MYELOPROLIFERATIVE DISORDERS

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Myeloproliferative diseases I. (MPD)

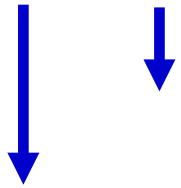
a heterogeneous group of hematological diseases characterized by chronic proliferation of one or more cell lines

4 units:

- polycythemia vera (PV)
- (primary) essential thrombocythaemia (ET)
- primary myelofibrosis (PMF)
- chronic myeloid leukemia (CML)

Myeloproliferative diseases II.

- clonal process at the level of a multipotent hematopoietic progenitor cell with preservation of differentiation capacity



bone marrow panhyperplasia
increased cell production of more cell lines
(myeloid, erythroid, megakaryocyte)

- variable tendency to transform into acute leukemia or other myeloproliferative disease

MPD classification according to WHO

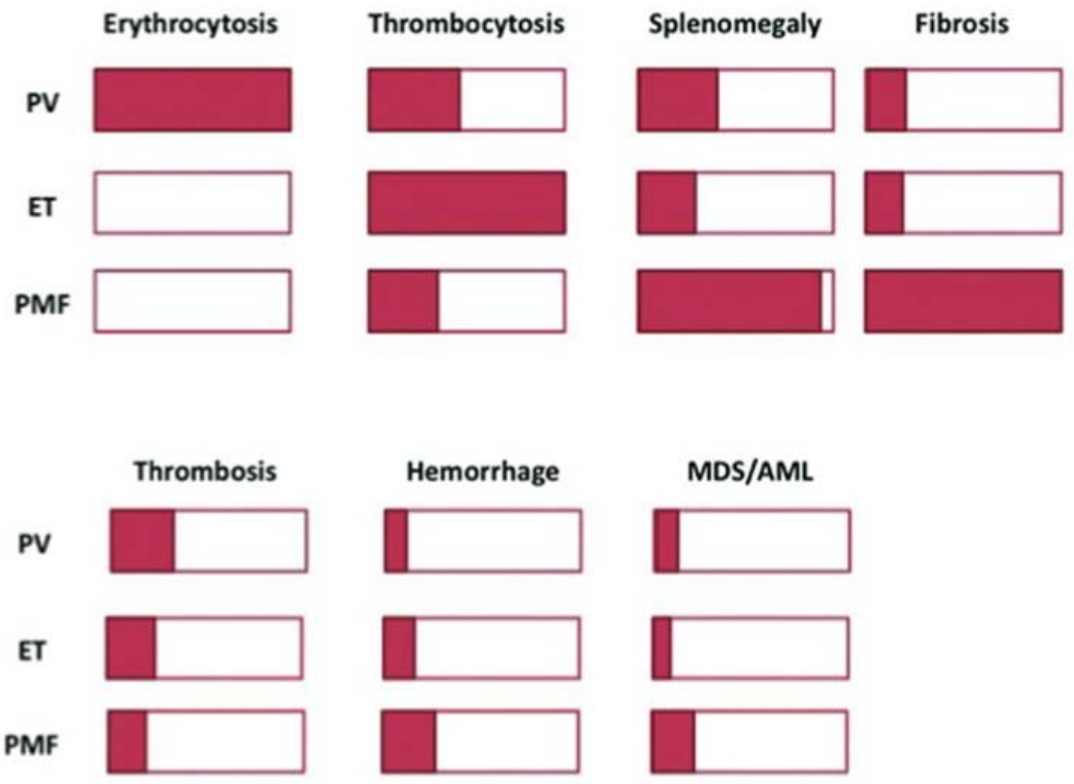
= MYELOPROLIFERATIVE NEOPLASIA (MPN)

WHO classification of myeloid malignancies:

- chronic myeloid leukemia
- chronic neutrophilic leukemia
- polycythemia vera (PV)
- primary myelofibrosis (PMF)
- essential thrombocythaemia (ET)
- chronic eosinophilic leukemia (and hypereosinophilic syndrome)
- myeloproliferative disease, unclassifiable

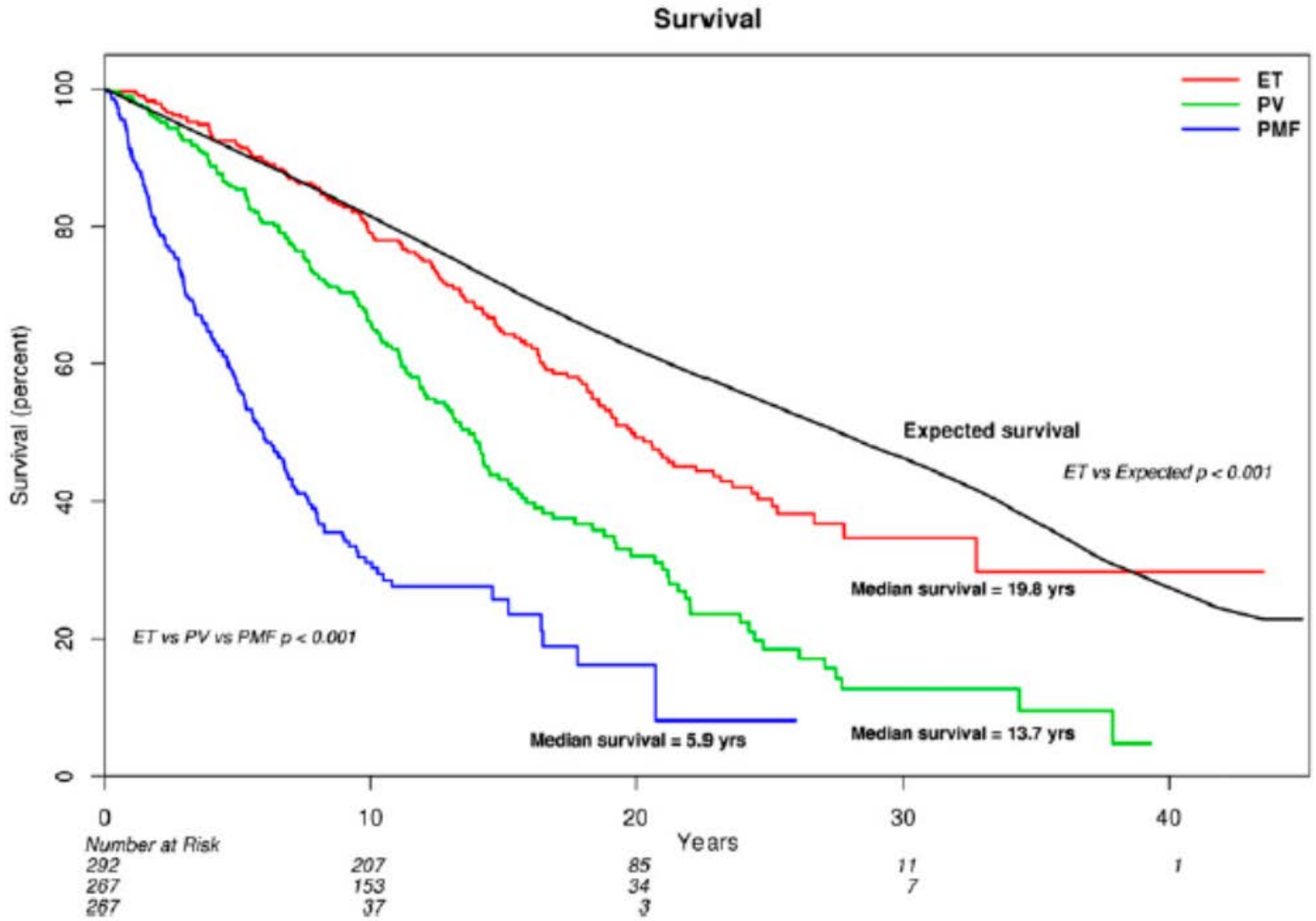
Typical features of Phmyeloproliferative neoplasias include:

- proliferation of one or more hematopoietic lines
- risk of developing bone marrow fibrosis and transformation into acute leukemia
- Splenomegaly
- risk of thrombotic and hemorrhagic complications



Kiladjian J, Hematology 20012

Prognosis of patients with MPN



Tefferi A, Blood 2014

Distribution of MPD according to presence Ph chromosome

Ph positive MPD:

- chronic myeloid leukemia

Ph negative MPD:

- polycythemia vera
- essential thrombocythemia
- primary myelofibrosis

➡ molecular markers in Ph neg: mutations JAK2, CALR, MPL

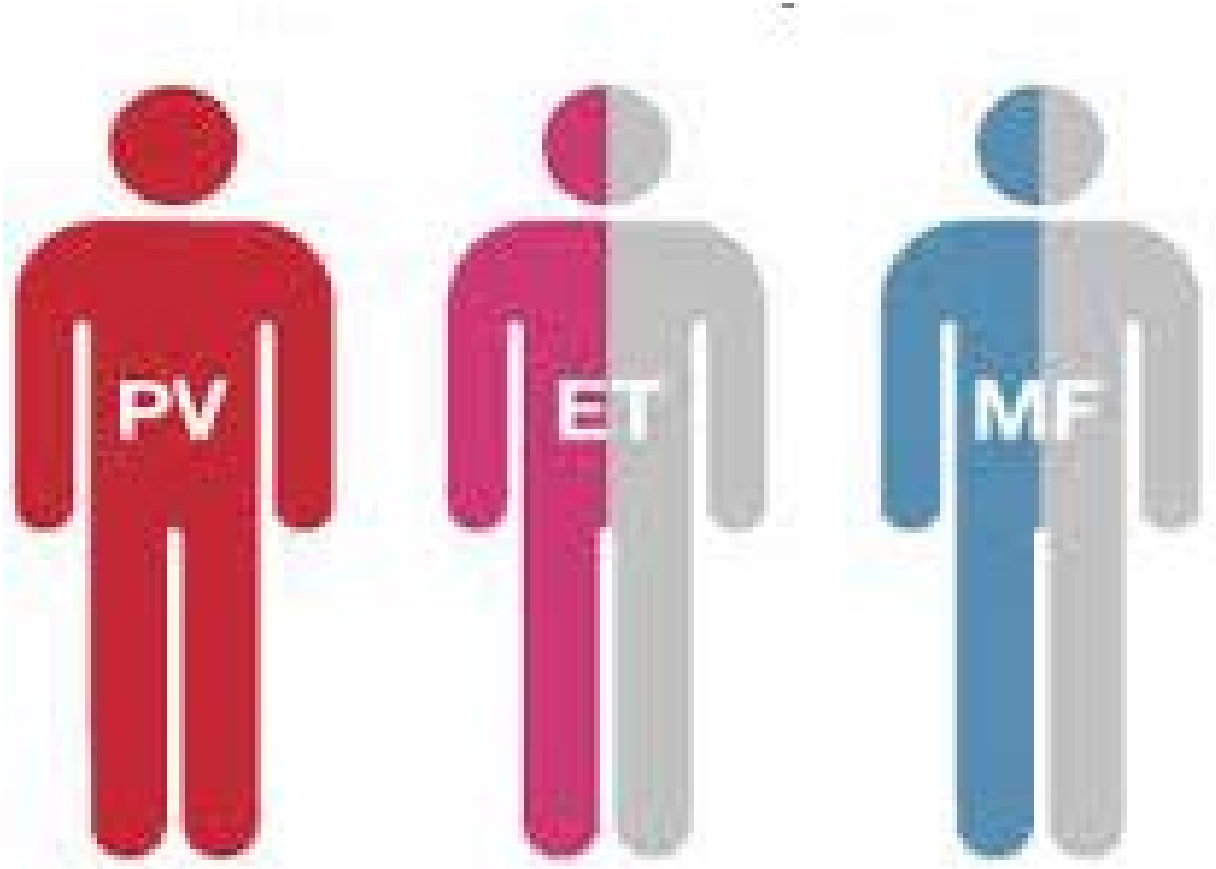
Gene mutation for Janus kinase 2 (JAK2)

- occurs in Ph negative myeloproliferative diseases:
  - PV (90 - 100%)
  - ET and MF (50 - 60%)

- mutation (V617F) causes tyrosine kinase activation
  kinase is important for the function of cytokines involved in hematopoiesis (EPO, TPO, G-CSF)

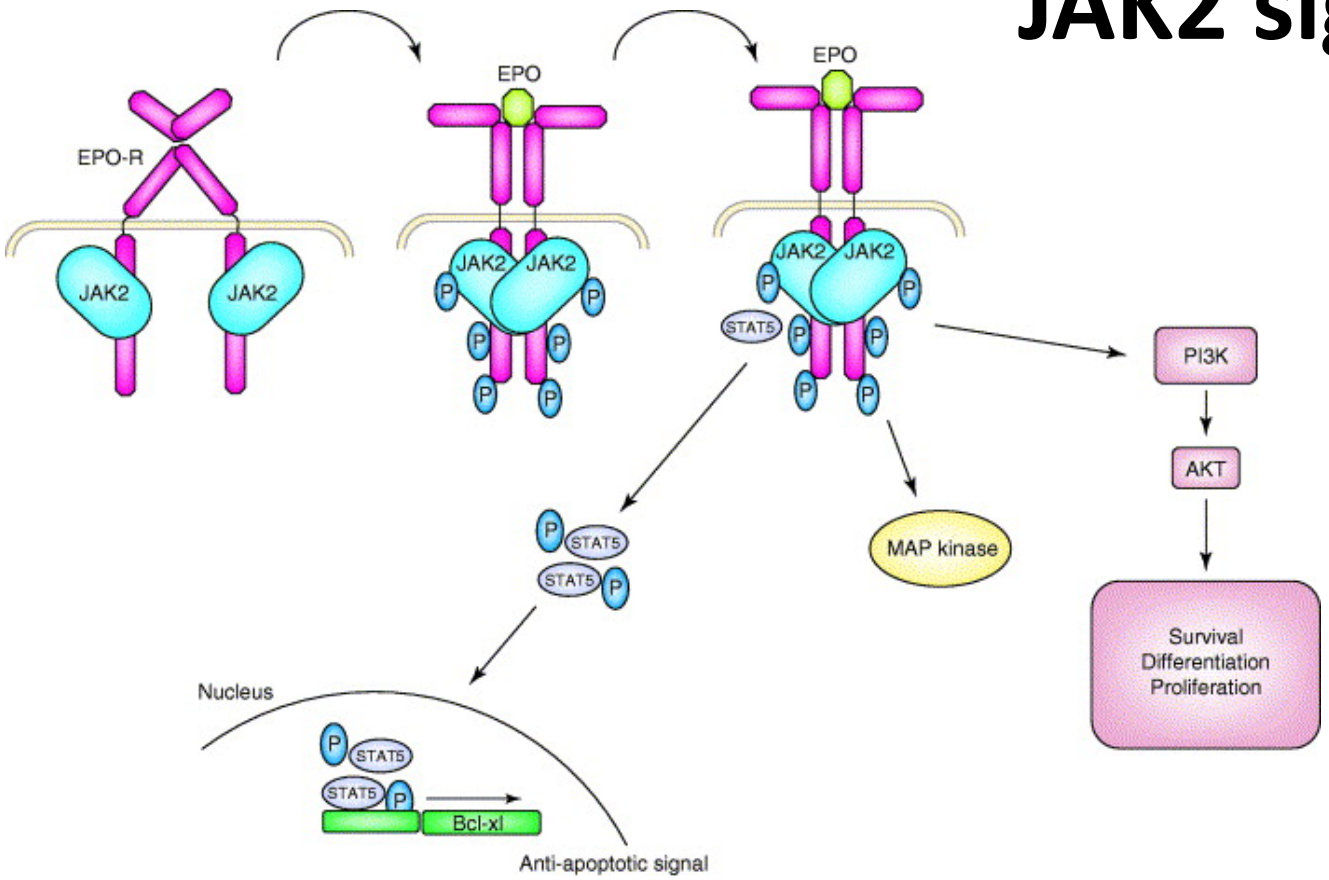
- its activation in turn affects the proliferation, differentiation and survival of hematopoietic cells and cytokine production

JAK2 positivity in myeloproliferation



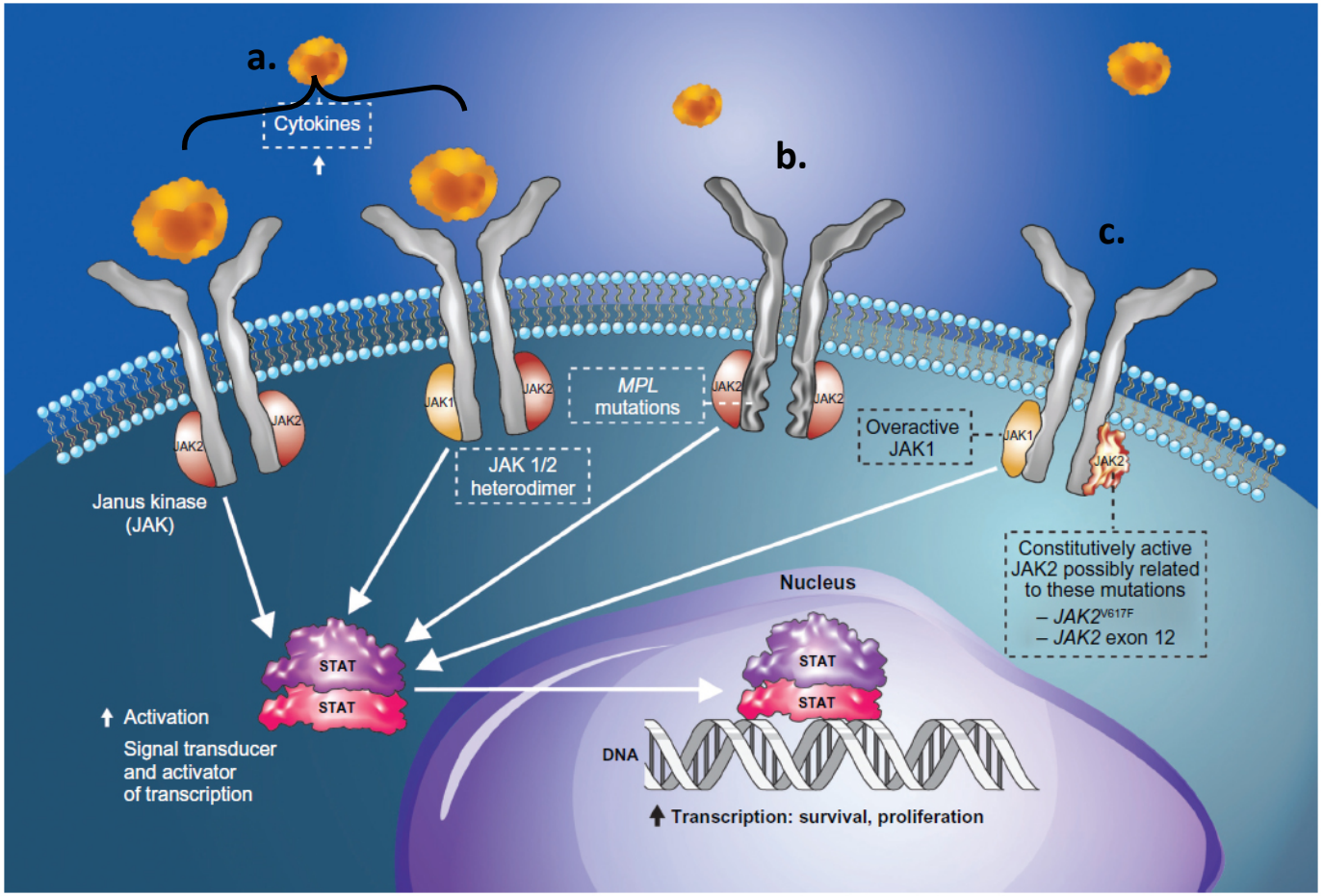
≈100% ≈50-60% ≈50-60%

JAK2 signalizace



- Janus kináza 2 (JAK2) je enzym, který prostřednictvím JAK/STAT drah ovlivňuje buněčnou proliferaci, aktivaci, migraci, apoptózu atd..
- má význam pro přenos signálů z receptorů pro růstové faktory (např. erytropoetin)
- bez signalizace EPOR je JAK2 inaktivní, po vazbě EPO se mění konformace receptoru, JAK2 se aktivuje a následně dochází k aktivaci JAK/STAT drah

