myelofibrosis and osteosclerosis in mice induced by overexpressing thrombopoietin (mpl ligand): Reversal of disease by bone marrow transplantation.* Blood 1996;88:402.