Lecture 11 by Dr.Alaa Fadhil Alwan
The Chronic Myeloproliferative Neoplasms
Essential Thrombocythemia, Polycythemia Rubra Vera, and Myelofibrosis

Nomenclature: we will include 1. Polycythemia Rubra Vera (PRV or PV); 2. Essential (Primary) Thrombocythemia (ET); and 3. Myelofibrosis (MF - also known as Agnogenic Myeloid Metaplasia [AMM], and Myelofibrosis with Myeloid Metaplasia [MMM]) within the category of the Chronic Myeloproliferative Diseases.

Concepts: these conditions are all clonal disorders of the hemopoietic stem cell, which lead to dysregulated production of blood cells, and fibrosis. The fibroblasts are not part of the clone. In Polycythemia Rubra Vera, overproduction of red blood cells is the dominant feature, although increased white cells and platelets are also often present. In Essential Thrombocythemia, overproduction of platelets predominates. Myelofibrosis may be the end result of PV, or may apparently occur *de novo*.

Genetics: virtually all cases of PV, and about half of ET and MF carry a gain-of-function mutation in JAK-2 (V617F). This kinase is downstream of the cytokine receptors for erythropoietin (EPO) and thrombopoietin (TPO). When constitutively activated by the mutation, cytokine-independent signaling takes place leading to increases in red cell and platelet counts. V617F-negative cases may have different mutations in the JAK-2 gene.

ESSENTIAL THROMBOCYTHEMIA (ET)

Regulation of platelet numbers in normal individuals: thrombopoietin (TPO) is produced constitutively in the liver. It is bound by normal platelets, and the remainder stimulates megakaryopoiesis. Thus, when the platelet count is low, there is more free TPO, and platelet production is stimulated, and *vice versa*.

Pathology: In most cases, ET is a neoplastic (clonal) stem cell disorder, which leads to excessive production of abnormal platelets. Some cases, especially in young women, may not be clonal. The abnormal platelets can lead to microvascular occlusion, frank thrombosis, and also to abnormal bleeding, especially after surgery.

Incidence: 'uncommon'. 1-2 per year . More in females than males. Peak incidence age 50-80.

Typical Blood Count:

WBC x 10^9/L	10.0	[4-11]
Hb g/L	156	[140-180]
MCV fl	85	[80-100]
Platelets x 10^9/L	1560	[150-450]
Neuts x 10^9/L	7.0	[2-7.5]
Lymphs x 10^9/L	2.0	[1.5-4]
Monos x 10^9/L	0.8	[0.2-0.8]
Eos x 10^9/L	0.1	[0-0.7]
Basos x 10^9/L	0.1	[0-0.1]
Film Comment:	many large and abnormal platelets present	

Clinical Findings: often asymptomatic. Thrombotic manifestations are both arterial (transient ischemic attacks (TIA), strokes, myocardial infarction, peripheral vascular occlusion), and venous (deep vein thrombosis). **Erythromelalgia** is an unpleasant burning and tingling sensation in the hands and feet, and the affected parts are usually red and swollen. It is caused by microvascular occlusion. The spleen may be enlarged, but usually not. **Bleeding** is uncommon, but surgery poses a particular hazard.

Diagnosis: can usually be made on the blood findings alone, and by excluding other causes of thrombocytosis. A marrow may help in cases of doubt. In young patients especially, Chronic Myeloid Leukemia must be excluded, as it can sometimes present as isolated thrombocythemia, and the treatment is different. The JAK-2 mutation is present in about 50% of cases.

Differential Diagnosis: reactive thrombocytosis (infection, bleeding, inflammation, connective tissue diseases, cancer), other myeloproliferative diseases, CML.

Treatment: asymptomatic young patients do not need any therapy. Occlusive symptoms respond well to aspirin in low dose. Control of the platelet count with hydroxyurea helps to prevent thrombosis, but leukemia is an important potential adverse effect of this drug, even though the incidence is low.

Clinical Course: with appropriate treatment, life expectancy is almost normal. The incidence of leukemia is probably greater than in normals, and may be increased by hydroxyurea.

POLYCYTHEMIA RUBRA VERA

Pathology: A neoplastic (clonal) stem cell disorder, which leads to excessive production of all myeloid cell lines, but predominantly red cells. The increase in whole blood viscosity causes vascular occlusion and ischemia, compounded by the increase in platelets. 90% of cases have a mutation in the JAK-2 gene, which causes activation of the pathway downstream of the erythropoietin receptor.

Incidence: peaks at 60-80 y: slightly commoner in males. 2/100,000 per year.

Typical Blood Count:

WBC x 10^9/L	18.0	[4-11]
Hb g/L	200	[140-180]
HCt	0.62	[.42-.51]
MCV fl	75	[80-100]
Platelets x 10^9/L	850	[150-450]
Neuts x 10^9/L	14.6	[2-7.5]
Lymphs x 10^9/L	2.0	[1.5-4]
Monos x 10^9/L	0.8	[0.2-0.8]
Eos x 10^9/L	0.1	[0-0.7]
Basos x 10^9/L	0.5	[0-0.1]

Film Comment: microcytosis: large and abnormal platelets present

Clinical Findings: headaches, itch, vascular occlusion, thrombosis, TIA, strokes. Splenomegaly is common.

Diagnosis:

a. exclude secondary causes of true polycythemia (smoking, COPD, left to right shunts, hypoxia, tumours or cysts which secrete erythropoietin)
b. look for features which suggest primary polycythemia (splenomegaly, increased basophil count, increased WBC and platelets)
c. measure erythropoietin level
d. look for the JAK-2 mutation

Differential Diagnosis:
a. secondary polycythemia (see above)
b. spurious polycythemia – this is a condition in which the plasma volume is spontaneously reduced, (aka Gaisbock's syndrome or stress polycythemia). A firm diagnosis requires a measurement of the 'red cell mass'

Treatment:
a. phlebotomy to control the hematocrit (less than 0.45)
b. low-dose aspirin – 81 mg/day
c. hydroxyurea if necessary
d. do not treat with iron

Clinical Course: with appropriate treatment, life expectancy is good (median 13 years). The incidence of leukemia (1.5%) is greater than in normals, and may be exacerbated by hydroxyurea. Some (25%) patients develop myelofibrosis.

MYELOFIBROSIS

Pathology: A neoplastic (clonal) hemopoietic stem cell disorder, which leads to marrow fibrosis and bone marrow failure. Myeloid metaplasia (extra-medullary hemopoiesis) occurs, especially in the liver and spleen.

Incidence: approximately 0.5/100,000 per year

Typical Blood Count:

WBC x 10^9/L	2.4	[4-11]
Hb g/L	88	[140-180]
MCV fl	85	[80-100]
Platelets x 10^9/L	60	[150-450]
Neuts x 10^9/L	1.0	[2-7.5]
Lymphs x 10^9/L	1.0	[1.5-4]
Monos x 10^9/L	0.2	[0.2-0.8]
Eos x 10^9/L	0.1	[0-0.7]
Basos x 10^9/L	0.1	[0-0.1]
Film Comment:	a few nucleated red cells and myelocytes (leukoerythroblastic). Tear drop poikilocytes	

Clinical Findings: symptoms of marrow failure. Discomfort from splenomegaly. Spleen is usually enlarged and may be huge

Diagnosis: can often be suspected from the blood count, and the clinical findings. A marrow aspirate is usually impossible ('dry tap') but a trephine biopsy will show the fibrosis.

Differential Diagnosis: secondary fibrosis e.g. in breast cancer, and other malignancies.

Treatment: supportive care, including blood transfusions. Splenectomy if necessary for pain, or thrombocytopenia.

Clinical Course: median survival 5 years.