obrázek: James Ch, Trends Mol Med 2005

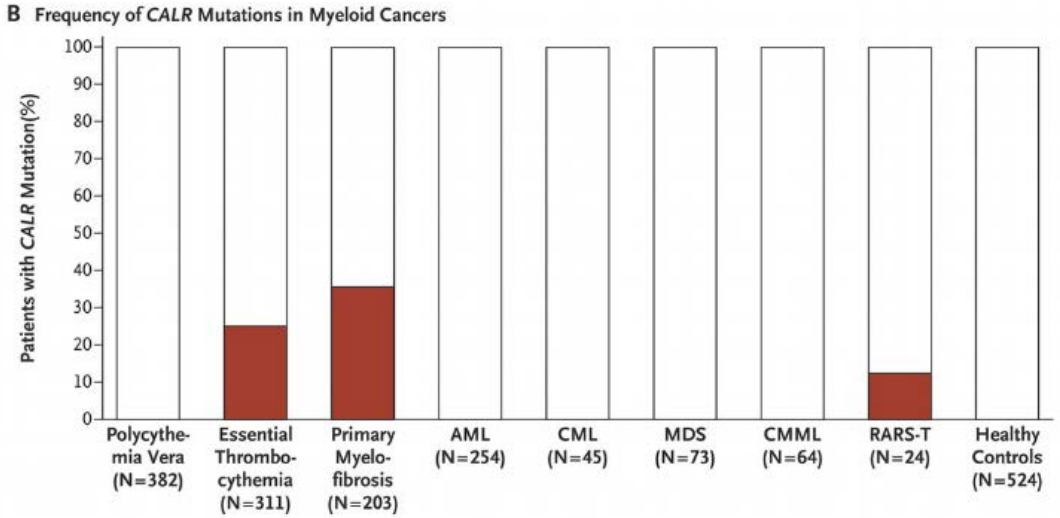


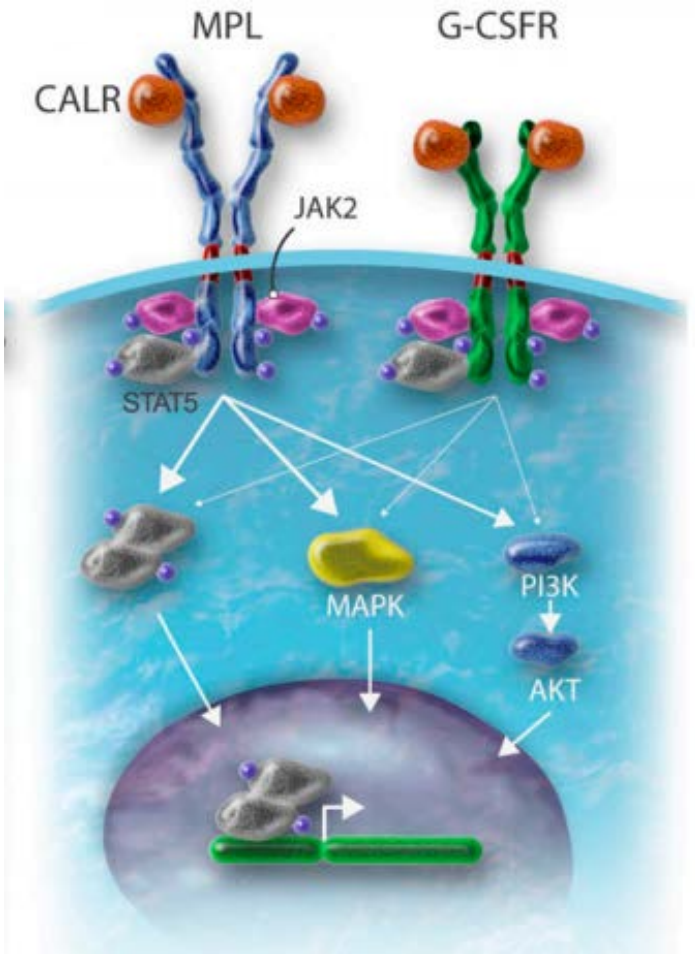
a) normal signaling state after ligand binding
b) ligand-independent signaling pathway activation - MPL receptor mutation causing thrombopoietin receptor activation
c) ligand-independent signaling pathway activation - JAK2 mutation or increased JAK1 function (constitutive activity)

MPL = receptor pro trombopoetin (myeloproliferative leukemia protein)
G-CSFR = granulocyte colony-stimulating factor receptor
EPOR = erythropoietin receptor

obrázek: Mughal T, Int J Gen Med 2014

Calreticulin mutations

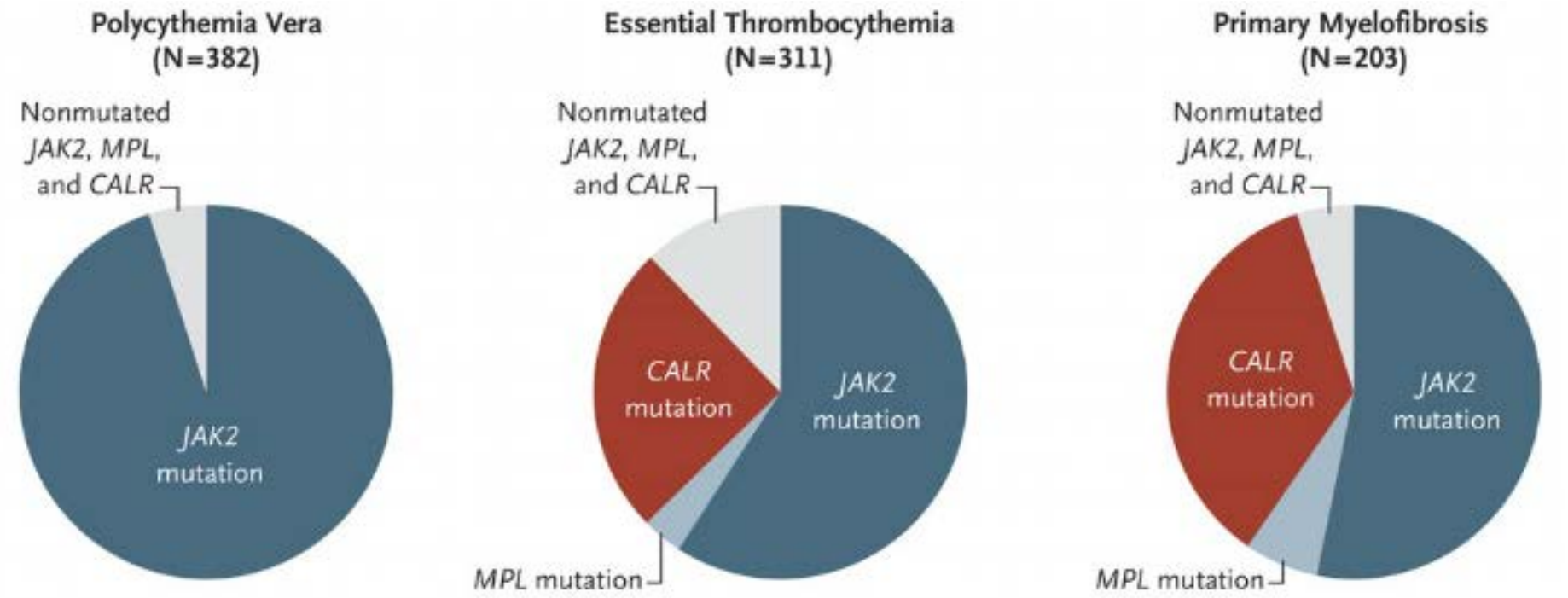




- calreticulin (CARL) mutations activate mainly MPL (less G.CSFR and EPOR in general)
- this explains the thrombocytosis associated with this mutation
- The CARL mutation is exclusive, it does not occur together with the JAK or MPL mutation

Klampfl T, NEJM 2013; Vainchenker W, Blood 2017

Mutations in Ph negative myeloproliferations



Klampfl T, NEJM 2013

Essential thrombocythemia

- clonal myeloproliferative disease affecting a multipotent hematopoietic cell

- characterized by excessive megakaryocyte proliferation and consequent persistent thrombocytosis

- absence of clonal marker (type Ph / bcr - abl)
- <5% with cytogenetic abnormality

ET (WHO) diagnostic criteria

clinical criteria for distinguishing ET from other MPNs and reactive thrombocytosis

MAJOR CRITERIA
1. thrombocytes ≥ 450x10^9/L
2. bone marrow biopsy with dominant proliferation of megakaryocyte lineage with increased number of enlarged, mature megakaryocytes
3. does not meet the criteria for PV, PMF, Ph + CML, MDS or other myeloid neoplasia
4. Mutation of JAK2V617F or CALR or MPL
MINOR CRITERIA
the presence of a clonal marker (abnormal karyotype) or the absence of evidence for reactive thrombocytosis

to dg .: must be filled with either ALL 4 LARGE or FIRST 3 LARGE + 1 SMALL

Clinical manifestations

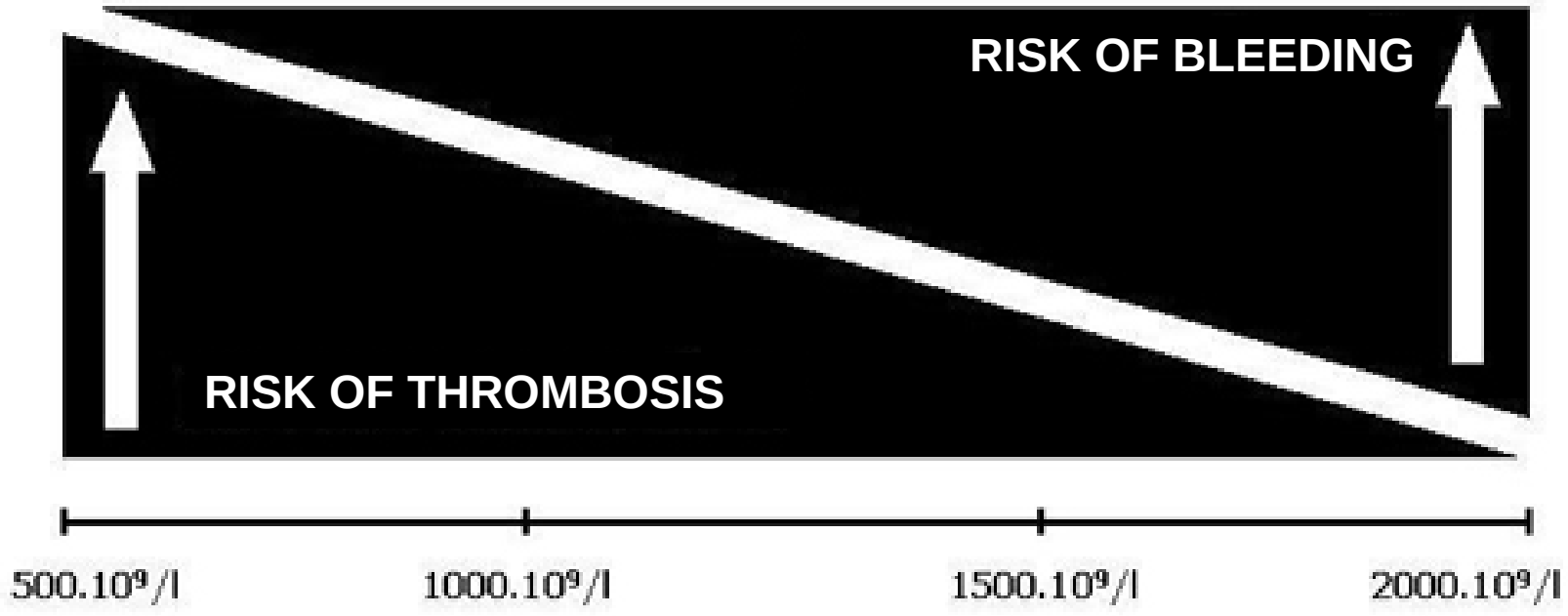
- 30 - 50% of patients are asymptomatic and it is an accidental finding in blood count
- if there are any symptoms, they are usually caused by **thrombotic or bleeding episodes**:
  - symptoms of microvascular occlusion (headache, blurred vision, dizziness) are common
  - venous or arterial thrombosis
  - bleeding is less common (more often in patients with platelets over 1000 x 109 / l, acquired von Willebrand's disease *)
  - splenomegaly (15 - 20%)

complication:

- transformation into myelofibrosis (5 - 10%)
- progress to AML / MDS (~ 1%)

*large vWF multimers are bound and removed from the circulation by multiplied platelets

Bleeding vs. thrombosis



Blood count

Krevní obraz					
B--Le	8,40	8,50		4 - 10	10^9/l
B--Ery	4,52	5,01		4 - 5,8	10^12/l
B--Hb	128	141		135 - 175	g/l
B--HTK	0,385	0,415		0,4 - 0,5	1
B--Obj ery.	85	83		82 - 98	fl
B--Hb ery	28,3	28,2		28 - 34	pg
B--Hb konc	332	340		320 - 360	g/l
B--Erytr.křivka	14,9	14,9		10 - 15,2	%
B--Trombo	1 147	638		150 - 400	10^9/l
B--Nbl abs	0,01	0,00		0 - 0,03	10^9/l
B--Nbl rel	0,001	0,000		0 - 0,006	1
Dif aut					
B--Seg	0,792	0,742		0,45 - 0,7	1
B--Ly	0,132	0,118		0,2 - 0,45	1
B--Mo	0,058	0,084		0,02 - 0,12	1
B--Eo	0,015	0,050		0 - 0,05	1
B--Ba	0,003	0,006		0 - 0,02	1
B--Seg - abs	6,60	6,30		2 - 7	10^9/l
B--Ly - abs	1,10	1,00		0,8 - 4	10^9/l
B--Mo - abs.	0,50	0,70		0,08 - 1,2	10^9/l
B--Eo - abs	0,10	0,40		0 - 0,5	10^9/l
B--Ba - abs	0,00	0,10		0 - 0,2	10^9/l

leukocytes:

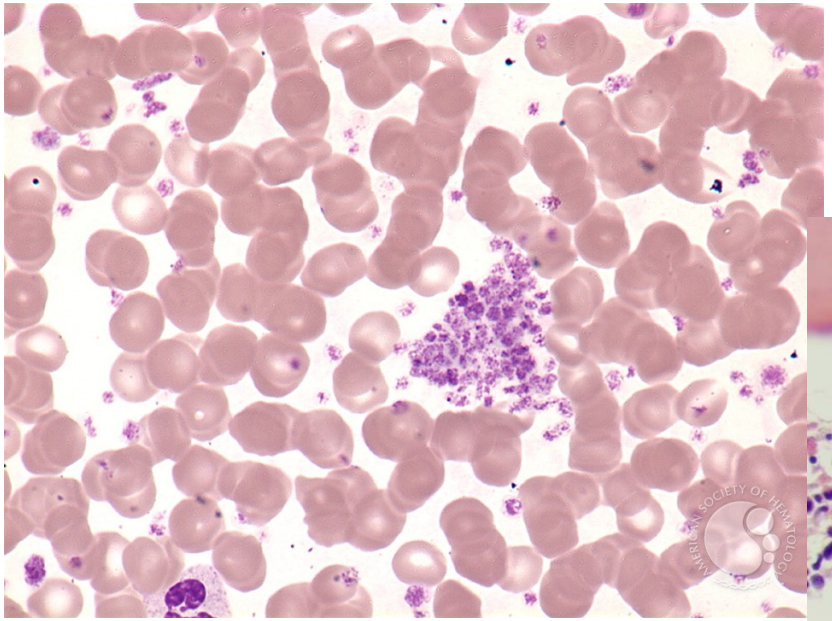
- mostly normal including differential, sometimes mild leukocytosis

platelets:

- main abnormality of KO, range from 450 to 2000 x 109 / l, anisocytosis

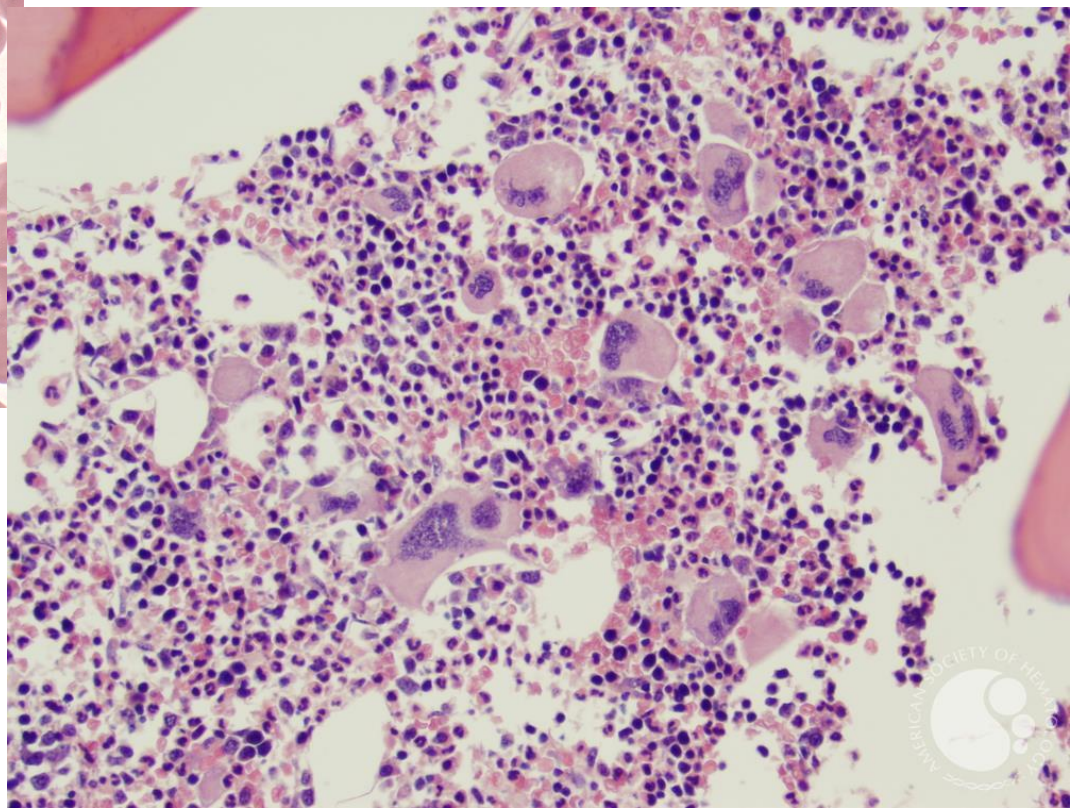
erythrocytes:

- usually normal, if there are no bleeding complications (then hypochromic, microcytic)

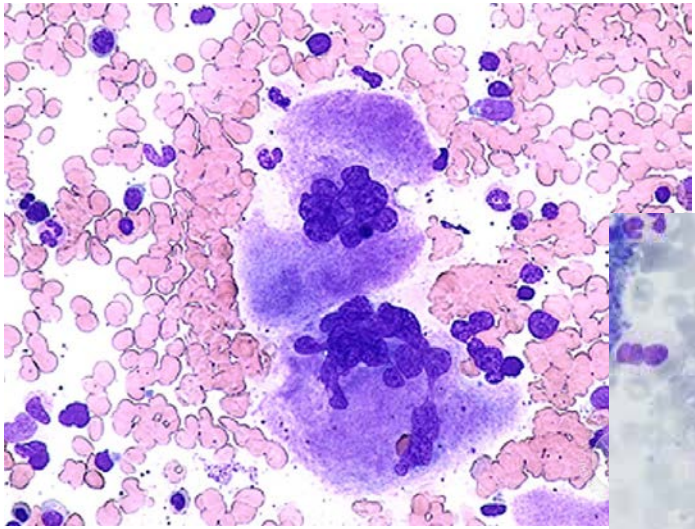


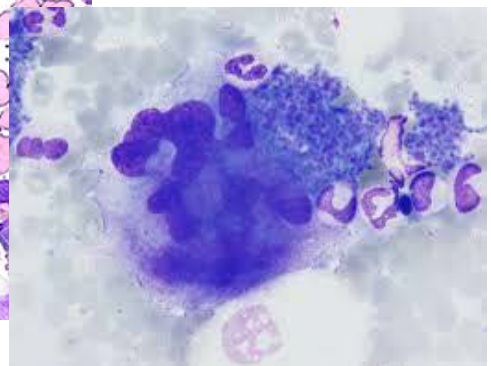
peripheral blood smear

bone marrow histology



bone marrow cytology





- increased number and size of megakaryocytes
- platelet clusters

Therapy

goal: to reduce the risk of complications and not to induce AML/MDS

we use treatment:

- antithrombotic - prevention of thrombotic complications (ASA)
- cyto / thromboreduction - to reduce platelet levels
  - Hydroxyurea
  - interferon alpha
  - anagrelid

