Leukaemia Section
Mini Review

Myelofibrosis with myeloid metaplasia (MMM), Idiopathic myelofibrosis, Agnogenic myeloid metaplasia

Antonio Cuneo, Francesco Cavazzini

Hematology Section, Department of Biomedical Sciences, University of Ferrara, Corso Giovecca 203, Ferrara, Italy

Published in Atlas Database: August 2006

Online updated version: http://AtlasGeneticsOncology.org/Anomalies/Myelofib.html

DOI: 10.4267/2042/38381


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Clinics and pathology

Disease
Chronic myeloproliferative disorder

Phenotype / cell stem origin
The disease is a chronic myeloproliferative disorder originating from a mutated pluripotent stem cell capable of producing red blood cells, granulocytes, megakaryocytes and lymphoid cells. Fibrosis of the marrow is the hallmark of the disease, however fibroblasts are not part of the malignant process and fibrosis represents a reaction of marrow stromal cells.

Epidemiology
MMM has an incidence of 0.3 to 1.5 new cases per year in 100,000 persons. Male predominance was observed in some studies and not confirmed in others. The average age at diagnosis is 60 years. Exposure to radiation and to organic solvents increases the risk of developing MMM.

Clinics
MMM usually presents with fatigue, weight loss, splenomegaly with or without symptoms. Anemia and various alterations of the white blood cell and/or platelet count are frequently seen at diagnosis. Thrombocytopenia-related bleeding may occur. MMM must be distinguished from myelodysplasia with fibrosis, from acute megakayoblastic leukemia and acute myelofibrosis.

As the disease progresses, increased marrow fibrosis with severe symptomatic peripheral cytopenias and extramedullary hemopoiesis predominate, with consequent massive splenomegaly, hepatomegaly with portal hypertension, pulmonary hypertension. Leukemic transformation may represent the terminal event in 5-20% of the cases.

Cytology
Teardrop poikilocytosis and leukoerythroblastosis are present in the peripheral blood (PB) smear. Platelets are increased in size. The bone marrow is usually hypercellular at presentation with remarkably increased megakaryocytes and, to a lesser degree, granulocytes. Reticulin fibrosis is always present. Hemopoietic cellularity is patchy, with some areas showing hypercellularity and other being depleted of hemopoietic cells. The spleen histology shows extramedullary hemopoiesis involving predominantly the sinusoids.

Treatment
The treatment depends on the patient’s general condition and symptoms. Supportive treatment is required for anemia and profound thrombocytopenia. Cytoreductive treatment with busulphan, hydroxyurea, thioguanine, low-dose melphalan or chlorambucil, interferon-a may be useful to control progressive splenomegaly. Irradiation of the spleen may be also employed. Danazol or low-dose dexamethasone can be used to ameliorate anemia. Allogeneic bone marrow transplantation should be considered for patients aged 60 years or less.
Prognosis

The median survival is approximately 5 years. Causes of death include infection, leukemic transformation, bleeding, hepatic failure with portal hypertension due to myeloid metaplasia, heart failure.

Cytogenetics

Cytogenetics morphological

a) Chromosome lesions:
The absence of the (9;22)/BCR-ABL fusion is an absolute diagnostic requirement. Approximately 40-50% of the patients analyzed at diagnosis show a clonal defect. The proportion of cytogenetically abnormal cases increases at disease transformation into acute leukemia, were up to 90% of the cases carry a clonal defect. Non-random chromosome aberrations are del(13q), del(20q) and gain of 1q. These abnormalities represented 65% of abnormal cases in a study. Other recurrent chromosome aberrations include trisomy 8 and del(12p), monosomy 7/del(7q), der(6)t(1;6)(q21-23;p21.3). The latter abnormality leads to trisomy 1q21-23 to 1qter and to loss of 6p21 to 6pter. FISH on deparaffinized bone biopsies showed a 56% incidence of cytogenetic lesions in a study using probes for 7q31, 12p, 13q14, 17p13, 20q13, 21q22, cen7, cen8, cen11 and cen17.

b) Prognostic significance:
The presence of abnormal karyotype does not appear to be an independent prognostic factor, whereas +8, 12p deletion and -7/7q- were associated with an inferior outcome at multivariate analysis.

Genes involved and Proteins

JAK2

Location: 9p24

Note: Janus Kinase JAK2 mutation (See also Polycythemia Vera).

Protein

A valine to phenylalanine substitution at position 617 (JAK2 V617F mutation) is present in approximately 50-55% of the patients leading to constitutive kinase activity.

The mutated JAK2 protein binds to the cytoplasmic domain of Epo-R and promotes signalling independent of Epo stimulation. The JAK2 protein is coded for by a domain of Epo-R and promotes signalling independent of Epo stimulation. JAK2 signaling involves the phosphorylation of several Y residues at the Epo receptor with activation of STAT, MAP kinase PI-3-kinase and AKT. These events lead to survival and proliferation of erythroid progenitors. JAK2 is involved in intracellular signalling following stimulation by IL3, TPO and GM-CSF, and erythroid progenitors in PV are hypersensitive to stimulation by these cytokines. Patients with JAK2 V617F mutation showed high white blood cell counts, required less transfusions and had an inferior outcome in a study.

In 5-9% of the patients a gain-of-function mutation of the thrombopoietin receptor (MPL) gene can be found, determining activation of the JAK-STAT pathway.

References


This article should be referenced as such: