

Hematopathology

Diseases of bone marrow

Terminology

- **Myeloid** tissues
= bone marrow
- **Lymphoid** tissues
= lymph nodes, thymus and spleen

Manifestation of bone marrow diseases

- **Increase** of blood cells („**-cytosis**“)

- Erythrocytosis ($> 160 \text{ g/l}$ (♀); $> 165 \text{ g/l}$ (♂))
- Leukocytosis (neu $> 12 \times 10^9/\text{l}$)
- Trombocytosis ($> 450 \times 10^9/\text{l}$)

- **Organomegaly** (hepatosplenomegaly)

= caused by either extramedullary hematopoiesis or infiltration by neoplastic cells

- **B symptoms** (subfebrile, weight loss, night sweats)

- **Depletion** of blood cells („**-cytopenia**“)

- Anaemia ($< 120 \text{ g/l}$ (♀); $< 130 \text{ g/l}$ (♂))
- Leukopenia (neu $1,8 \times 10^9/\text{l}$)
- Trombocytopenia ($< 150 \times 10^9/\text{l}$)

Manifestation of bone marrow diseases

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- **B symptoms** (subfebrile, weight loss, night sweats)

increased number of cells in contrast to fluid



aggregation, obstruction...



microcirculation disorders



hypoperfusion of peripheric tissues

= „**hyperviscosity syndrome**“

typical symptoms:

headache, vertigo, tinnitus, blurred vision,
skin and mucosal bleeding...

Manifestation of bone marrow diseases

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Thrombosis

Massive thrombocytosis ($> 1000 \times 10^9 / \text{l}$)



relative depletion of von Willebrand factor



paradoxal bleeding

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= caused by either extramedullary hematopoiesis or infiltration by neoplastic cells

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Manifestation of bone marrow diseases

- **Increase** of blood cells („-cytosis“)

Anemic syndrome

**Risk of infections
Febrile neutropenia**

Skin and mucosal bleeding

- **Depletion** of blood cells („-cytopenia“)

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Hematolymphoid neoplasms

Myeloid neoplasms

- Myeloproliferative neoplasms (MPN)
- Myelodysplastic syndrome (MDS)
- Acute myeloid leukaemia (AML)
- *and some other
(like mastocytosis, MDS/MPN etc.)*

+ other specific neoplasm like histiocytosis etc.

Lymphoid neoplasms

- from precursor cells
 - Acute lymphoblastic leukaemia (ALL)
- from mature cells
 - Hodgkin lymphoma
 - Non-Hodgkin lymphomas

Terminology

- **Leukaemias**

- = „**liquid**“ neoplasms

- = myeloid or lymphoid neoplasm with widespread involvement of bone marrow and typically also peripheral blood

- **Lymphomas**

- = „**solid**“ neoplasms

- = lymphoid neoplasm forming solid tissue mass

! some **lymphomas** can have also **leukemic presentation** !

Leukaemias

Classification

	Acute (blastic)	Chronic
Myeloid	AML	MPN (CML and Ph- MPN)
Lymphoid	B-ALL T-ALL	CLL HCL

Hematolymphoid neoplasms

Myeloid neoplasms

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Lymphoid neoplasms

- from precursor cells
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 - Hodgkin lymphoma
 - Non-Hodgkin lymphomas
 - **CLL** and **HCL**

MYELOID NEOPLASMS

Myeloproliferative neoplasms

Myeloproliferative neoplasms (MPN)

= clonal neoplastic disorders of hematopoietic stem cell characterized by **excessive production** of **mature myeloid cells** (white blood cells, erythrocytes, and/or platelets)

„hypereffective hematopoiesis“

Myeloproliferative neoplasms (MPN)

Pathogenesis

- Alteration of the genes for various **tyrosine kinases**
 - constitutively activated
 - **growth factor-independent proliferation and survival of myeloid progenitors**
 - overproduction of 1 or more mature myeloid cell type
- Differentiation is not impaired → no signs of dysplasia

Myeloproliferative neoplasms (MPN)

Common features

- Increased production of 1 or more myeloid cell type
 - increased proliferation in bone marrow (usually hypercellularity in bone marrow)
 - **„-cytosis“** in peripheral blood
- Extramedullary hematopoiesis
 - **hepatosplenomegaly**
- Risk of progression
 - a. to **„spent“ phase“** (fibrosis in bone marrow) → manifestation as blood marrow failure
 - b. to **„blast phase“** → manifestation as acute leukaemia

Myeloproliferative neoplasms (MPN)

Classification

- **Ph-positive MPN**
 - Chronic myeloid leukaemia (CML)
- **Ph-negative MPN**
 - Polycythaemia vera (PV)
 - Essential thrombocythaemia (ET)
 - Primary myelofibrosis (PMF)

Chronic myeloid leukaemia (CML)

= myeloid neoplasms characterized by presence of **Philadelphia chromosome** and/or **fusion gene *BCR::ABL1*** and **neutrophilic granulocytosis** in peripheral blood