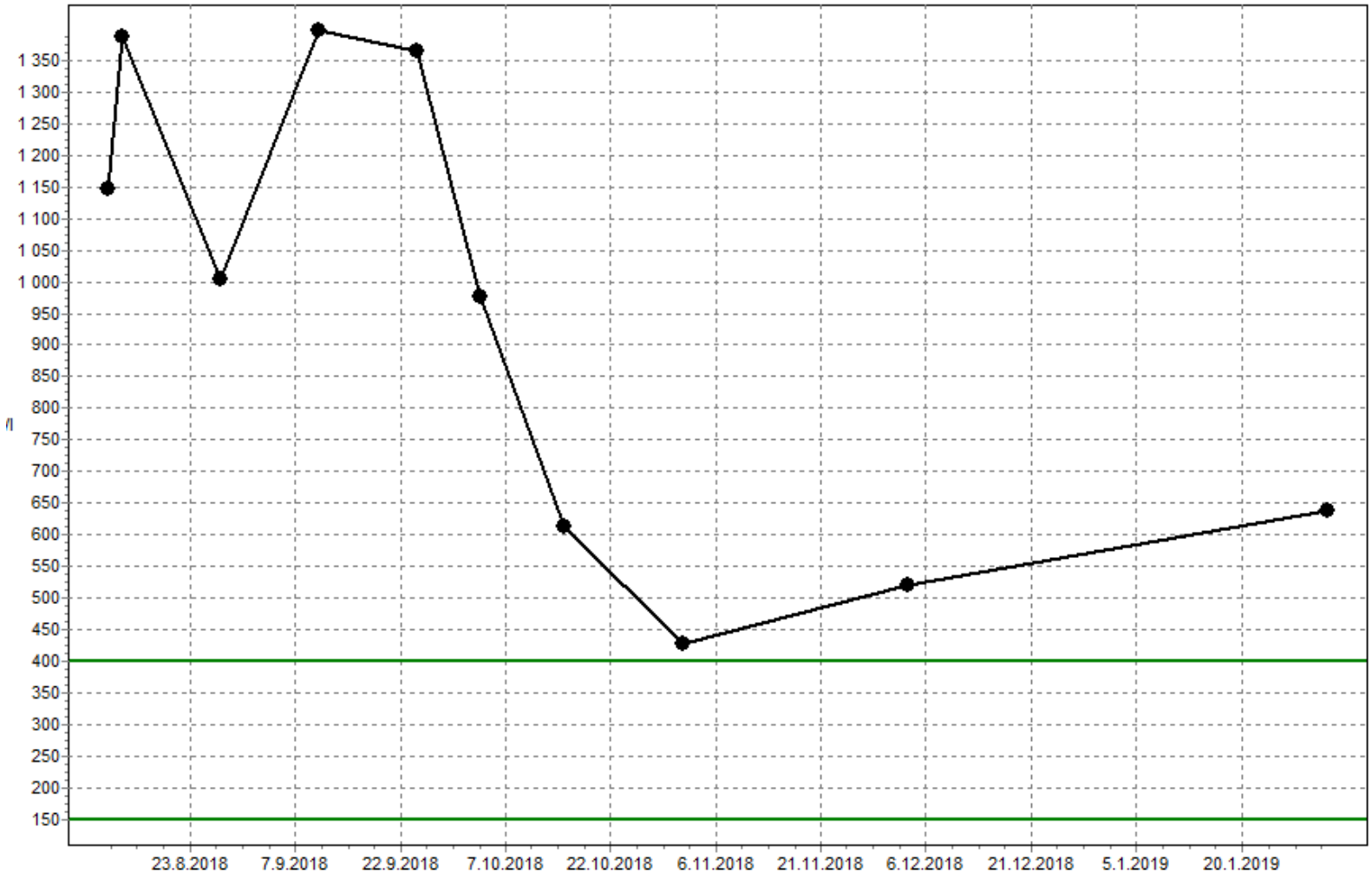
the risk of thrombosis (so-called IPSET score) is assessed, according to which treatment:

- low / medium risk patients
  - without treatment or low dose ASA
- high risk patients
  - always ASA + cytoreduction

IPSET = International Prognostic Score for Thrombosis in Essential Thrombocythemia

Development of blood count during treatment with anagrelide

platelet level



Conditions associated with reactive thrombocytosis

- Infection
- inflammatory processes: vasculitis, rheumatoid arthritis
- surgery, tissue damage (myocardial infarction, pancreatitis)
- malignancy (solid tumors, lymphomas)
- sideropenic anemia, hemolytic anemia
- acute blood loss
- condition after splenectomy
- "Rebound" after chemotherapy, immune thrombocytopenia

only a small proportion of patients with thrombocytosis have primary MPN
and an even smaller part of ET
reactive thrombocytosis has minimal clinical consequences ➡
Thrombocytosis per se is not a risk

Polycythemia (polyctemia vera, rubra, M. Vasques-Osler

- clonal disease at the level of hematopoietic stem cells characterized by uncontrolled proliferation of mainly erythroid, but also granulocyte and megakaryocyte lines

X

POLYCYTEMY = abnormal increase in red blood cell mass (of any etiology)

Classification of polycythemia / erythrocytosis

PRIMARY:

polycytemia vera

SECONDARY:

hypoxia:

1. altitude
2. chronic lung disease
3. right-left short circuit
4. hemoglobinopathy (O2 O2 affinity)
5. CO intoxication

kidney disease:

1. renal artery stenosis
2. nephrotic sy, glomerulonephritis

tumors:

1. EPO-producing tumors
   - renal, hepatic, ovarian Ca
   - pheochromocytoma
2. adrenocortical tumors

drugs:

1. androgens
2. recombinant erythropoietin

RELATIVE:

hemoconcentration at:

- stress
- dehydrated

smoking

Clinical picture

- the disease usually develops slowly and may be unrecognized for many years
- the **initial clinical presentation** may be:
    - accidental finding in an asymptomatic patient (~ 30%)
    - thrombosis (~ 30%)
    - splenomegaly or other symptoms of the disease

typical symptoms:

- headache, weakness, sweating, weight loss
- pruritus - 40% (after bath or shower)
- splenomegaly - 75%
- hepatomegaly - 30%
- hypertension, shin ulcers, angina pectoris
- neurological symptomatology (dizziness, headache, visual impairment)

Complication

thrombotic and hemorrhagic complications - 1/4 - 1/3 of patients

- mainly caused by hyperviscosity, RCM elevation, increased cell turnover and cytokine production
- venous and arterial thrombosis - involvement of any vessel (incl. CNS)
- erythromyalgia - may be preceded by dg. PV (manifested by erythema, burning, pain - especially of the lower limbs), associated with thrombocytosis
- Budd-Chiari syndrome (occlusion of the liver or inferior vena cava)
- gastric ulcers (cytokines, thrombocytosis)

thrombotic and hemorrhagic complications are the most common cause of death in patients with PV

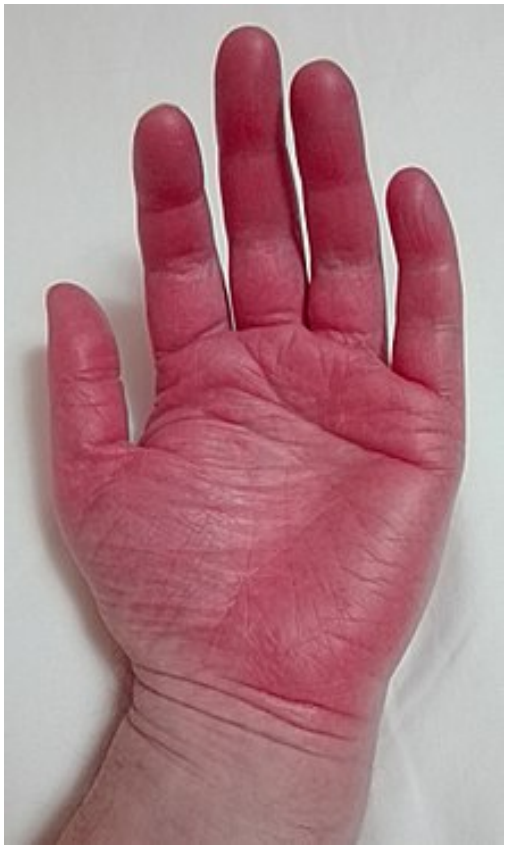
RCM = red cell mass

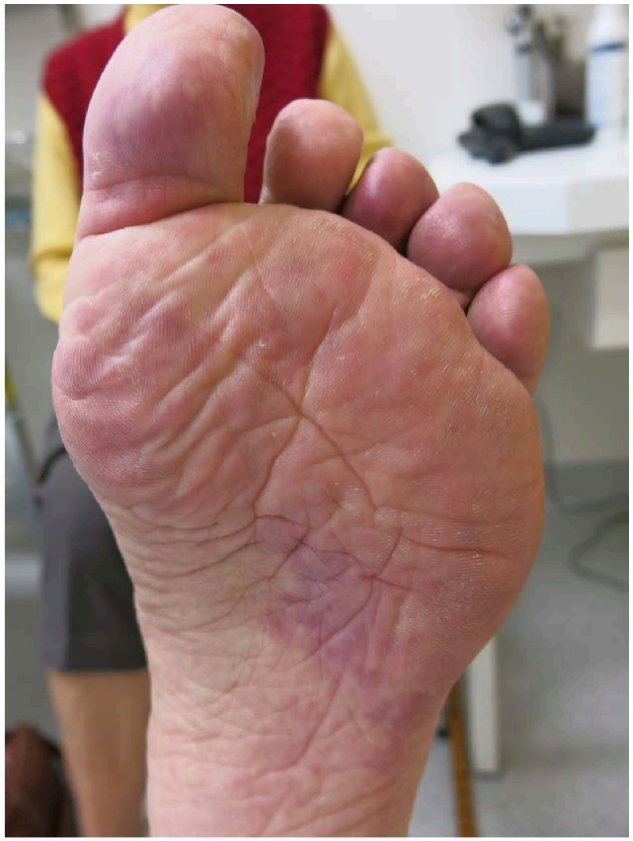
Diagnostická kritéria (WHO)

MAJOR KRITÉRIA
1. Hb > 165 g/L u mužů Hb > 160 g/L u žen nebo HTK > 0,49 u mužů HTK > 0,48 u žen nebo zvýšení RCM (red cell mass) >25% nad očekávanou hodnotu
2. biopsie KD: - hypercelulární KD vzhledem k věku nemocného - trilineární proliferace s přítomností zmnožených zralých megakaryocytů
3. mutace JAK2
MINOR KRITÉRIA
1. snížená hladina sérového erytropoetinu

k dg. PV musí být naplněna buď VŠECHNA 3 VELKÁ anebo PRVNÍ 2 VELKÁ + 1 MALÉ

erythromyalgia affecting the limbs





erythromyalgia affecting the limbs, seizure-like redness and overheating, burning pain in the skin of the legs or hands, accompanied by paleness or cyanosis, with a palpable pulse

Diagnostic criteria (WHO)

MAJOR CRITERIA
1. **Hb > 165 g/L male** **Hb > 160 g/L female** **or** **HTK > 0,49 male** **HTK > 0,48 female** **or** increase in RCM (red cell mass)> 25% above the expected value
2. BM biopsy: - hypercellular KD due to the patient's age - trilinear proliferation with the presence of multiplied mature megakaryocytes
3. mutation JAK2
MINOR CRITERIA
1. **decreased serum erythropoietin levels**

dg. PV: must be filled with either ALL 3 LARGE or FIRST 2 LARGE + 1 SMALL

Blood count

Krevní obraz				
B--Le	8,60		4 - 10	10^9/l
B--Ery	8,73		4 - 5,8	10^12/l
B--Hb	242		135 - 175	g/l
B--HTK	0,712		0,4 - 0,5	1
B--Obj ery.	82		82 - 98	fl
B--Hb ery	27,8		28 - 34	pg
B--Hb konc	340		320 - 360	g/l
B--Erytr.křivka	21,3		10 - 15,2	%
B--Trombo	196		150 - 400	10^9/l

erythrocytes:

- increased levels of erythrocytes, hemoglobin, hematocrit erythropoietin level is reduced (x sec. polycythemia)

leukocytes:

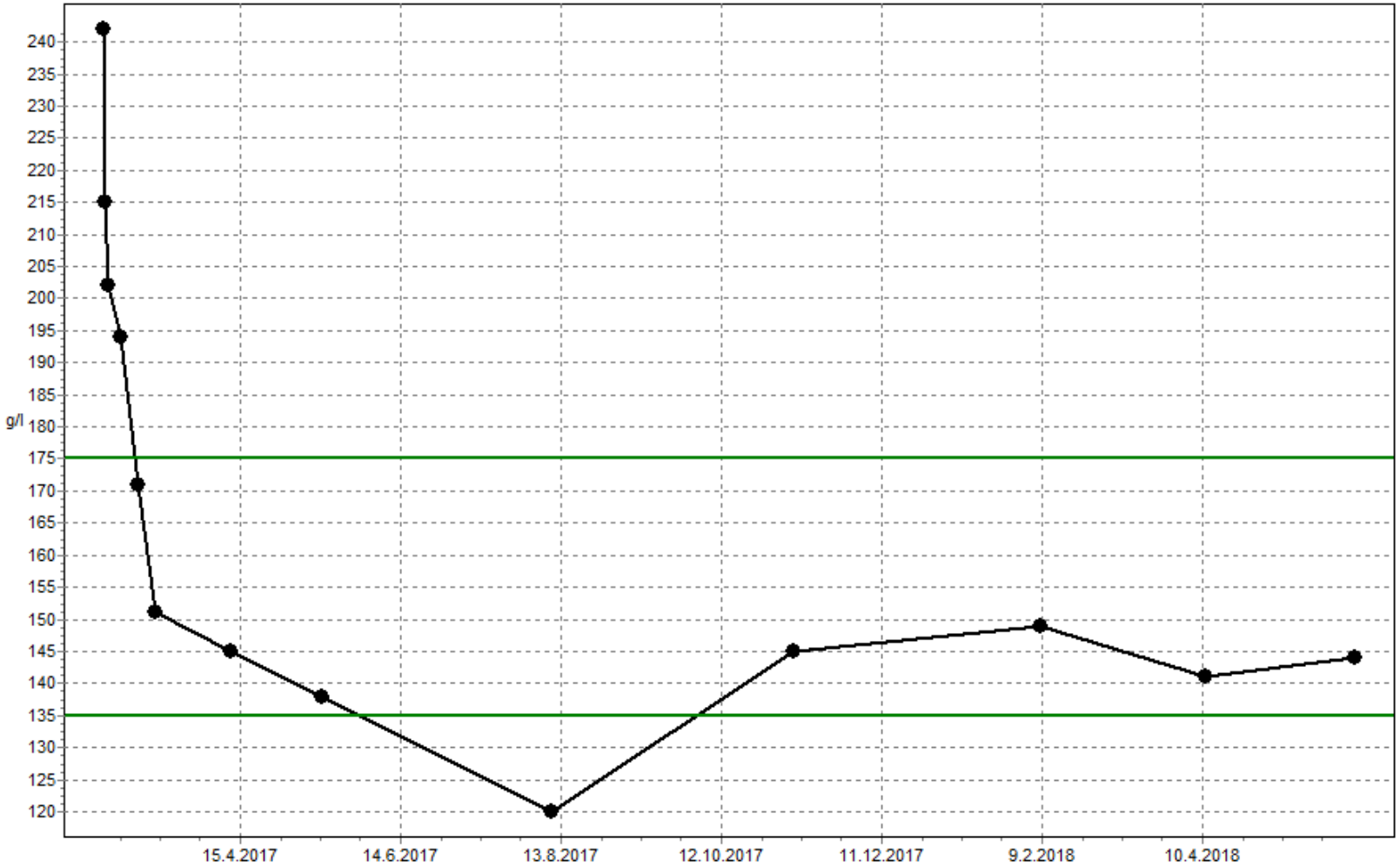
- often slightly elevated (neutrophilia)

platelets:

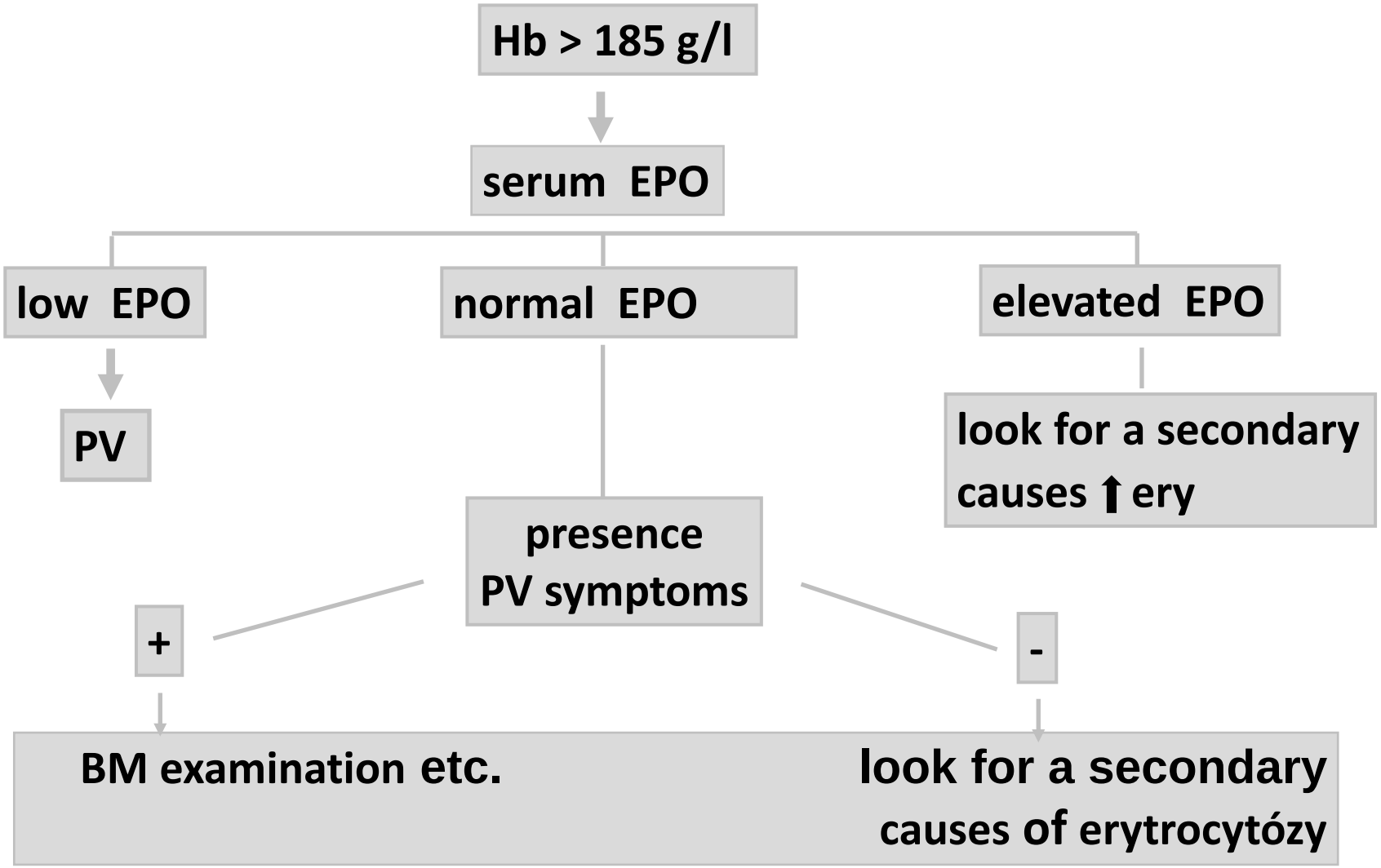
- up to 50% of patients also have thrombocytosis

Development of KO in hydroxyurea treatment

Hemoglobin level



Diagnostic algorithm



Treatment

goal: ➡ prevent thrombotic (hemorrhagic) complications

➡ reduce the risk of transformation in acute leukemia or myelofibrosis

we use treatment:

