Reactive changes in the bone marrow

Alexandar Tzankov
Content

• Introduction
• Normal bone marrow
• Reactive bone marrow changes – patterns
• Treatment-induced changes
• Specific clinico-pathological conditions
• Summary
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Introduction

- Reactive bone marrow changes
  - Common
  - Unspecific
    - Specifically interpretable in the proper clinical context
  - Mimickers of malignant processes
    - May accompany and even mask malignant processes
  - Vice versa, malignant process mimic reactive changes
  - Important differential diagnostic considerations
Dysmegakaryopoiesis (due to Azathioprine)
Myelopoietic hyperplasia due to CSF
Granulomatous reaction in HL infiltration
Accompanying T-cells in MZL
Accompanying T-cells in AML M5a
Content

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Normal bone marrow

• Hematopoiesis

• Interstitium with supporting and reactive cells
  – Perivascular stem cell niche, lymphocytes, histiocytes, plasma cells
  – Stroma
    • Fatty tissue, vessels, fibers

• Bony substance
  – Compact bone and spongy bone (trabeculae)
  – Osteoblasts, osteocytes and osteoclasts (TRAP+)
Osteoblast occasionally mimicking plasmablast
Content

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Reactive bone marrow change patterns

- Quantitative changes in the hematopoietic compartment
- Qualitative changes in the hematopoietic compartment
- Lymphoid-, plasma cell- and histiocytic proliferations
- Stromal changes
- Abnormal bony trabeculae
Quantitative changes in the hematopoietic compartment

• Assessment
  – On adequate samples
  – Hematopoietic areas/total marrow spaces

• Interpretation
  – Always with respect to age
  – Knowledge of peripheral blood counts, growth factor application and septic conditions etc.
Age dependent changes of the cellularity
Caveats in assessing cellularity – pseudoaplastic subcortical marrow spaces
A-/hypoplastic bone marrow

- Congenital (Sunday session)
- Acquired
  - Aplastic anemia
- Mimickers
  - Hypoplastic MDS, AML, ALL
  - Paraneoplastic aplasia in lymphoproliferative disorders
  - Systemic mastocytosis
  - Infections
Aplastic anemia
Hypoplastic MDS
Aplastic anemia with LPL
Systemic Candida sp. infection
Reactive erythropoietic changes

• Red cell a-/hypoplasia
  – Diamond-Blackfan syndrome, Fanconi anemia
  – Parvovirus B19 infection, autoimmunity
  – ASCT with AB0 incompatibility
  – Paraneoplastic (T-LGL)

• Hyperplasia
  – Megaloblastic anemia
  – Rebound hyperplasia in hemolytic anemias
Pure red cell aplasia after ABO incompatible ASCT
Pure red cell aplasia after ABO incompatible ASCT
Parvovirus B19 infection

Megaloblastic anemia
Mimickers

• Acute leukemias (e.g. M6)

• Lymphoprolifertions masked by rebound hyperplasia in hemolytic anemias
Reactive myelopoietic changes

• Myeloid cell hypoplasia
  – Aplastic anemia
  – Paraneoplastic (T-LGL)

• Myeloid maturation arrest
  – Drug-induced (Clozapine, Metamizole, Thiamazole etc.)
  – Parainfectious (e.g. CMV)

• Hyperplasia
  – Septic conditions/“leukemoid” reactions/paraneoplastic
  – Application of steroids and growth factors
  – Rebound hyperplasia in autoimmune neutropenias
Carbamazepine-induced maturation arrest
Rebound hyperplasia and left shift in autoimmune neutropenia
Mimickers

- Myelodysplastic-myeloproliferative neoplasms
  - CMML
  - MDS/MPN, U

- Myelomas
Reactive megakaryopoietic changes

• Megakaryopoietic hypoplasia
  – Parainfectious (e.g. CMV)
  – Paraneoplastic (T-LGL)

• Dysmegakaryopoiesis
  – Drugs (Mycophenolate, Valproate, Tacrolimus etc.)
  – Parainfectious (e.g. HIV)

• Hyperplasia
  – Septic conditions/“leukemoid” reactions/paraneoplastic
  – Application of growth factors
  – Rebound hyperplasia and left shift in ITP
Dysmegakaryopoiesis (due to Azathioprin)
MPN-like changes after THPO/EPO

Am J Clin Pathol 2002;117:844
Mimickers

• Myelodysplastic syndromes
  – 5q- syndrome
  – RCMD

• Myelomas
Typical megakaryocytes of 5q- syndrome
Lymphocytoses

• Hematogones
  – Postinfectious
  – Post-chemotherapy

• Nodular B- and T-cell aggregates
  – Increasing with age

• T-cell lymphocytoses
  – CD8/LGL skewed in virus infections and autoimmunity
  – CD4 skewed in drug reactions
TdT+ hematogones after chemotherapy
CD8 lymphocytosis in EBV
Ring granulomas in CMV infection
Felty syndrome

CD57

GrB

CD8

CD3

T-cell aggregates after Rituximab
Germinal centers, not always benign
Mimickers

• ALL
  – Microarchitectural pattern, grouping (>5 cells)
  – Phenotypic homogeneity, CD123 and LMO2

• T-cell lymphomas (!)