Chronic myeloid leukaemia (CML)

- **20%** of all leukaemias
- Incidence: 1-2 : 100 000, increases with age (median 63 years)
- Pathogenesis:
 - 90-95% of patients have typical reciprocal translocation **t(9;22)(q34;q11.2)**
 - **Philadelphia (Ph) chromosome**
 - **BCR::ABL1 fusion gene**
 - remaining cases have either variant translocations or cryptic translocations, but still detectable *BCR::ABL1* fusion gene

Chronic myeloid leukemia (CML)

- Manifestation:
 - Peripheral blood:
 - **leukocytosis** (median $80 \times 10^9/L$, but can be much higher)
 - mainly neutrophilic leukocytosis with **shift to the left**
 - usually also absolute basophilia and eosinophilia
 - normal or elevated platelets
 - normal or decreased erythrocytes
 - **Hepatosplenomegaly**
 - **Hyperviscosity syndrome**, fatigue, malaise, weight loss, night sweats

Chronic myeloid leukaemia

Bone marrow

- **Hypercellular** (practically 100%)
- **Increased granulopoiesis**
(at all stages of maturation)
with also increased number of
eosinophils and basophils
- **Decreased erythropoiesis**
- Increased megakaryocytes
- typically small hypolobated
(**dwarf megakaryocytes**)
- **No dysplasia**

Chronic myeloid leukaemia (CML)

- Complications:
 - Without treatment **ALWAYS** progression to **blastic phase** (usually in few years)
- Treatment:
 - **Imatinib** or other tyrosinkinase inhibitors → long-term control of the disease
 - Transplantation of haematopoetic stem cells

Polycythaemia vera (PV)

= Ph-negative myeloid neoplasm
with dominant **excessive production of erythrocytes**,
typically associated with activating mutations of gene **JAK2**

Polycythaemia vera (PV)

- Incidence: 1-2,5 : 100 000, increases with age
- Pathogenesis:
 - activating **mutations** of gene **JAK2** (most common p.V617F)
 - stimulation to proliferation of hematopoietic progenitors
 - panmyelosis (but typically dominant erythropoiesis)

Polycythaemia vera (PV)

- Manifestation:

- Peripheral blood:

- **erythrocytosis**
- normal or elevated platelets
- normal or elevated leukocytes

- Hepatos**plenomegaly**

- **Thrombosis** or **bleeding, plethora**, fatigue, **pruritus, hyperviscosity syndrome**, night sweats...

vs. secondary erythrocytosis:

- chronic hypoxia caused by chronic heart or lung diseases
- high levels of Epo
- = approximately **66%** of all erythrocytosis

Polycythaemia vera (PV)

Bone marrow

- **Hypercellular** (but usually not more than 80%)
- **Panmyelosis**
(increased numbers of all 3 lineages)
- Most important for diagnosis is morphology of megakaryocytes
 - typically large forms with hypersegmented (**staghorn-like**) nuclei forming loose clusters
- Usually absent or mild myelofibrosis
- **No dysplasia**

Polycythaemia vera (CML)

- Complications:
 - Progression of myelofibrosis → bone marrow failure
 - Less common is progression to AML
- Treatment:
 - Phlebotomy (ev. erythrocytapheresis) + platelet aggregation inhibitors (Aspirin etc.)
 - Event. cytoreduction

Essential thrombocythaemia (ET)

= Ph-negative myeloid neoplasm
with dominant **excessive production of thrombocytes**

Essential thrombocythaemia (ET)

- Incidence: 1-2: 100 000, increases with age
- Pathogenesis:
 - activating **mutations** of either **JAK2** or **CALR** or **MPL**
- Manifestation:
 - Peripheral blood:
 - typically **isolated thrombocytosis** (approximately 1/2 of the patients asymptomatic)
 - Usually just mild splenomegaly
 - **Thrombosis** or **bleeding**, fatigue, headache...

vs. secondary thrombocytosis:

- injury, infection, iron deficiency etc.

Essential thrombocythaemia (ET)

Bone marrow

- **Normocellular**
- Marked proliferation of megakaryocytes
 - large forms with hypersegmented (**staghorn-like**) nuclei
 - forming loose clusters
- **No myelofibrosis**
- **No dysplasia**

Essential thrombocythemia (ET)

- Complications:
 - Progression of myelofibrosis is **very rare**
 - Progression to AML practically **never**
- Treatment:
 - Platelet aggregation inhibitors (Aspirin etc.)
 - Event. cytoreduction

Primary myelofibrosis (PMF)

= Ph-negative myeloid neoplasm

with dominant **proliferation of megakaryocytes** and **progressive myelofibrosis**

Primary myelofibrosis (PMF)