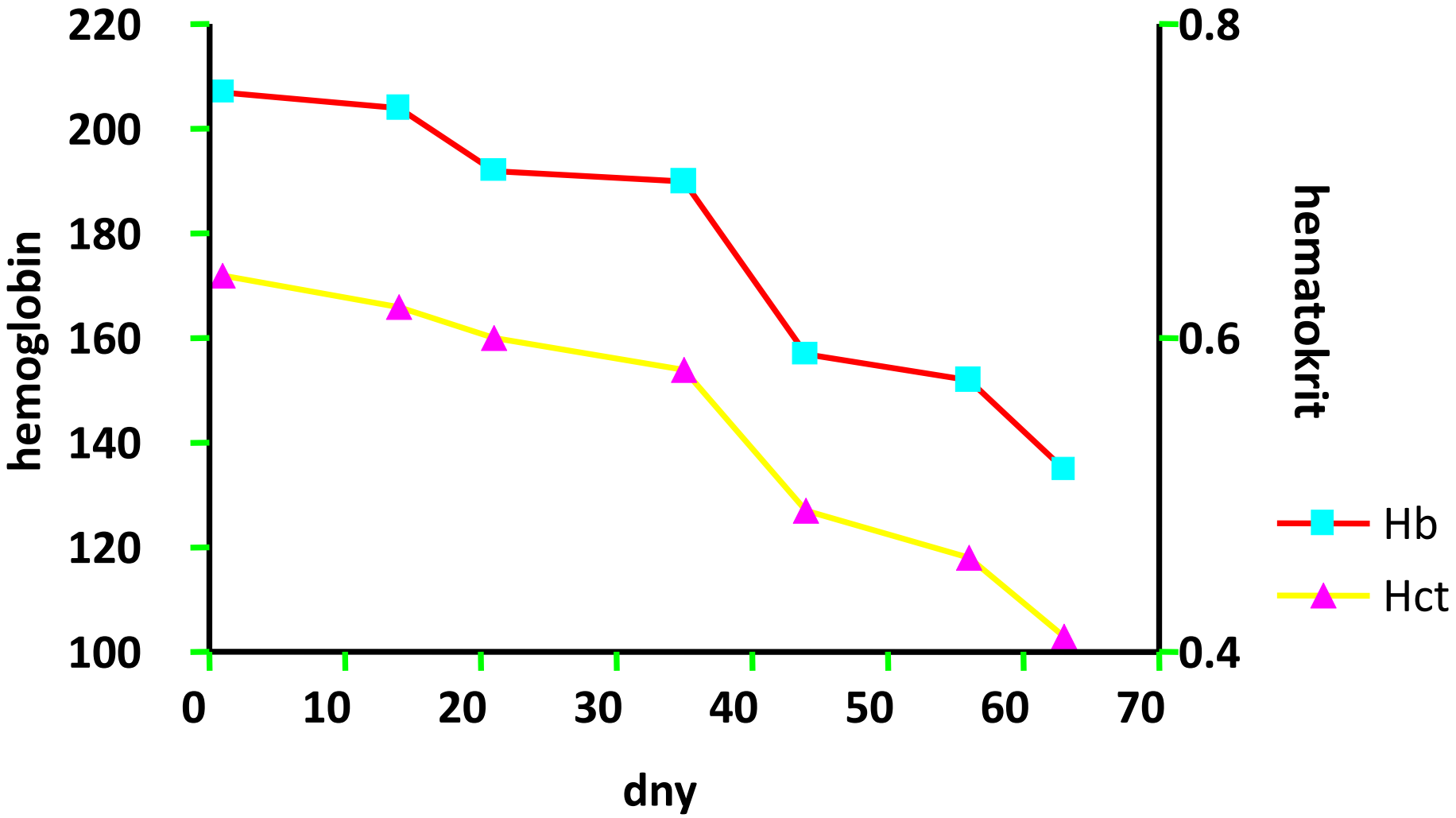
- Phlebothomy (reduction of erythrocyte mass and hyperviscosity)
- cytoreductive therapy: hydroxyurea, interferon alfa
- antiplatelet therapy to prevent thrombosis: ASA
- anticoagulation: only in case of thrombosis

the risk of thrombosis is assessed on the basis of:

- patient's age (> 60 years)
- history of thrombosis

based on normalization of hematocrit (<0.45) by phlebothomy or erythrocyte apheresis + low dose ASA

case: response to weekly phlebothomy 0.5 l



Primary myelofibrosis (PMF)

pathogenesis: three basic features

- clonal hemopathy (overproduction of era, leuko, thrombo)
- bone marrow fibrosis (increase of fibrosis network in BM) *
- extramedullary hematopoiesis (tumor clone settles and grows outside the bone marrow - liver, spleen)

*fibrotization is caused by growth factors that stimulate fibroblasts to produce collagen

Clinical picture

most often **non-specific**, usually resulting from the presence of:

- anemia, thrombocytopenia, leukocytopenia
- splenomegaly (shortness of breath, abdominal pain, portal hypertension)
- general symptoms

other findings:

- hepatomegaly (50 - 75% of patients)
- bleeding symptoms
- hypermetabolic state (weight loss, febrile, sweating and severe bone pain), very unfavorable prognostic

splenomegaly - often very massive

- the disease progresses slowly, splenomegaly may
- precede other signs of the disease for months to years

Laboratory findings

typical finding: "leukoeytroblast" finding in a peripheral blood count (younger elements of white and red series)
⇨ manifestations associated with extramedullary hematopoiesis

ERYTROCYTES

- dramatic changes in morphology: anisocytosis (size), poikilocytosis (shape), teardrop-shaped red cells
- anemia

LEUKOCYTES

- normal or leukocytosis (usually up to 50 x 109 / l), □CD34 + (stem) cells
- later leukopenia (progression of fibrosis)

THROMBOCYTES

- increased, later rather thrombocytopenia, dysfunction various sizes and strange shapes (also giant platelets)

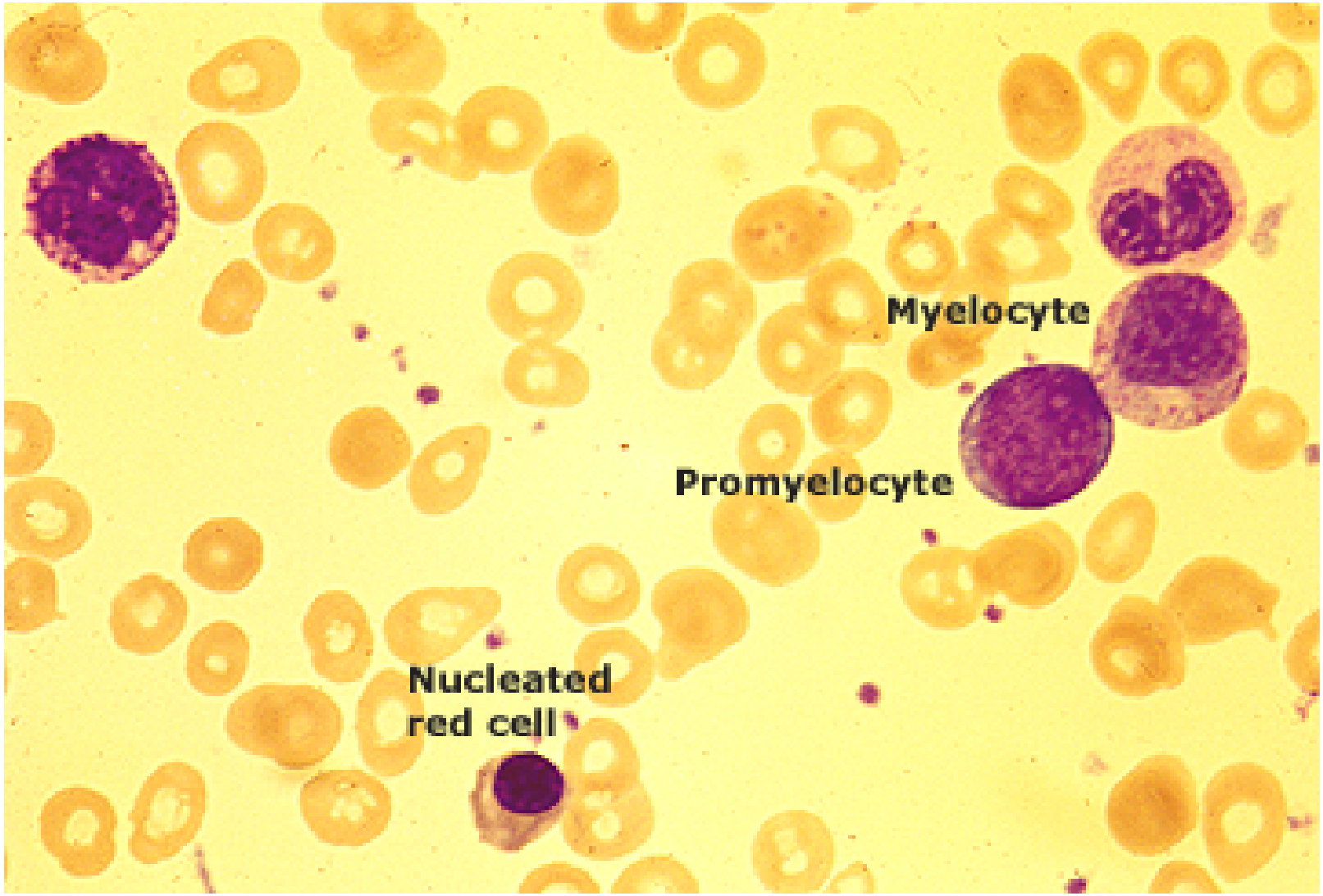
BONE MARROW:

- initially hyperplasia, in advanced stages fibrosis with loss of hematopoiesis (in biposia the marrow is difficult to aspirate)

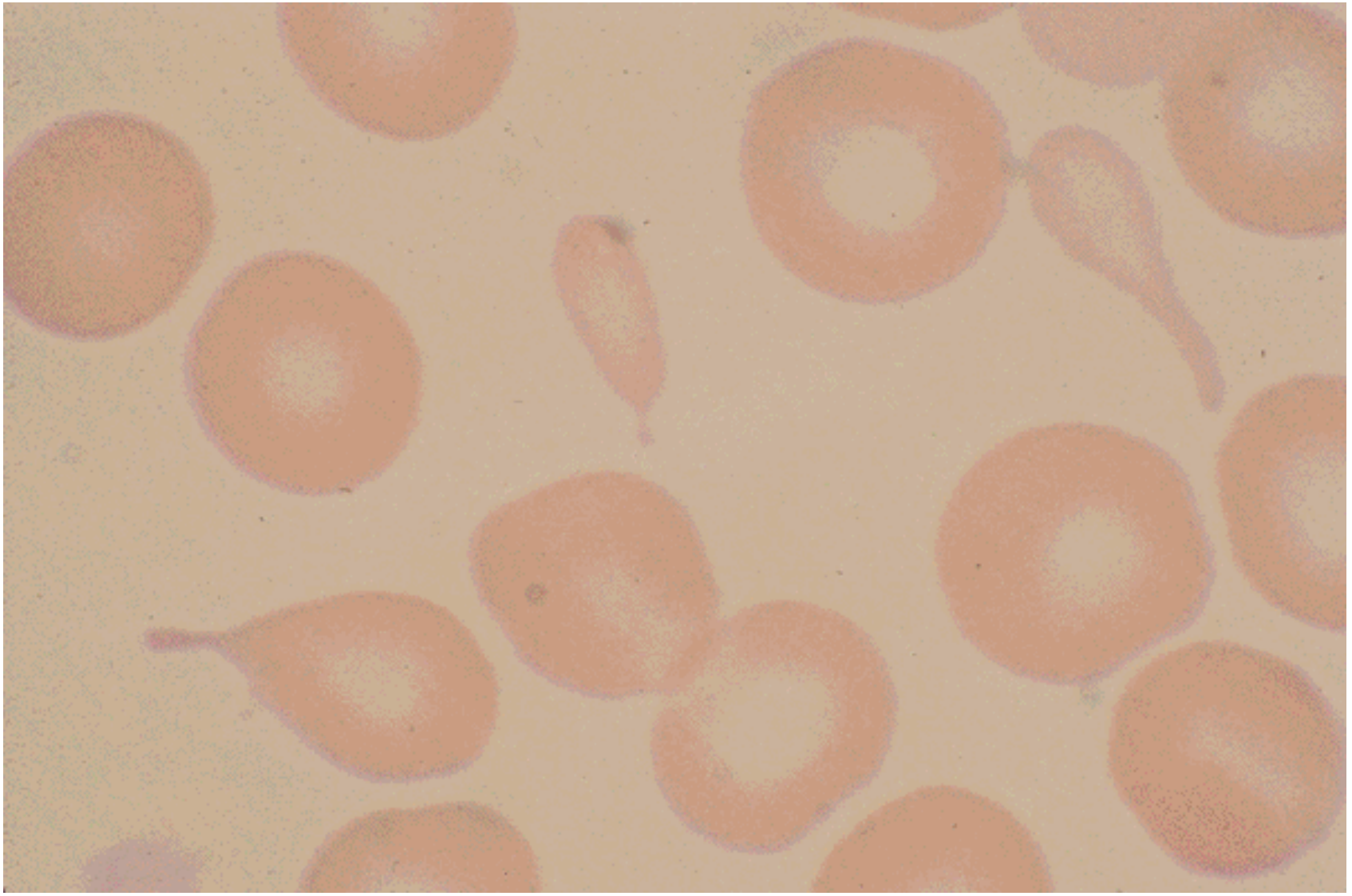
Blood count - *example*

Krevní obraz				
B--Le	1,50		4 - 10	10^9/l
B--Ery	3,23		4 - 5,8	10^12/l
B--Hb	102		135 - 175	g/l
B--HTK	0,291		0,4 - 0,5	1
B--Obj ery.	90		82 - 98	fl
B--Hb ery	31,7		28 - 34	pg
B--Hb konc	352		320 - 360	g/l
B--Erytr.křivka	22,9		10 - 15,2	%
B--Trombo	27		150 - 400	10^9/l
B--Ret př. rel	0,007		0,005 - 0,025	1
B--Retikulocyty př	0,023		0,025 - 0,1	10^12/l
Dif mikr.				
B--Seg	0,96		0,47 - 0,7	1
B--Tyc	0,03		0 - 0,04	1
B--Ly	0,01		0,2 - 0,45	1
B--Nbl	1/100		0 - 0	1
B--Ovalocyty	+			
B--Polychromazie	+			
B--Vakuolizace	+			
B--Slzičkovité ery	+			
B--Anizocytoza ery	++			
B--Makrotrombocyty	+			

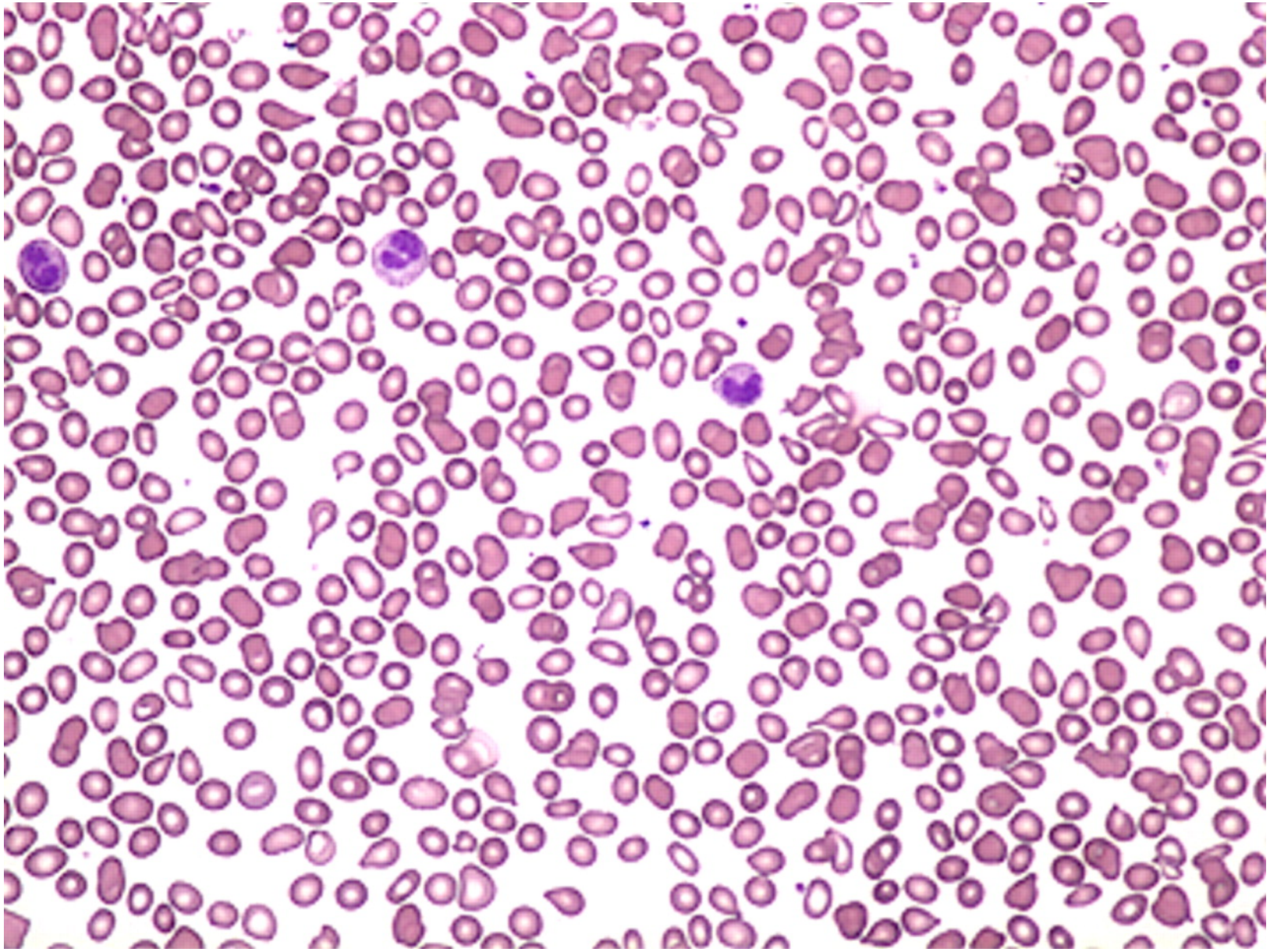
trepanobiopsy:
the intertrabecular spaces are mostly filled with connective tissue. Hematopoiesis is reduced, we find several megakaryocytes, few erythroid precursors, isolated elements of the granulocyte lineage.
conclusion:
Myeloproliferative disease - the appearance of osteomyelofibrosis.