• B-cell lymphomas
  – Microarchitectural pattern, localization, size
  – CD3/CD5/CD20/CD79a subtraction
  – Cyclin D1, SOX11 ...

Virchows Arch 2005;447:920
Plasmacytoses

• Accompanying
  – Chronic inflammatory/autoimmune diseases
  – Increase with age

• Morphology
  – Perivascular
  – Occasionally Russell-/exceptionally Dutcher bodies
  – Polytypic
    • Kappa/Lambda 5:1 to 1:3
    • Alpha/Gamma/Delta/My 5:1:0.5:0.1
  – Cyclin D1-, CD56-
Kappa/Lambda doublestains
CD38/cyclin D1 doublestains
Histiocytic proliferations

• Granulomas
  – Caseating-/non-caseating
  – Lipogranulomas, fibrin ring granulomas
  – Foreign body granulomas

• Interstitial histiocytoses
  – Increased turnover (sea blue histiocytes)
  – Storage disorders (congenital, crystal storage)
  – Infections (e.g. atypical mycobacterioses, Mb. Whipple)
  – Restoration after myeloablation

• Hemophagocytic histiocytoses
Crystal storing histiocytosis in myeloma
Post-myeloablative foamy histiocytes
Hemophagocytic histiocytosis in EBV
Mimickers

- Granulomas and histiocytic proliferations masking neoplasms (e.g. Hodgkin lymphoma)
- Genuine histiocytic and metabolic disorders
  - e.g. Erdheim-Chester or Rosai-Dorfman
Eosinophilia

- Parainfectious
- Accompanying (auto)immune disorders
  - GvHD
- Drug hypersensitivity
- Paraneoplastic [TCL, cHL, B-ALL t(5;14)]
- Neoplastic
Eosinophilia after ASCT
MLNE with t(5;12), *ETV6-PDGFRB*
Diagnostic algorithm in eosinophilia

unexplained eosinophilia

- consider benign reactive causes, especially allergy, drug reaction, pneumonitis, infection
- consider malignant reactive causes, especially T-cell lymphoma (or abnormal T-cell subsets), cHL

conventional karyotype

- 8p11 or 5q31-33 rearrangement

MLNE

- PGFRA rearrangement by FISH

Morphology consistent with CML but t(9;22) negative

- apparent CMML
- with eosinophilia

- apparent AML
- with eosinophilia

- apparent ALL
- T-ALL with eosinophilia
- B-ALL with eosinophilia

apparent SM, but KIT D816V negative

Foucar 2010
Mimickers

- CML
- MPN
- MDS/MPN (CMML)
- AML with inv(16)
- MLNE
- CEL/HES
Basophilic and mast cell proliferations

- Tuesday session Prof. Horny
- Cave rebound proliferations after myeloablation
  - AML
Necrosis

• Myeloablative therapy (fibrinoid necrosis)
• Microcirculatory disorders
  – DIC, sickle cell anemia, infections, anti-phospholipid syndrome
• Malignant processes
  – ALL, AML, neuroblastoma ...
Fibrinoid necrosis after myeloablation
Focal cellular necrosis in «prodromal» AML
Osteonecrosis with Liesegang rings
Stromal changes

- Fibrosis
- Gelatinous/serous oedema
- Microvascular changes
Fibrosis

• Always pathologic
• Non-neoplastic conditions
  – autoimmune myelofibrosis, HIV-associated myelopathy, metabolic disorders (renal osteopathy), ... grey platelet syndrome
• Paraneoplastic
  – Myeloproliferative neoplasias, hairy cell leukemia, systemic mastocytosis, lymphomas, metastases
Reticulin and collagen fibrosis

MPN

Metastasis
Gelatinous transformation

- Malnutrition
- Anorexia nervosa
- AIDS
- Post-chemotherapy

- Mimicker
  - Amyloidosis

Acta Haemtol 2008; 19:104
Vascular changes

• Increased microvascular density
  – Paraneoplastic (MDS, MPN, AML …)
  – Parainflammatory
  – In all fibrosing processes

• Vascular dilatation
  – Paraneoplastic (MPN + i.v. hematopoiesis)
  – Post-chemotherapy

• Mimickers
  – Angiosarcomas
  – Osseous hemangiomatosis, hereditary teleangiectasia
Vascular dilatation after myeloablation
Metastatic angiosarcoma
Metastatic angiosarcoma
Content

- Introduction
- Normal bone marrow
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- Specific clinico-pathological conditions
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Treatment-induced changes

- Chemotherapy
- Immunosuppressive drugs
- Cytokines and growth factors
- Drugs with immunoallergic and direct myelotoxic impact
Bone marrow changes after chemotherapy