- Incidence: 0,5-1: 100 000, increases with age
- Pathogenesis:
 - activating **mutations** of either **JAK2** or **CALR** or **MPL**
- Manifestation:
 - Peripheral blood:
 - initially **isolated thrombocytosis**
 - thrombocytopenia, anaemia vs. leukocytosis +/- **leukoerythroblastic (LEB) blood picture**
 - Usually massive **hepatosplenomegaly**, also extramedullary hematopoiesis in many other tissues
 - Thrombosis, **fatigue, fever**, anorexia, **weight loss, night sweats...**

Primary myelofibrosis (PMF)

Bone marrow - prefibrotic phase

- **Hypercellular**
- Marked proliferation of megakaryocytes
 - large forms with hyperchromatic bulbous nuclei with marked defects in maturation
 - forming loose and also **cohesive** clusters
- Intrasinusoidal hematopoiesis
- **Absent or mild myelofibrosis**
- **No dysplasia**

Bone marrow - fibrotic phase

- **Moderate or severe myelofibrosis**
 - **osteosclerosis**
- **Minimal residual hematopoiesis** with dominant proliferation of **megakaryocytes** with **maturation defects** forming **cohesive** clusters

Primary myelofibrosis (PMF)

- Complications:

- Bone marrow failure
- Progression to AML

- Treatment:

- Platelet aggregation inhibitors (Aspirin etc.)
- Transplantation of hematopoietic stem cells (in fibrotic phase)

Myelodysplastic syndrome

Myelodysplastic syndrome (MDS)

= **heterogenic** clonal neoplastic disorders of hematopoietic stem cell characterized by **dysplasia** and **peripheral cytopenia** of 1 or more lineages (white blood cells, erythrocytes, and/or platelets), with risk of **progression to acute myeloid leukaemia**

„ineffective haematopoiesis“

Myelodysplastic syndrome (MDS)

- Age-adjusted incidence 4:100 000 (increases with age; median 77 years)
vs. rare distinct type „childhood MDS“

Myelodysplastic syndrome (MDS)

Pathogenesis

- **multifactorial** (molecular abnormalities, bone marrow microenvironment etc.)
- exogenic (toxins, radiation, chemotherapy etc.)
and endogenous (aging, inflammation, predisposition syndromes etc.) factors
 - initial genetic alterations in haematopoietic stem cells
(usually mutations of genes involved in splicing machinery, epigenetic regulation, differentiation, and cell signaling)
 - „**clonal haematopoiesis of unknown significance (CHIP)**“
or „**clonal cytopenia of unknown significance (CCUS)**“
 - selection and clonal expansion
 - + accumulation of other genetic alterations
 - **myelodysplastic syndrome (MDS)**

Myelodysplastic syndrome (MDS)

Pathogenesis

- **Early MDS**

- Maturation defects and increased apoptosis
- Normal blast count ($< 2\%$ in PB and $< 5\%$ in BM)

- **Late MDS** (accumulation of other genetic alterations)

- Increased proliferation (in contrast to decreased apoptosis)
- Increased blasts ($\geq 2\%$ in PB or $\geq 5\%$ in BM)

→ **progression to AML** ($\geq 20\%$ of blasts in PB or BM)

Myelodysplastic syndrome (MDS)

Manifestation

- **Cytopenia** in 1 or multiple myeloid lineages
 - Anaemia (typically macrocytic)
 - Leukopenia
 - Thrombocytopenia
- No hepatosplenomegaly

Myelodysplastic syndrome (MDS)

Diagnostic approach

- **Peripheral blood count:** cytopenia
- **Cytology:** dysplastic features, blast count etc.
- **Bone marrow biopsy:** cellularity, blast count, dysplastic features, myelofibrosis etc.
- **Flow cytometry:** aberant immunophenotype, blast count
- **Molecular examination:** detection of mutations and karyotype abnormalities

Myelodysplastic syndrome (MDS)

Bone marrow

- **Hypercellular** vs. normocellular or hypocellular
- **Dysplasia** in 1 or multiple lineages
 - G: shift to left
 - E: shift to left, abnormal paratrabecular localisation
 - M: increased in number, loose clusters, small forms or even micromegakaryocytes, abnormal paratrabecular localisation
- **Blast count** (ALIP phenomena)
- **Absent or mild myelofibrosis**

Myelodysplastic syndrome (MDS)

Diagnostic approach

- **Peripheral blood count:** cytopenia
- **Cytology:** dysplastic features, blast count etc.
- **Bone marrow biopsy:** cellularity, blast count, dysplastic features, myelofibrosis etc.
- **Flow cytometry:** aberant immunophenotype, blast count
- **Molecular examination:** detection of mutations and karyotype abnormalities

Myelodysplastic syndrome (MDS)

- Complications:
 - **Progression to AML**
(high-risk patients with median within 1 year)
- Treatment:
 - Supportive care (blood transfusions, growth factors etc.), immunomodulators etc.
 - In high-risk patients chemotherapy or allogeneic transplantation of hematopoietic stem cells

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