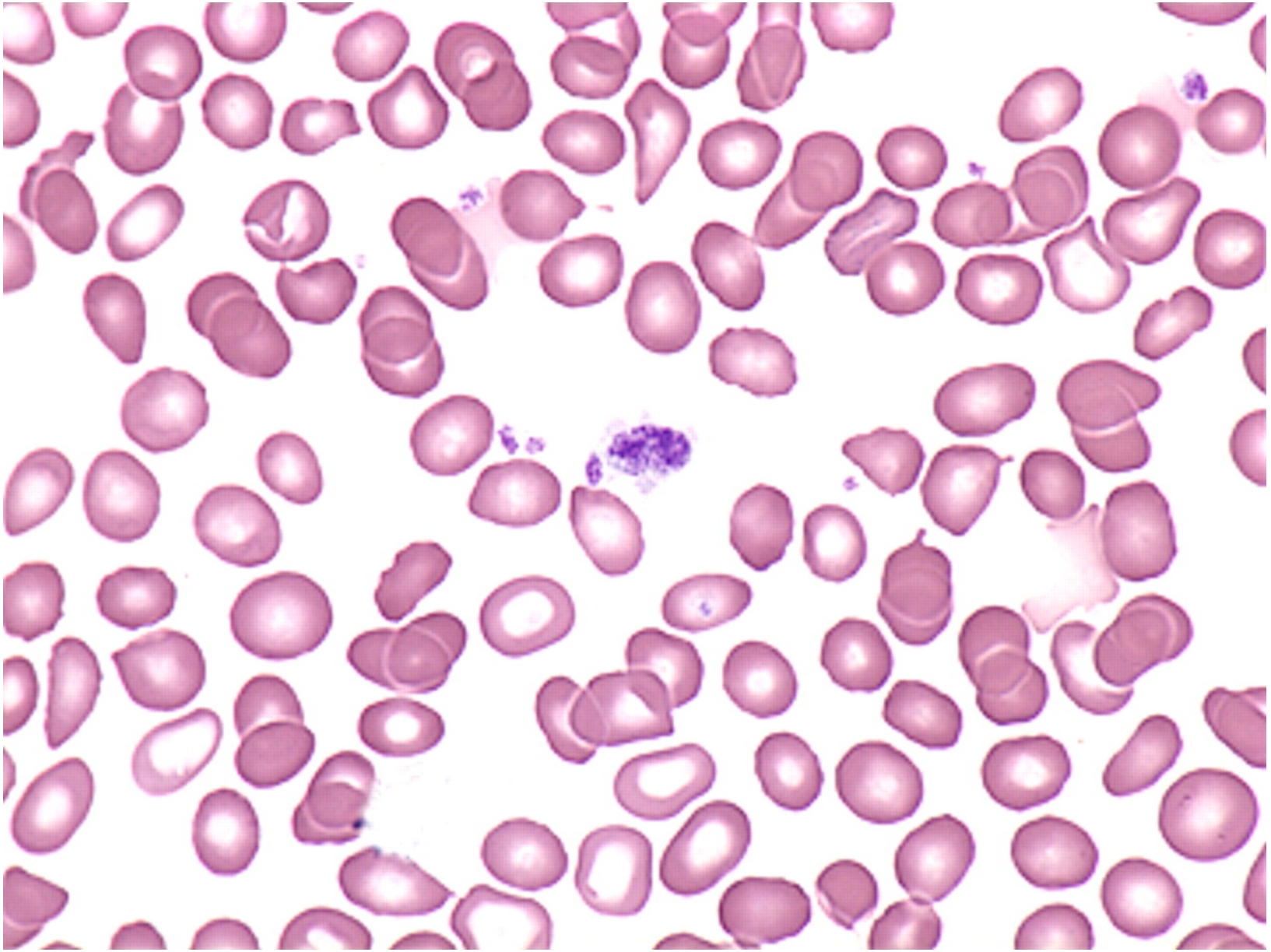
leukoerythroblast image: presence of nuclear erythrocytes a immature leukocytes



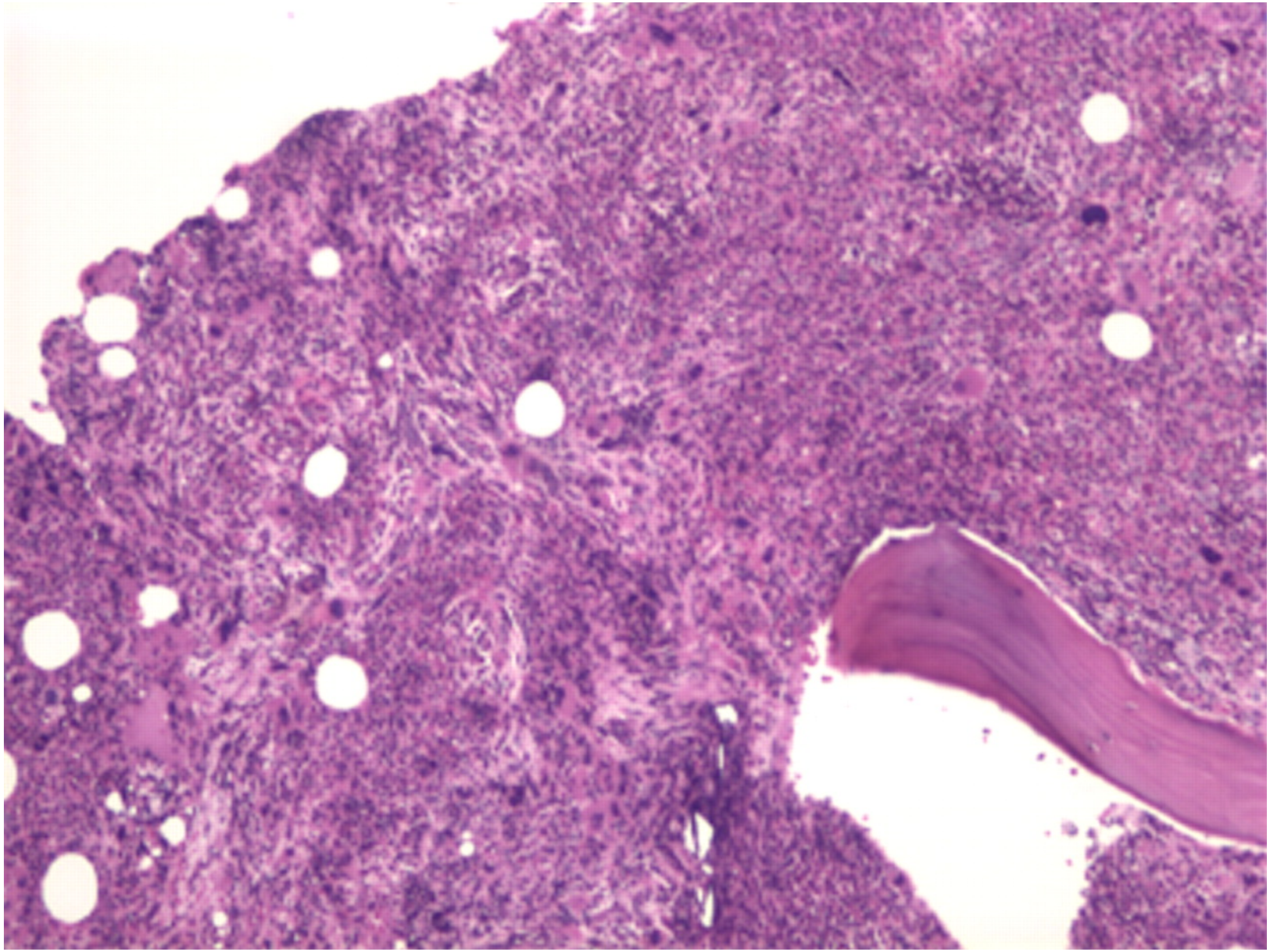
peripheral blood smear: teardrop shaped red cells



peripheral blood smear: poikilocytosis



peripheral blood smear: atypical large platelets (giant)



bone marrow biopsy: fibrosis (collagen and reticulin)

Diagnostic criteria (WHO)

MAJOR CRITERIA

1. (morphological) biopsy of KD - increased number of atypical megakaryocytes, increased cellularity of KD, proliferation of granulopoiesis and often reduction of erythropoiesis

2. (clinical) non-fulfillment of criteria for Ph + CML, ET, MDS or other myeloid neoplasias

3. (genetic) mutation JAK2, CALR nebo MPL

- or another clonality marker (most mutations ASXL1, EZH2, TET2, IDH1 / 2, SFSF2, SF3B1)
- or absence (exclusion) of reactive reticulin fibrosis (infection, autoimmunity ..)

MINOR CRITERIA

1. anemia not caused by other diseases
2. leukocytosis ≥ 11 x 109 / l
3. splenomegaly
4. increase in LDH above normal

dg. PMF: must be filled with ALL 3 LARGE AND AT LEAST 1 SMALL

The most important complications

1. ANEMIA
2. SPLENOMEGALY
3. THROMBOTIC and HEMORHAGIC COMPLICATIONS
4. GENERAL SYMPTOMS
5. PANCYTOPENIA -> bleeding + infectious complication

therapy:

symptomatic + specific (JAK inhibitors)

6. TRANSFORMATION to AML

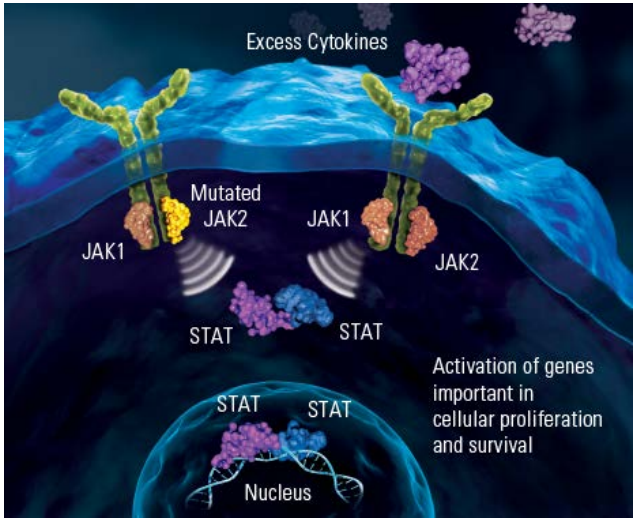
therapy:

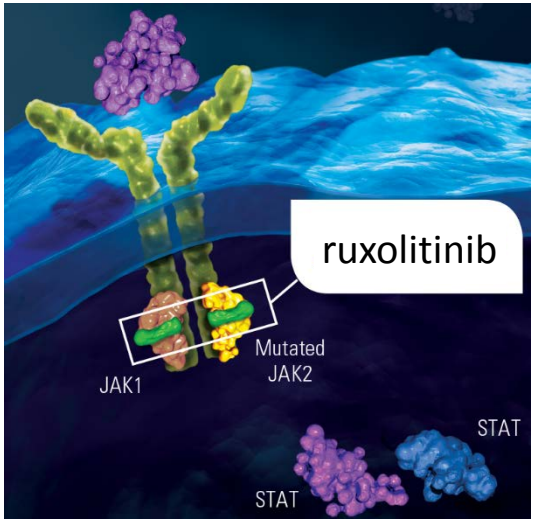
alogenneic bone marrow transplantation

Therapy

therapy options:

- observation (without major changes in KO and splenomegaly)
- cytoreduction: chemotherapy (hydroxyurea, busulfan), IFN
- substitution therapy, erythropoietin
- JAK2 inhibitors (ruxolitinib, pacritinib)
- allogeneic bone marrow transplantation

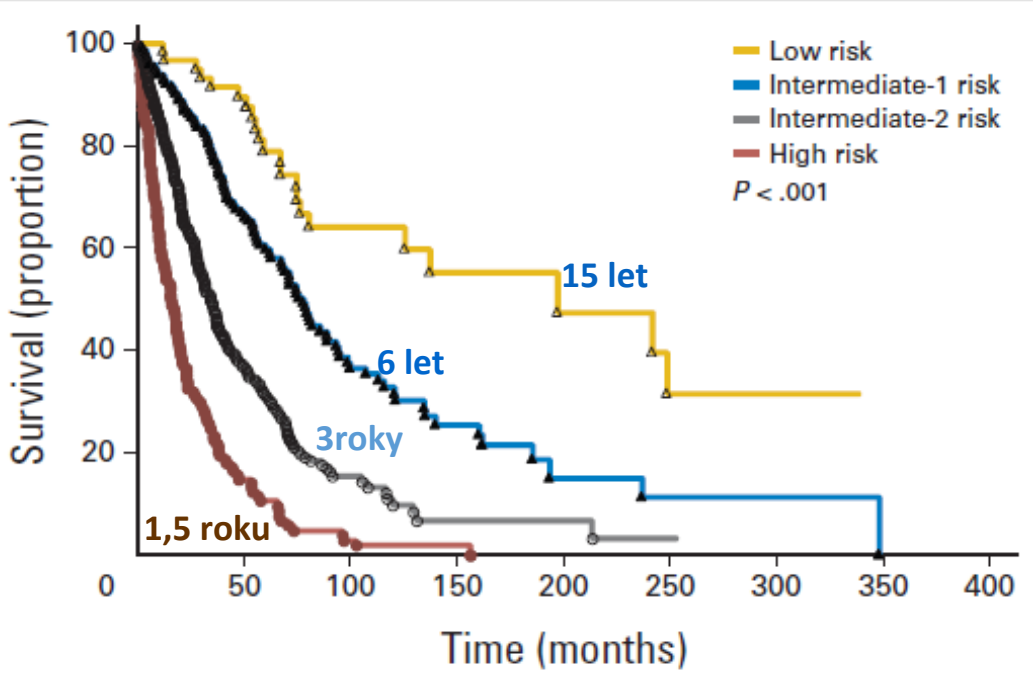




- JAK1 signals proinflammatory cytokines, JAK2 growth factors
- ruxolitinib blocks JAK2 (mutated and wild-type)

Disease risk assessment

- chronic (progressive) disease
- since diagnosis, the median long-term survival is 4-5 years (shorter than for PV, ET)



- several risk groups based on: age, KO values, general symptoms, cytogenetics, etc.
- higher risk patients are candidates for allogeneic transplantation

Gangat N, JCO 2011

Differential diagnostics

CML (may have fibrosis in the bone marrow)

- resolution: Ph chromosome or bcr / abl

polycythemia vera and essential thrombocythemia:

- resolution can be difficult
- 15-25% of affected PV progresses to postpolycytemic myelofibrosis

hairy-cell leukemia

so-called secondary myelofibrosis

- reactions to the presence of certain diseases:

❶ **Hematological**

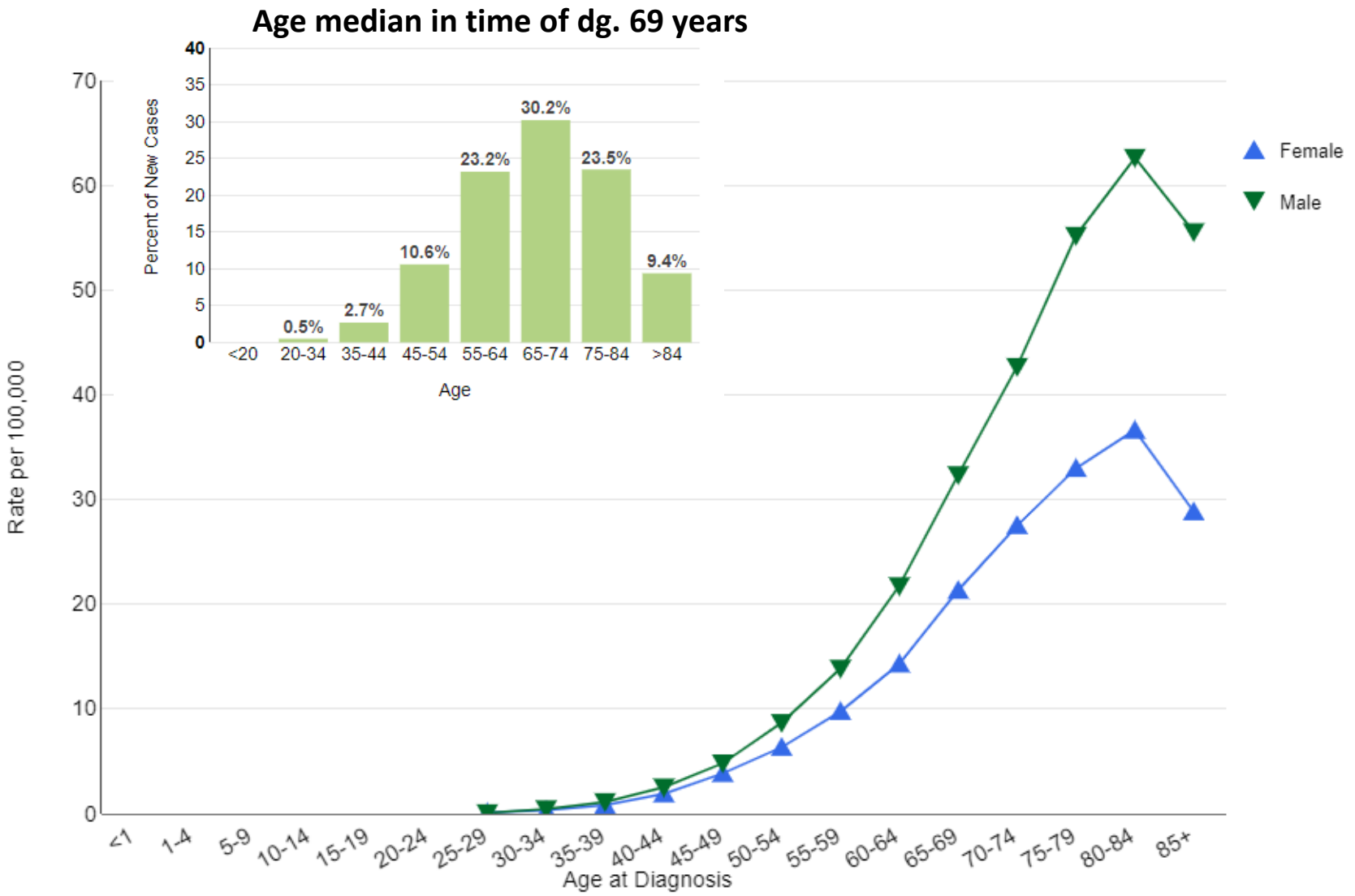
⇨ leukemias
⇨ lymphomas
⇨ multiple myeloma
⇨ metastatic carcinomas

❷ **Non-hematological**

⇨ renal osteodystrophy
⇨ system lupus erytematodes
⇨ polyarteritis nodosa
⇨ infection (TBC, HIV)
⇨ after exposure to toxins (eg benzene, X-rays, etc.)

MULTIPLE MYELOMA
(plazmocytoma, M.Kahler)

Age distribution of patients with MM



data seer.cancer.gov 2012 - 2016

What is a paraprotein ?

- a monoclonal immunoglobulin or only an immunoglobulin light chain detectable in blood or urine
- it is produced by clonal proliferation of plasma cells or B-lymphocytes
- synonyms: M-protein, light chains in urine ➡ Bence-Jones

The most common diseases associated with paraproteinemia

- multiple myeloma
- monoclonal gammopathy of unclear significance (MGUS)
- Waldenström's macroglobulinemia

PARAPROTEIN ≠ MYELOMA

2/3 paraproteinemias without malignancy

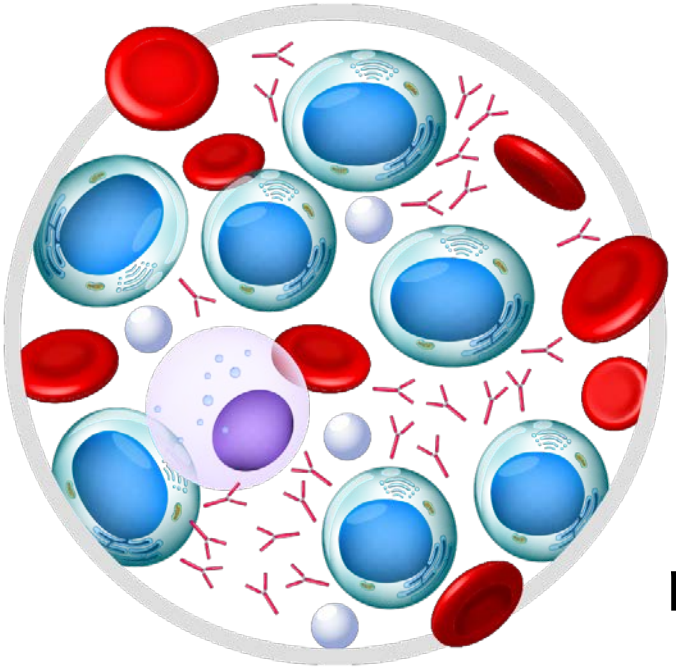
Multiple myeloma

- uncontrolled proliferation and accumulation of plasma cells derived from a malignant clone of B-lymphocytes with the usual maximum localization in the bone marrow and the production of monoclonal immunoglobulin

- the clinical variant is plasmacellular leukemia, smoldering (asymptomatic, SMM) and extramedullary plasmacytoma represents about 10-15% of hematological tumors

- 90% of the disease occurs in patients over 50 years of age

SMM = smoldering multiple myeloma



malignant plasma cells

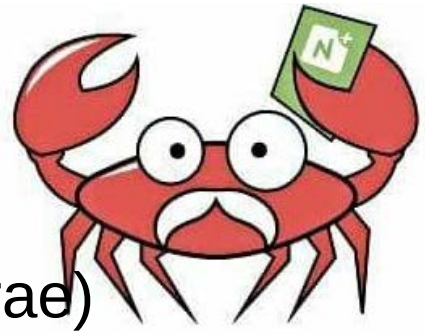
tumor effect

- bone lesions
- bone marrow failure

effect of paraprotein

- kidney failure
- hyperviscosity
- amyloid
- immune defect

Clinical picture



- skeletal pain, spontaneous fractures (vertebrae)
- anemic syndrome
- extramedullary propagation of myeloma
- manifestations of **hypercalcemia** (disorientation, weakness)
- manifestations of **hyperviscous syndrome**
  - deterioration of microcirculation - especially CNS, retina
  - headaches, visual disturbances
- **complication:**
  - neurological (spinal cord compression during vertebral compression)
  - kidney failure (up to dialysis program)

Diagnostic criteria

diagnosis with the classical trias:

- bone marrow infiltration by plasma cells
- osteolytic deposits / pathological fractures
- high paraprotein / Bence-Jones

Laboratory findings

laboratory findings:

- high sedimentation
- variously expressed anemia (possibly also thrombocytopenia, leukopenia)
- the presence of paraprotein resp. Bence-Jones proteins (light chains) - serum / urine electrophoresis
- calcium levels, renal tests, β2-microglobulin

bone marrow examination:

- bone marrow aspiration (plasma cell infiltration)

graphic examinations:

- bone X-ray, magnetic resonance of the skeleton (osteolytic deposits, osteoporosis)
- bone scintigraphy (+ -)

Examples

plasmacellular leukemia (anemia, thrombocytopenia, diffus plasma cells)