- Single cell death
- Wide spread fibrinoid necrosis
- Decreased cellularity to bone marrow aplasia
- Reduction of marrow fat
- Stromal edema
- Sinus dilatation
- Increased bone marrow macrophages
- Perivascular plasmacytosis
- Siderosis
- Reticulin fibrosis
Azacitidine-induced apoptosis
Azathioprine-induced changes
Pharmakogenetics of Azathioprine-associated bone marrow toxicity

- 3-6/1000 deficient of thiopurine methyltransferase
- Risk of potentially life-threatening bone marrow toxicity with conventional doses of Azathioprine or Mercaptopurine; cumulative to Allopurinol
- Possibility to test patients for enzyme activity
Pharmakogenetics of Azathioprine-associated bone marrow toxicity
Granuloma formation after IFN-α
Drugs commonly associated with bone marrow T-cell proliferations

- Allopurinol, Phenytoin ...
- Rituximab (Alemtuzumab)
- Imatinib
- HBV immunization
- Histopathology
  - Occasionally clonal, CD4 skewed T-cell increase (PD-1!)
  - Myelopoietic maturation arrest
  - Eosinophilia & Granulomas

MJHID 2010;6207
Blood 2002;100:435
Hum Pathol 2008;39:194
Allopurinol induced DRESS
Directly myelotoxic drugs, e.g. Chloramphenicol

- Oxidative stress
- Mitochondrial damage
- Sensitivity
  - MPOX
  - Fe content
  - Mitochondrial density
# Tab. 1: Summary of typical morphological drug-induced bone marrow changes, mimicking malignant processes, and their possible misinterpretations

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Examples</th>
<th>Bone marrow changes</th>
<th>Possible misinterpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytostatics</td>
<td>All kinds</td>
<td>Erythropoietic and megakaryopoietic atypia</td>
<td>Myelodysplastic syndromes</td>
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<tr>
<td></td>
<td></td>
<td>Haematogone increase</td>
<td>Acute lymphoblastic leukaemias</td>
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<td>Macrophage increase</td>
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<td>Haemophagocytosis</td>
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<td>Plasmacytosis</td>
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<td>Hypocellularity</td>
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<td>Serous stromal changes</td>
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<td></td>
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<td>Sinus dilatation</td>
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<td>Reticulin fibrosis</td>
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<td>Siderosis</td>
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<td>Fibrinoid necrosis</td>
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<tr>
<td>Cytokines and growth factors</td>
<td>Granulocyte- or granulocyte-macrophage colony stimulating factors</td>
<td>Expanded, left shifted myelopoiesis</td>
<td>Acute myeloid leukaemias</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td></td>
<td>Erythropoietic and megakaryopoietic hyperplasia</td>
<td>Myeloproliferative syndromes</td>
</tr>
<tr>
<td>Thrombopoietin</td>
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<td>Drugs with immuno-allergenic/myelotoxic potential</td>
<td>Allopurinol, Antibiotics, Carbimazole, Crbamazepine, Clozapine, Phenytoin, Non-steroidal anti-rheumatics, Sulfonamides</td>
<td>Hypoplasia</td>
<td>Aplastic anaemia</td>
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<tr>
<td></td>
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<td>Increased apoptosis</td>
<td>T-cell lymphoma</td>
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<td>Eosinophilia</td>
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<td>Plasmacytosis</td>
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<td>Lymphocytosis</td>
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<td></td>
<td>Serous stromal changes</td>
<td></td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>Azathioprine, Methotrexate, Rapamycin</td>
<td>Severe haematopoietic atypia, especially of megakaryocytes</td>
<td>Myelodysplastic syndromes</td>
</tr>
</tbody>
</table>
Content

• Introduction
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Specific clinico-pathological conditions

• Anemia of chronic disease
• Autoimmune myelofibrosis
• “Hepatic myelopathy”
• Bone (marrow) changes in chronic renal failure
Anemia of chronic disease
Anemia of chronic disease

Blood 2008;112: 219
Autoimmune myelofibrosis
Autoimmune myelofibrosis
Autoimmune myelofibrosis
«Hepatic myelopathy»
«Hepatic myelopathy»
Renal osteopathy

http://alf3.urz.unibas.ch/pathopic
Mimickers

• Myelodysplastic syndromes
• Myeloproliferative neoplasms
• Myelodysplastic-myeloproliferative neoplasms
• Paget’s disease
Content

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Reactive bone marrow changes

• Commonest observable alterations

• Unspecific
  – Specificity only in clinico-pathological context

• Mimickers and/or maskers of malignant processes that must be unmasked by subtraction, falsification, verification ...
Take home message

• Always consider reactive changes
• Verify/falsify this possibility
  – Ask for current medication
  – Ask for concurrent and previous diseases
  – Look for signs of specific (malignant) diseases
  – Consider other methodologies’ results
  – Communicate and discuss your concerns
• Done this you will specifically solve 80% of cases
• Don’t worry giving a descriptive report in the rest