Krevní obraz				
B--Le	14,30	4 - 10	10^9/l
B--Ery	2,72	3,8 - 5,2	10^12/l
B--Hb	90	120 - 160	g/l
B--HTK	0,248	0,35 - 0,47	1
B--Obj ery.	91	82 - 98	fl
B--Hb ery	33,0	28 - 34	pg
B--Hb konc	362	320 - 360	g/l
B--Erytr.křivka	15,8	10 - 15,2	%
B--Trombo	44	150 - 400	10^9/l
B--Nbl abs	0,01	0 - 0,02	10^9/l
B--Nbl rel	0,001	0 - 0,003	1
Dif mikr.			
B--Seg	0,15	0,47 - 0,7	1
B--Tyc	0,03	0 - 0,04	1
B--Ly	0,31	0,2 - 0,45	1
B--Mo	0,01	0,02 - 0,1	1
B--MMc	0,02	0 - 0	1
B--Plasmat. buňka	0,47	0 - 0	1
B--Prolymfocyt	0,01	0 - 0	1

anemia

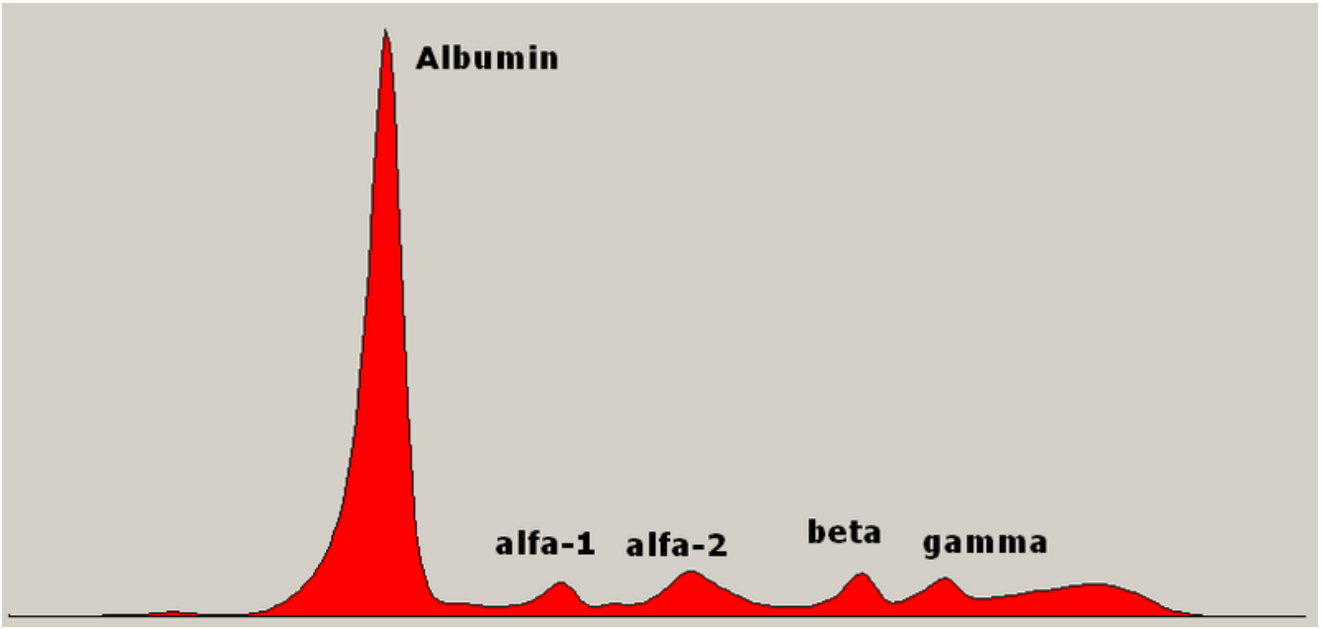
Krevní obraz				
B--Le	8,60	4 - 10	10^9/l
B--Ery	2,46	3,8 - 5,2	10^12/l
B--Hb	83	120 - 160	g/l
B--HTK	0,237	0,35 - 0,47	1
B--Obj ery.	96	82 - 98	fl
B--Hb ery	33,7	28 - 34	pg
B--Hb konc	351	320 - 360	g/l
B--Erytr.křivka	14,8	10 - 15,2	%
B--Trombo	230	150 - 400	10^9/l

ELFO: M protein, light chains, BJ protein in urine

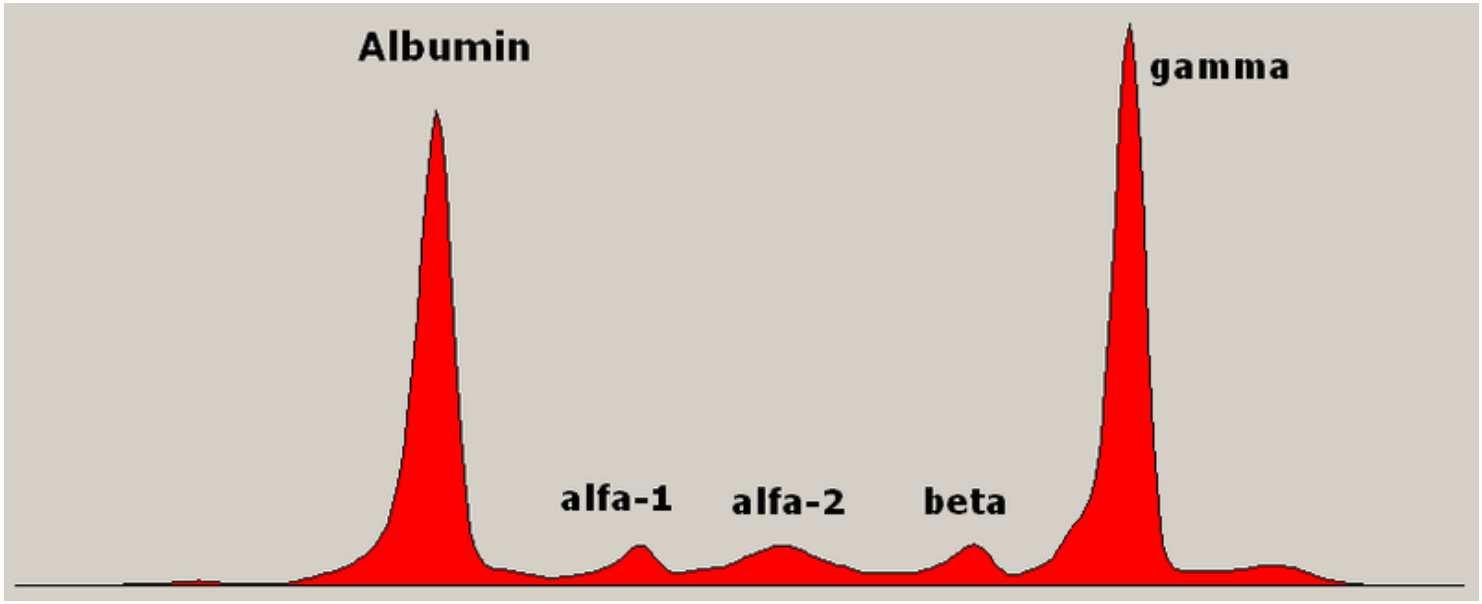
Interpretace ELFO	Typ monoklo	Typ monoklo			
S--Albumin	0,341	0,342	-	0,53 - 0,65	1
S--Alfa 1-globulin	0,029	0,027	-	0,02 - 0,04	1
S--Alfa 2-globulin	0,086	0,073	<	0,08 - 0,13	1
S--Beta-globulin	0,076	0,069	<	0,09 - 0,16	1
S--Gama-globulin	0,468	0,489	-	0,115 - 0,19	1
S--Imunofix. ELFO	IgA kappa	IgA kappa			_
S--M-protein kvant.	48,1	47,4	-		g/l
S--Kappa-volné ř.	118,20			3,3 - 19,4	mg/l
S--Lambda-volné ř.	6,60			5,71 - 26,3	mg/l
qS--Index kapp/lamb	17,91			0,26 - 1,65	1
U--Bence-Jones kval.		POZITIV.			arb.j.

high total protein and B2M

P/S--Celk.bílkovina	103,6	102,7	-	65 - 85	g/l
P/S--Albumin	29,3			35 - 50	g/l
P/S--CRP	6			< 8	mg/l
Spec. bioch. vyšetře					
P/S--Beta-2-mikrogl.	6,06			0,9 - 3	mg/l

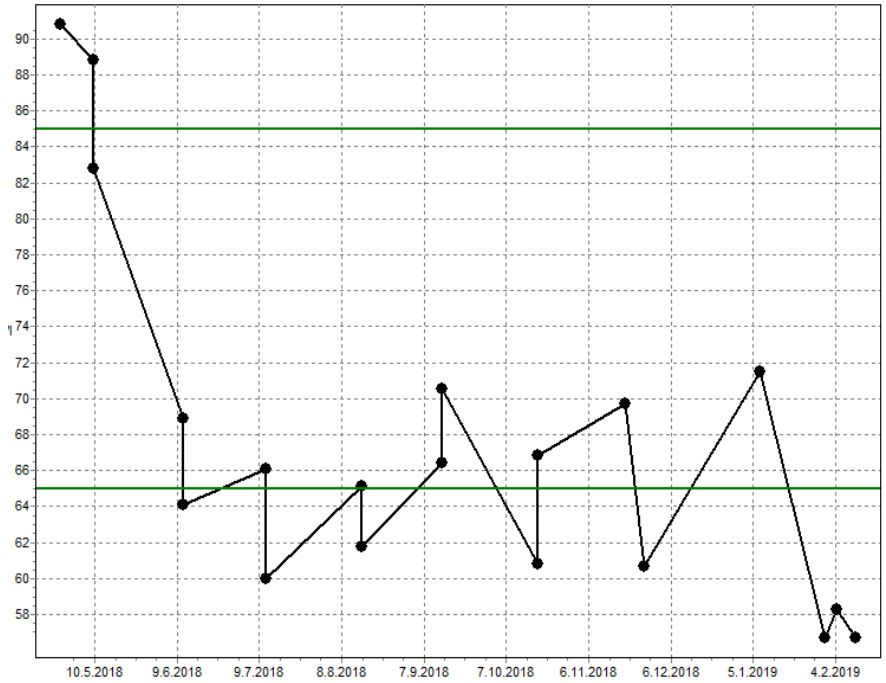


electrophoresis
normal serum

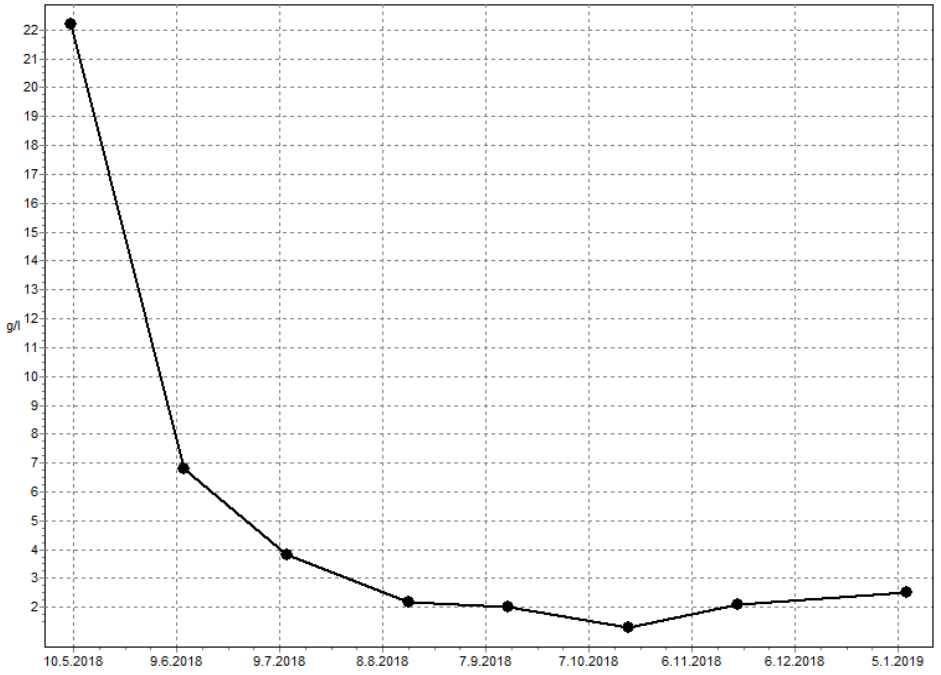


monoclonal gammopathy (paraprotein, M-peak) in pac. with multiple myeloma

Example: M-protein level during treatment



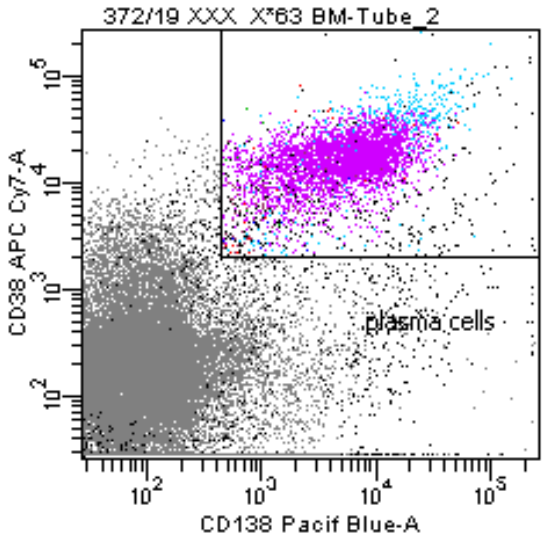
total protein

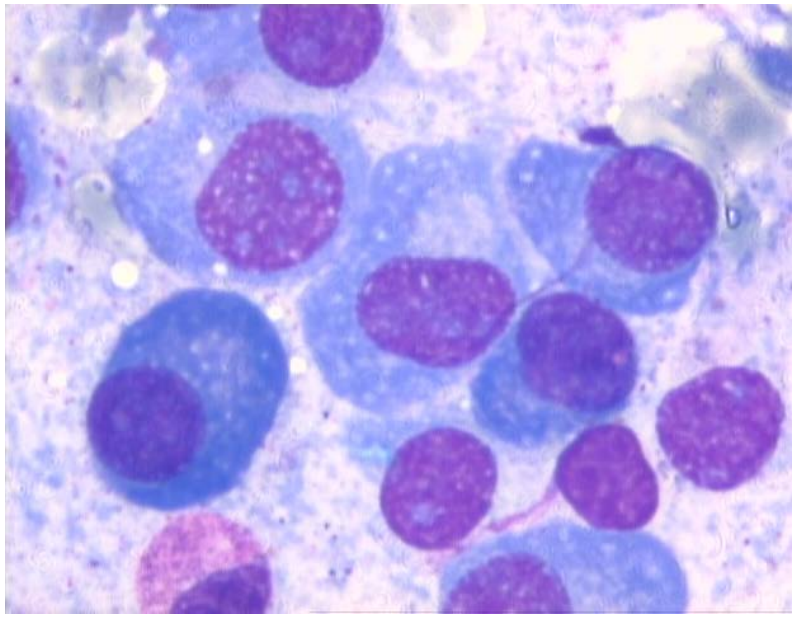


M-protein

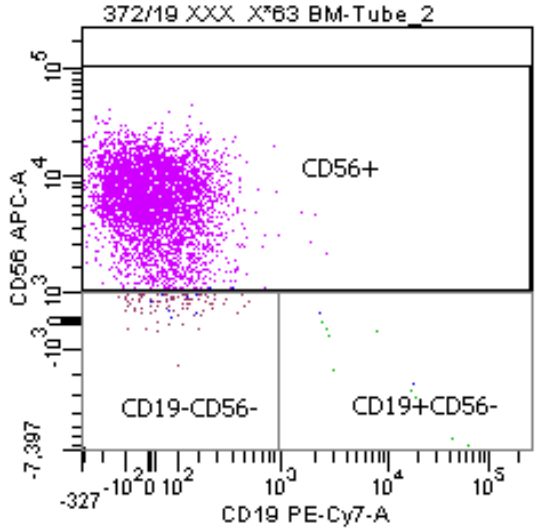
Morfology and flowcytometry

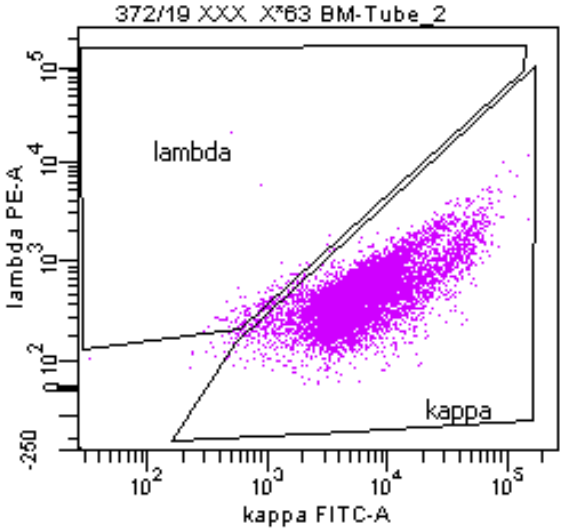
bone marrow flowcytometry

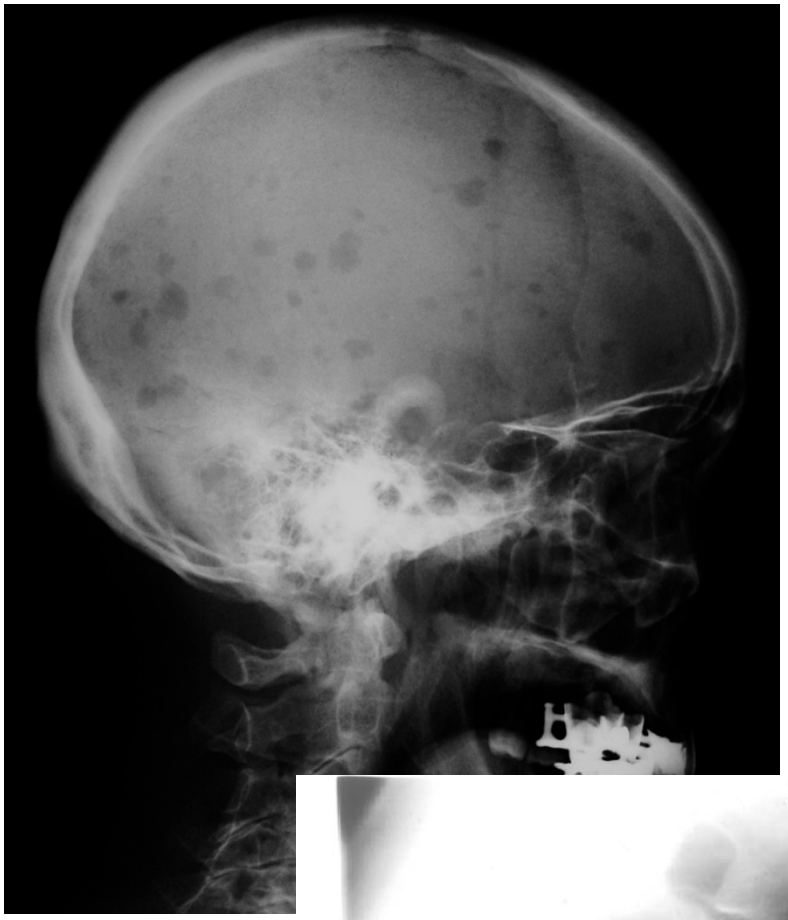




bone marrow morphology

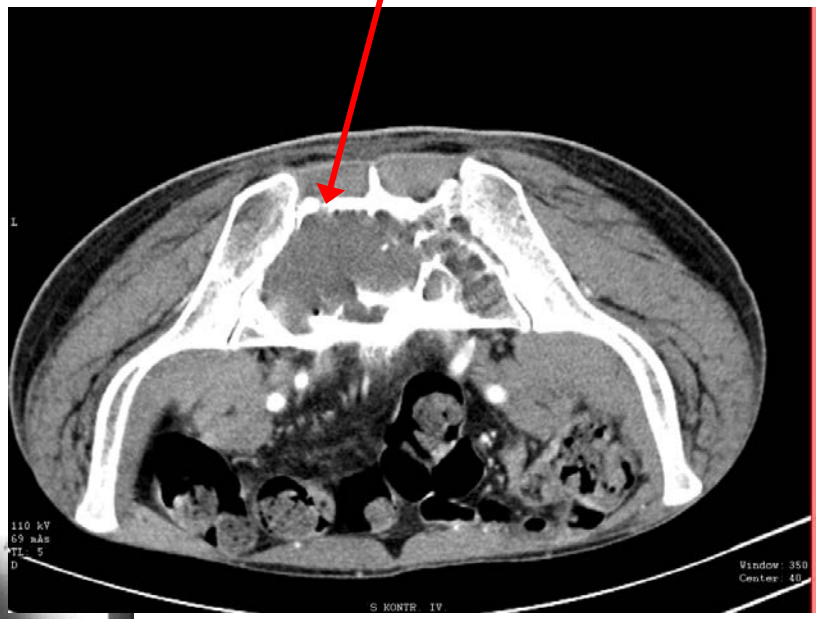


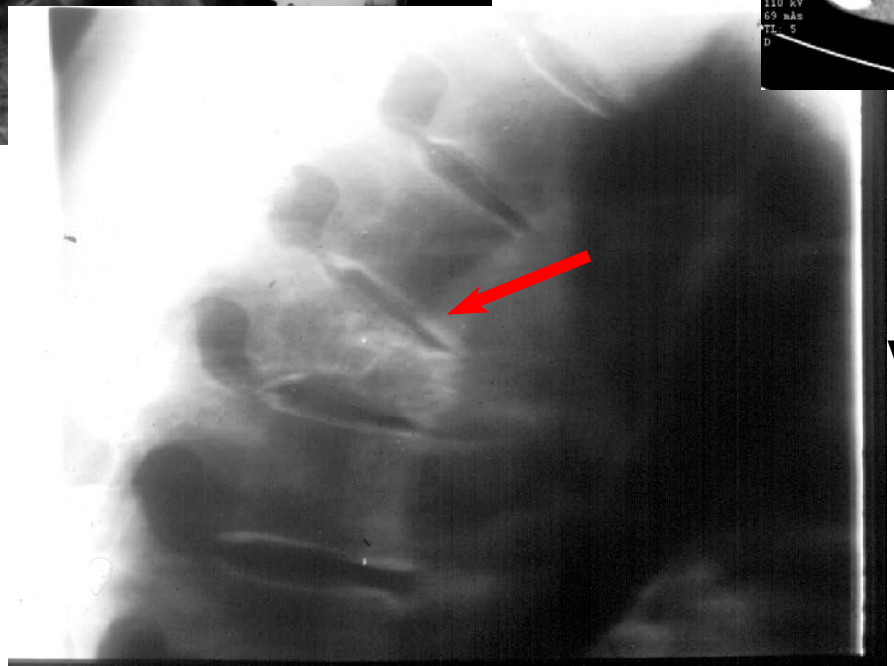




osteolytic defects on the calf

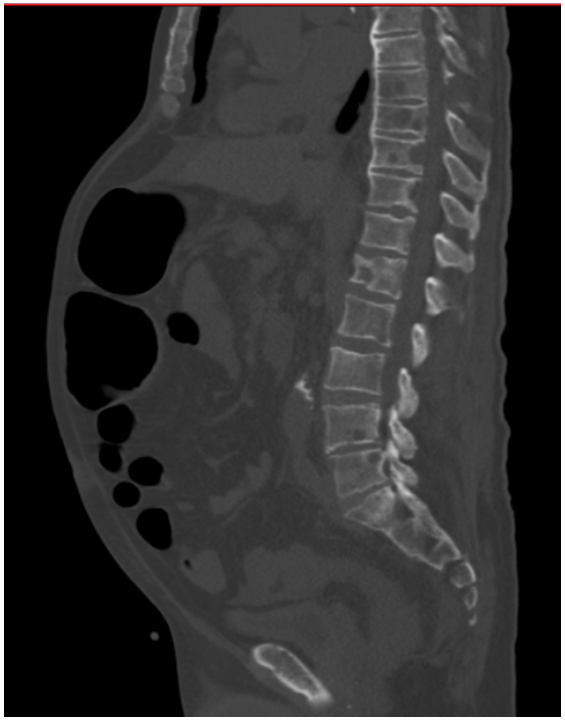
extramedullary myeloma lesion

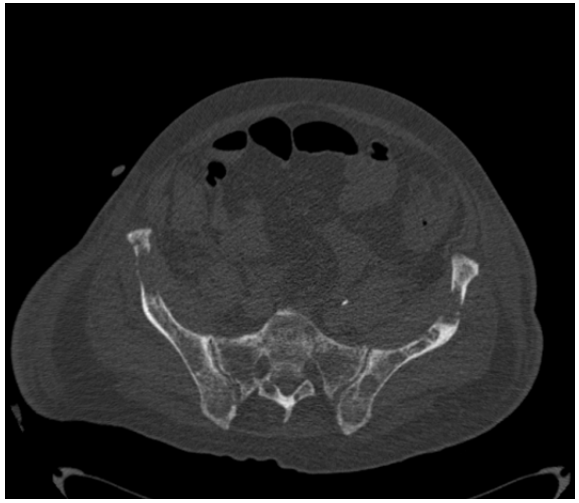


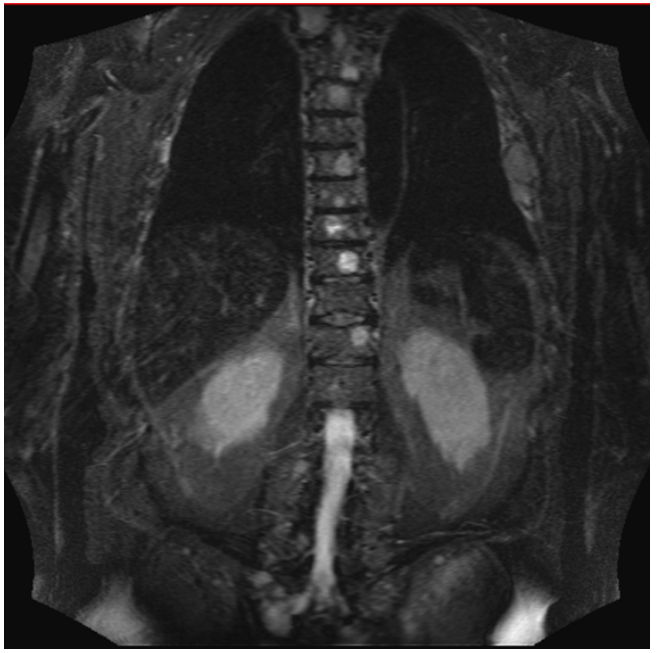


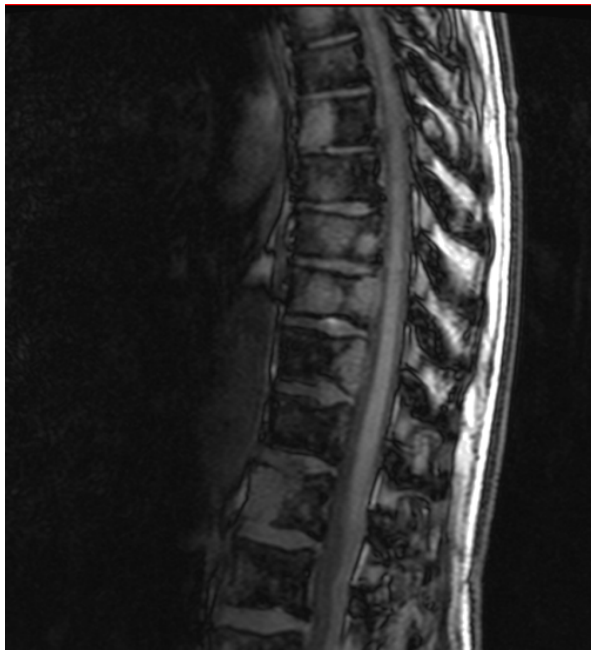
vertebral compression fracture

MRI - myeloma involvement

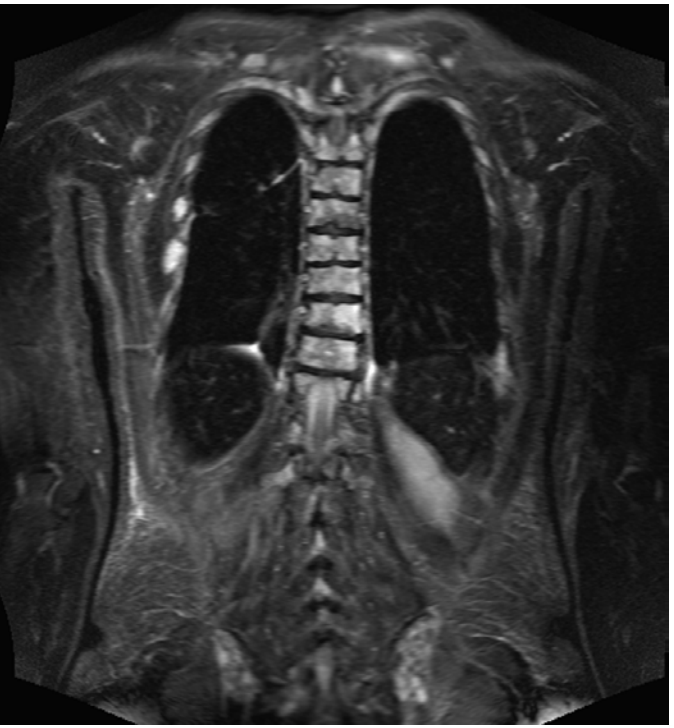




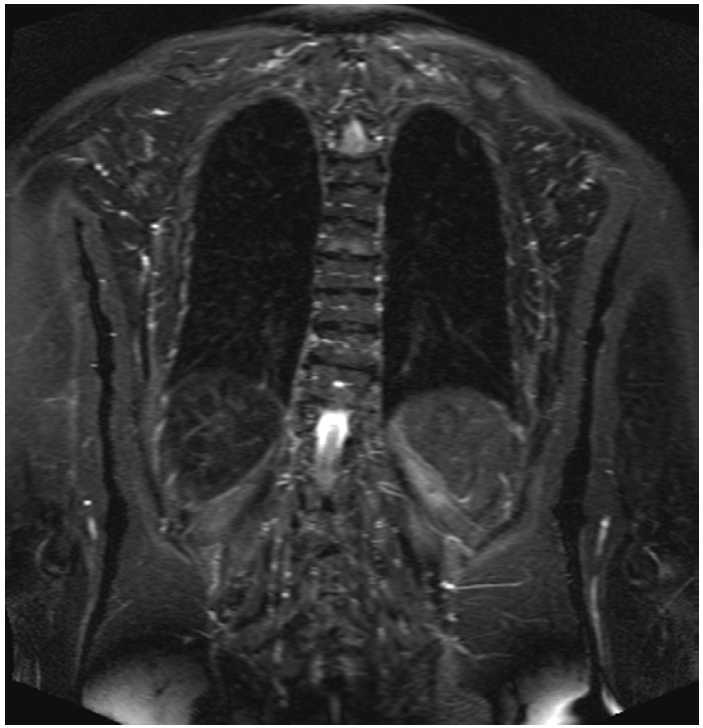




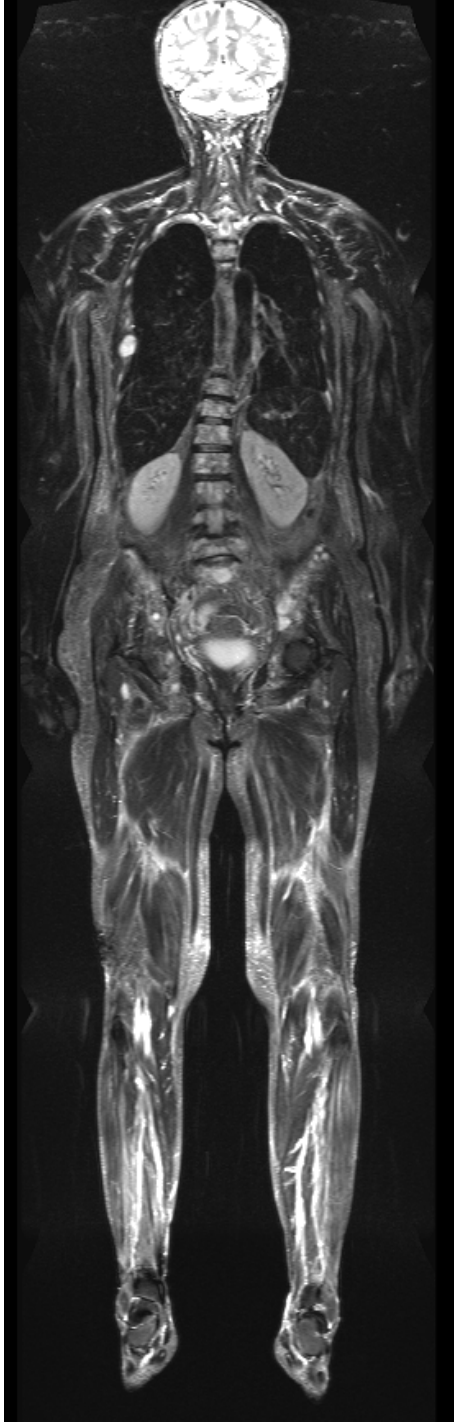
MRI – postižení myelomem



před léčbou (hyperintenzity v obratlech, žebrech a pánvi



po léčbě, intenzita ložisek se snížila



whole body - obraz před léčbou

Prognostic factors

- survival can range widely from 3 to 10 years
- **the forecast is determined by:**
    - clinical stage
    - cytogenetic changes
    - albumin and β2M levels

	high risk	**intermediate risk**	**standard risk**
incidence	20 %	20 %	60 %
median survival (years)	**3**	**4-5**	**8-10**
	del 17p	t(4;14)	hyper-diploidie
	t(14;16)	del 13	t(11;14)
	t(14;20)	hypo-diploidie	t(6;14)

Mikhael JR, Mayo Clin Proc 2013

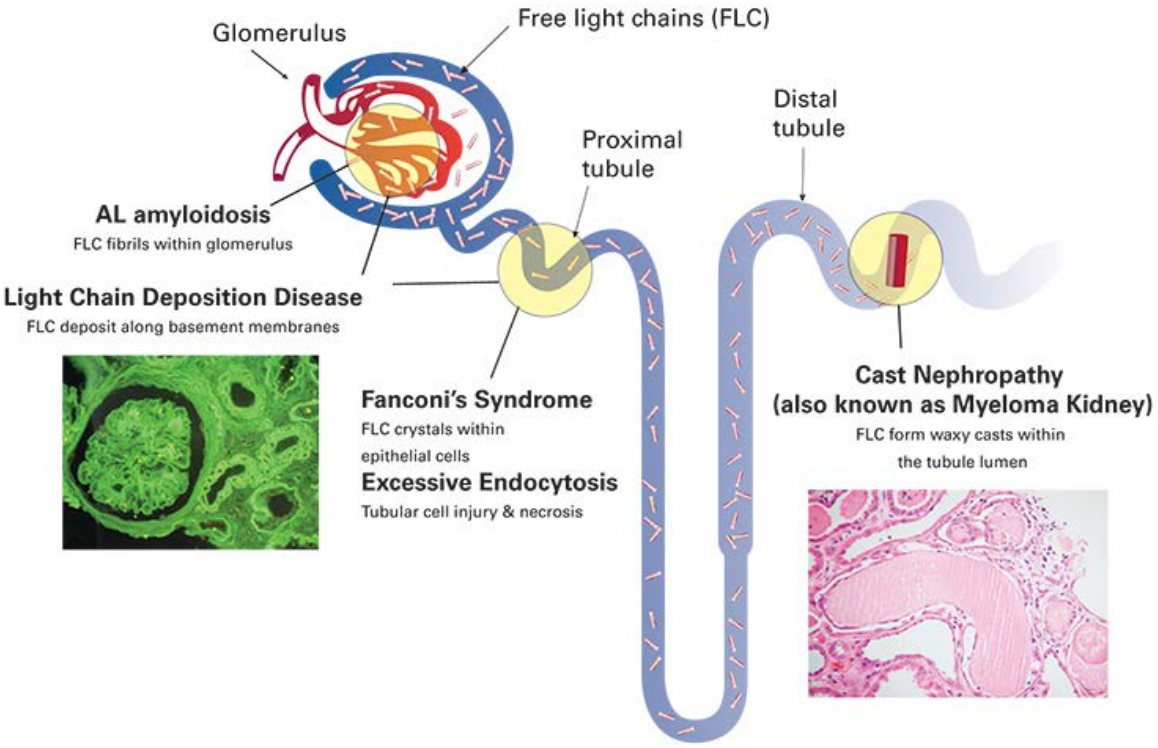
Kidneys in multiple myeloma

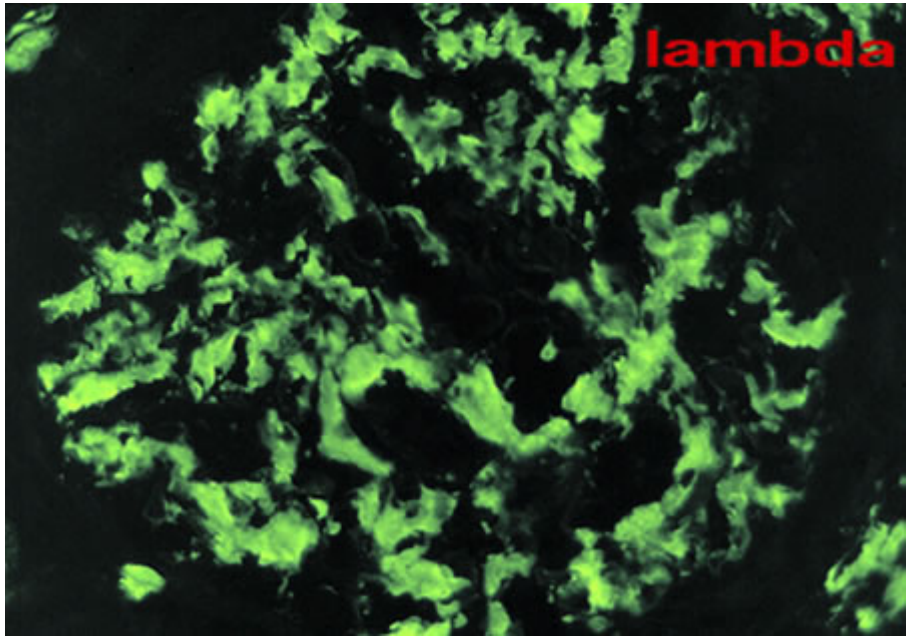
paraprotein and its light chains are excreted by the kidneys and impair their function:

- tubule obstruction and damage to tubule cells by light chains
- light chain deposits
- AL amyloid

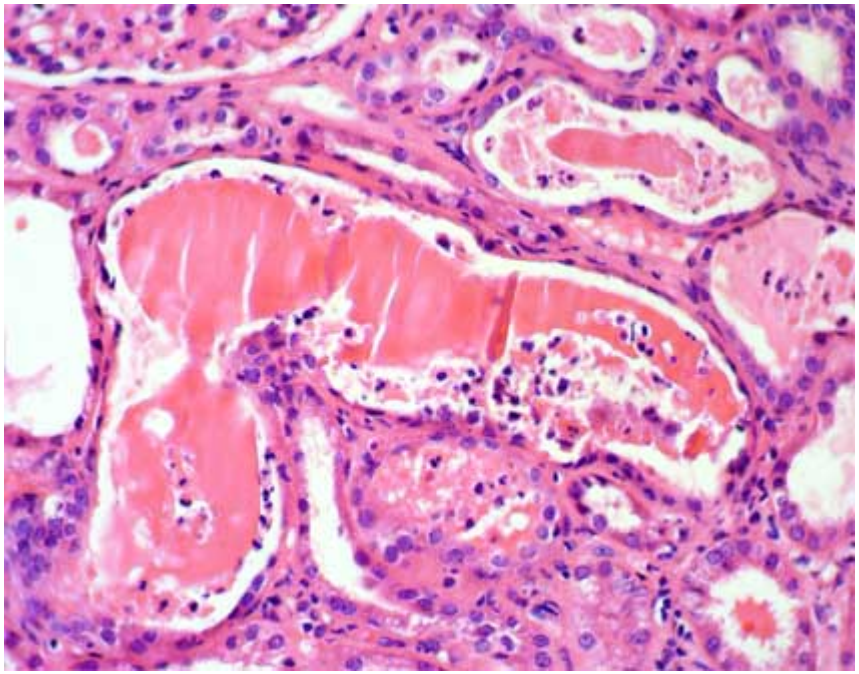
damage further emphasize

- hypercalcemia
- dehydration
- hyperuricemia





light chain deposits



the light chains, together with the Tamm-Horstfall protein, form cast cylinders in the distal tubule

Therapy

tumor treatment - chemotherapy:

- induction followed by high-dose (HD-CHT) chemotherapy with autologous transplantation

new drugs:

- bortezomib, carfilzomib
- lenalidomide, pomalidomide (IMIDs)
- anti-CD38 antibody (daratumumab)

allogeneic transplantation - considered in adverse MM

bisphosphonates:

- inhibit bone resorption by acting on osteoclasts
- they also have an antitumor effect

Treatment of complications

bone lesions:

- local radiotherapy for localized findings
- solution of pathological fractures

anemia: erythropoietin in patients with low EPO levels

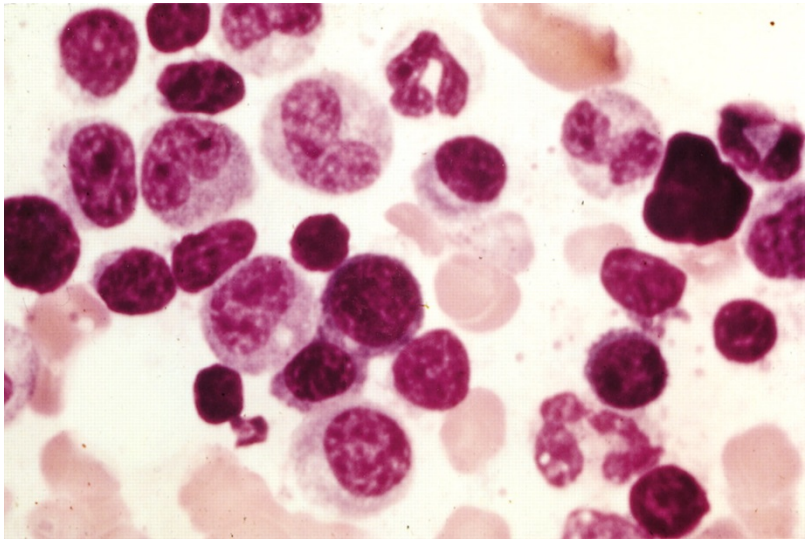
hypercalcemia: hydration, bisphosphonates, procalcitonin

renal failure: hemodialysis

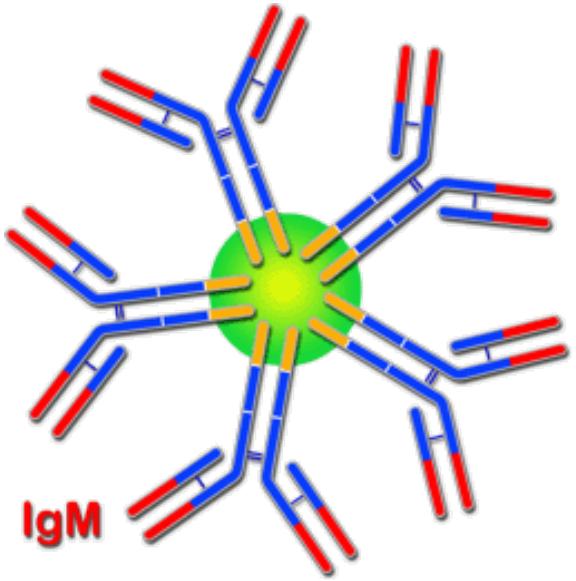
MACROGLOBULINEMIA (Waldenström's disease, lymphoplasmocytic lymphoma)

Characteristics

lymphoproliferative disease at the border between the plasmacytoma (IgM paraprotein) and lymphoma (adenomegaly, splenomegaly)



lymphoplasmocytic infiltrates



monoclonal IgM protein

symptoms caused by:

a) bone marrow infiltration with suppression of physiological hematopoiesis (anemia, thrombocytopenia, neutropenia)

b) monoclonal immunoglobulin (neuropathy, hyperviscosity, cryoglobulinemia ..)

c) manifestations of extramedullary lymphoma proliferation (lymphadenopathy, splenomegaly)

Clinical picture

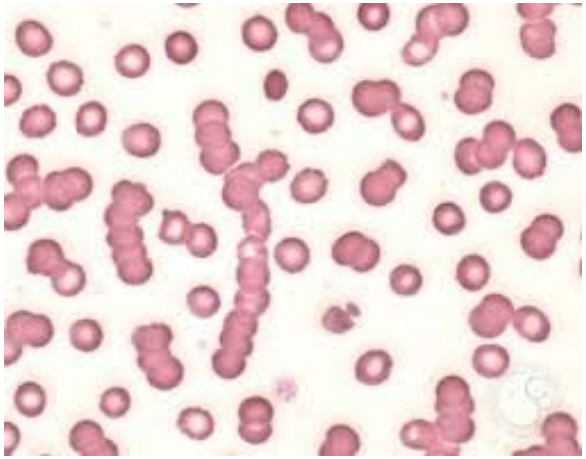
incidence:

- rarer than myeloma (0.3 / 100,000)

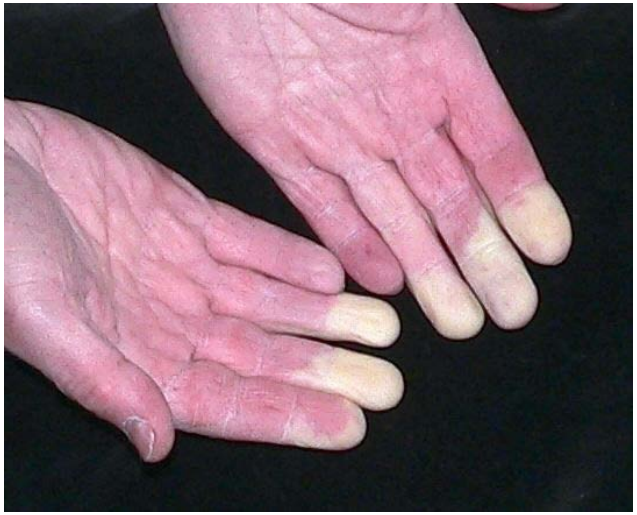
symptoms	frequency of occurrence
fatigue	70 %
general symptoms	20-25 %
lymphadenopathy, hepatosplenomegaly	15-25 %
anemia	40 %
clinical signs of **hyperviscosity** (headache, visual impairment, confusion, epistaxis)	15 - 30 %
bleeding (thrombocytopenia due to bone marrow infiltration or acquired von Willebrand's disease)	cca 20 %
polyneuropathy (IgM antibodies against the target antigen - eg myelin; IgM deposition)	25 - 50 %
acrocyanosis and Raynaud's phenomenon (due to the presence of cryoglobulin or cold agglutinins)	cryoglobulin in 20 % (5 % symptoms) cold agglutinins in 5-10 %
osteolytic skeletal lesions	exceptionally (< 2 %)

Complication

- IgM immunoglobulin can act as an autoantibody and cause autoimmune complications (autoimmune hemolysis)
- bleeding by paraprotein binding to platelets or von Willebrand factor (acquired deficit)
- cryoglobulinemia (Ig, precipitates at <37 ° C): Raynaud's phenomenon, acrocyanosis on parts of the body exposed to cold



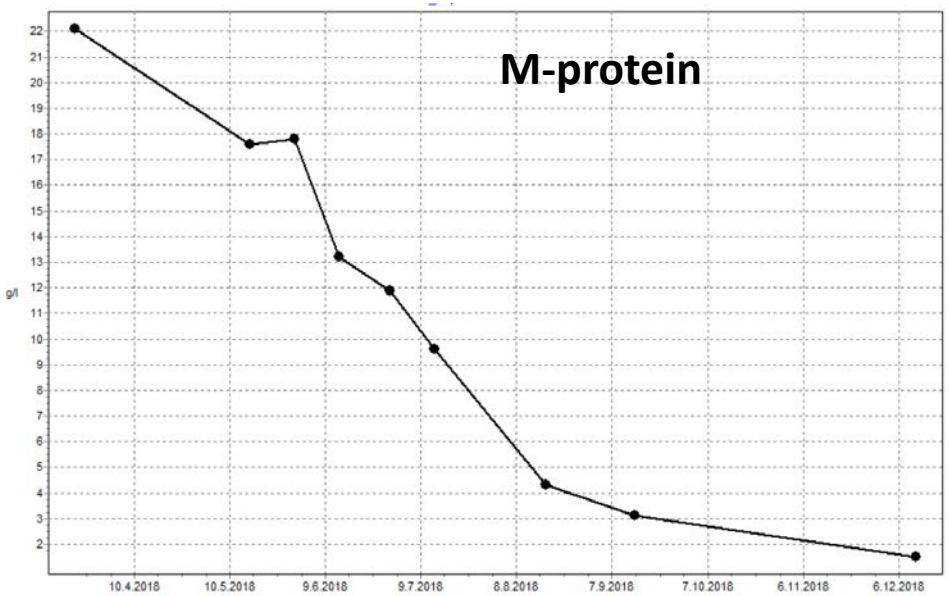
Rouleaux fenomen



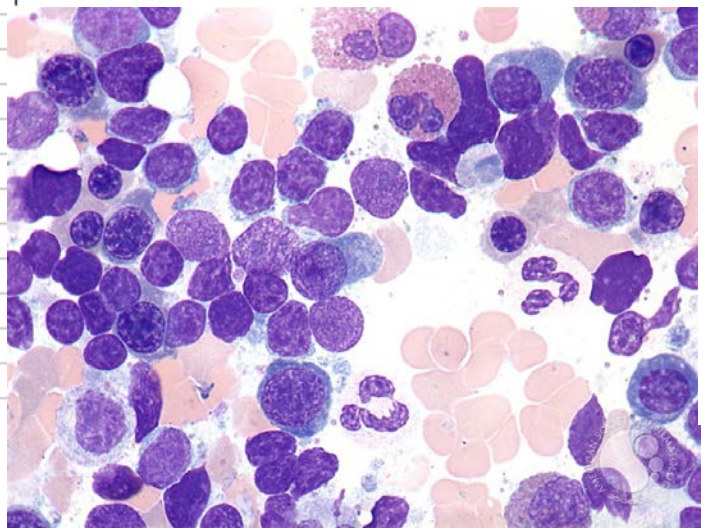
Raynaud fenomen

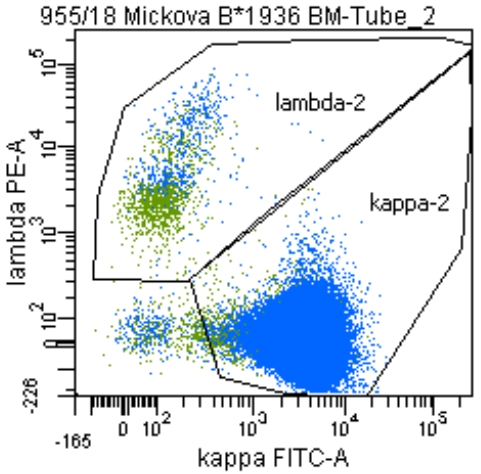
Laboratory findings

Krevní obraz				
B--Le	8,40		4 - 10	10^9/l
B--Ery	3,12		3,8 - 5,2	10^12/l
B--Hb	96		120 - 160	g/l
B--HTK	0,281		0,35 - 0,47	1
B--Obj ery.	90		82 - 98	fl
B--Hb ery	30,8		28 - 34	pg
B--Hb konc	343		320 - 360	g/l
B--Erytr.křivka	18,1		10 - 15,2	%
B--Trombo	255		150 - 400	10^9/l



ELFO skupina				
Interpretace ELFO	Typ monoklo			
S--Albumin	0,384		0,53 - 0,65	1
S--Alfa 1-globulin	0,028		0,02 - 0,04	1
S--Alfa 2-globulin	0,107		0,08 - 0,13	1
S--Beta-globulin	0,102		0,09 - 0,16	1
S--Gama-globulin	0,379		0,115 - 0,19	
S--Imunofix. ELFO	IgM kappa			
S--M-protein kvant.	31,6			
S--Kappa-volné ř.	164,30		3,3 - 19,4	
S--Lambda-volné ř.	11,00		5,71 - 26,3	
qS--Index kapp/lamb	14,94		0,26 - 1,65	
U--Bence-Jones kval.	Pozitiv.			
Humorální imunita				
S--IgG	5,25		7 - 16	
S--IgA	1,57		0,7 - 4	
S--IgM	56,60		0,4 - 2,3	





Hyperviscous syndrome

- caused by increased viscosity and increased plasma volume (IgM paraprotein - high molecular weight)
- hyperviscosity may be the first sign of disease
- the most common symptoms of hyperviscosity are:
    - visual impairment (bleeding into the retina, thrombosis, papillary edema)
    - bleeding from the mucous membranes
    - neurological symptoms (headache, dizziness, nausea, tinnitus, stroke)
- the rheological consequences of hyperviscosity can be seen in the ocular background

Changes on the eye background

changes before plasmapheresis: papillary swelling, retinal haemorrhage, „sausiging“ (for AV crossing)

Diagnosis and treatment

diagnostics:

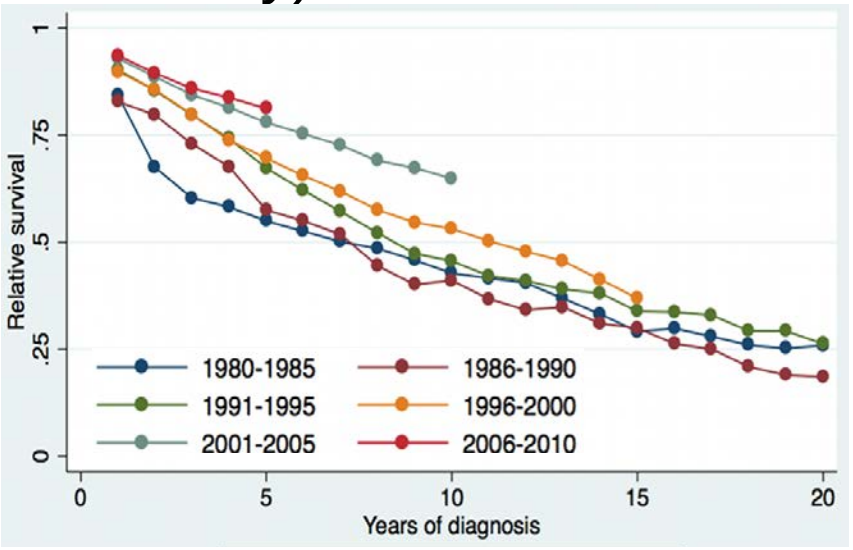
- detection of IgM paraprotein
- bone marrow findings (lymphoplasmocyte infiltration)
- molecular genetics (MYD88 mutation)

therapy:

- chemotherapy (CPA, benamustine, bortezomib ..), anti-CD20
- plasmapheresis (in severe hyperviscosity)

prognosis:

- median survival 8 years



Morel P, Blood 2009; Castillo JJ, Blood 2014

POEMS syndrome

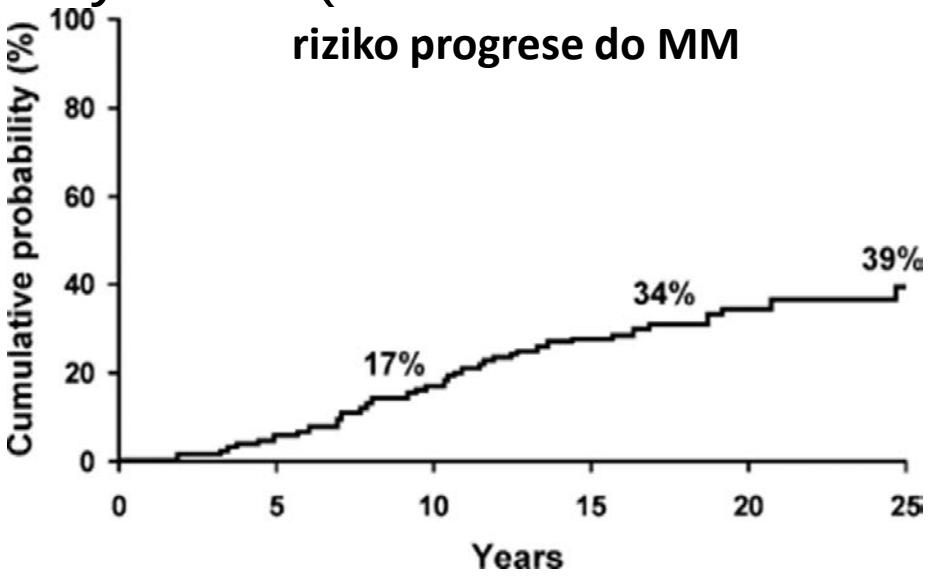
(Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammapathy, Skin changes)

- rare disease
- is characterized by multiorgan disorders:
  - sensorimotor polyneuropathy
  - organomegaly (hepatosplenomegaly, lymphadenopathy)
  - diabetes mellitus, amenorrhea, gynecomastia
  - monoclonal gammopathy
  - Hyperpigmentation
  - osteosclerotic bone deposits
- bone marrow infiltration by plasma cells smaller than in myeloma
- it is treated similarly to multiple myeloma

Monoclonal gammopathy of undetermined significance (MGUS)

Introduction

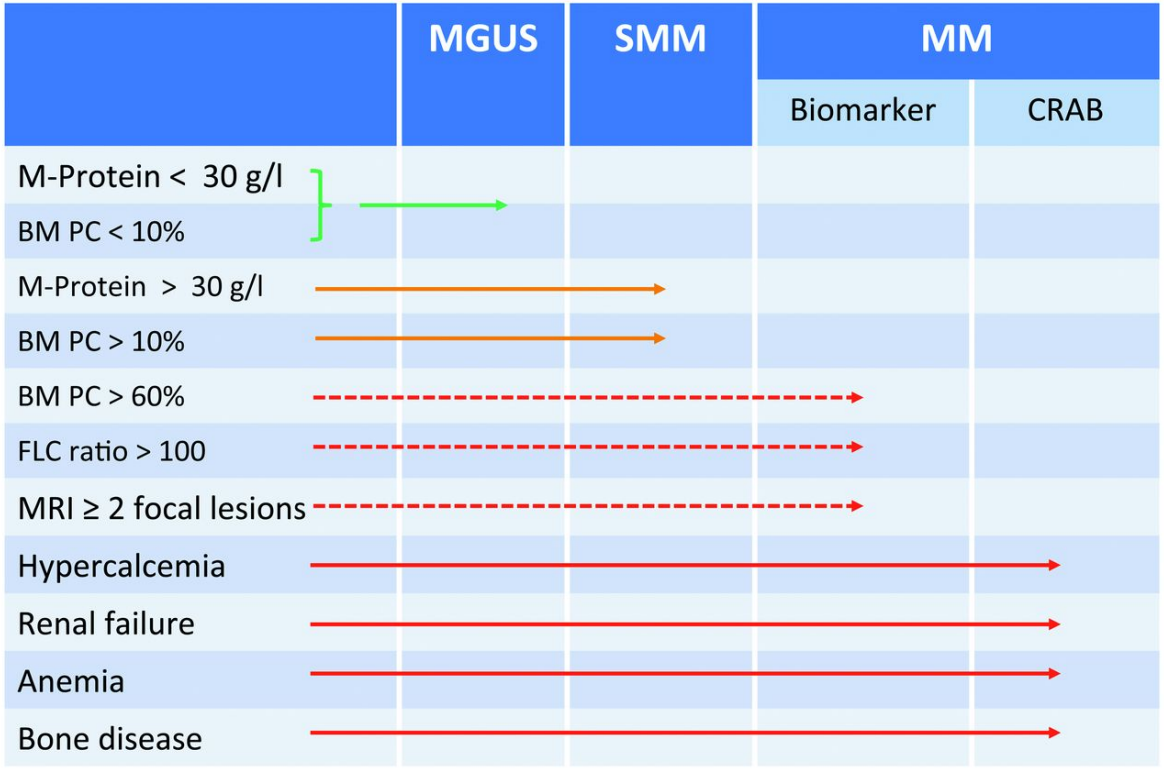
- make up about 65% of all gammopathy
- may progress to multiple myeloma
- 1 - 3% of the population (older people)
- about 15% develop multiple myeloma (~ 15 years)
- dispensarization



	MGUS	MM
M protein	up to 30 g/l	any quantity
% plasmocytes in BM	up to 10%	over 10 %
clinical signs of CRAB	Absent	present

Diagnostic criteria

- low and stable blood paraprotein concentration (x myeloma)
- plasma bb. <10% of marrow cellularity, no bone marrow failure (anemia, etc.)
- absence of osteolytic deposits, anemia, hypercalcemia, renal insufficiency (CRAB)



PRIMARY AMYLOIDOSA (AL amyloidosis)

primary amyloidosis:

- has no obvious cause (0 evidence of lymphoproliferative disease)
- sometimes accompanied by malignant monoclonal gammopathy (multiple myeloma, Waldenström's macroglobulinemia)
- clonal expansion of B-lympho - differentiate into plasma cells and produce amyloidogenic protein
- amyloid formed by immunoglobulin light chains (AL)
- accumulation in various organs: heart (heart failure), kidneys, lungs, neuropathy, skin, etc.

After a long time it can turn into multiple myeloma.

PRIMARY AMYLOIDOSA (AL amyloidosis)

clinical picture:

- determined by the type of affected organ (amyloid deposition)
  a biopsy of the affected tissue is required for diagnosis
- in AL amyloidosis: slightly increased plasma cells in the bone marrow, in B-J urine

prognosis:

- slow progression with affected organ failure
- median survival 1-2 years

therapy:

- chemotherapy, HD chemotherapy - uncertain effect, high mortality (up to 40% on HD-CHT)

Thank you for your attention