Lymphoid infiltrates in the bone marrow

PathoBasic: Bone Marrow
10. November 2015
Program

- Introduction
- Benign lymphoid aggregates
- Lymphoma
  - General Aspects
  - CLL, FL, MCL, HCL, LPL, (DLBCL, HL, PTCL)
- Summary
BM investigation: diagnostic tools

- Cytology
  - Cytochemistry
- Histology
  - Immunohistochemistry
  - FISH
- Flow cytometry
- Genetics
  - Cytogenetics
  - FISH
  - Molecular genetics
- *In vitro* Culture
- Clinical information
Molecular pathology

See lecture of MAMA
**Lymphoid aggregates in the bone marrow**

- Very common finding
  - reactive versus neoplastic
  - Infancy/children (hematogones)
- Elderly
- Chronic immune disorders (autoimmune disease)
- Therapy related
- Lymphoma infiltration
Normal bone marrow
Morphology of Peripheral Blood

- B-CLL
- Hairy cell leukemia
- Sezary’s syndrome
- Follicular lymphoma
- T-LGL leukemia
- Prolymphocytic leukemia
Morphologic evaluation of lymphoid infiltrates in bone marrow

- Infiltration pattern and topography
  - interstitial
  - intrasinusoidal
  - nodular
  - central (± germinal center)
  - paratrabeal
  - diffuse
  - mixed
- Extent of infiltrate
- Cytological composition
- Fibrosis
Patterns of BM infiltrates in NHL

- Ddx reactive
- Nodular
- Paratrabecular
- Interstitial
- Diffuse
- Sinusoidal
- Mixed

Parrens M, AIP monography
DD reactive vs neoplastic infiltrates

<table>
<thead>
<tr>
<th>Reactive</th>
<th>Neoplastic (lymphoma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Single</td>
<td>• Multiple</td>
</tr>
<tr>
<td>• Well circumscribed</td>
<td>• Ill defined</td>
</tr>
<tr>
<td>• Intertrabecular (non-paratrabecular)</td>
<td>• Peritrabecular/mixed</td>
</tr>
<tr>
<td>• Perivascular</td>
<td>• Intrasinusoidal</td>
</tr>
<tr>
<td>• Sometimes reactive GC</td>
<td>• Reactive GC rare</td>
</tr>
<tr>
<td>• No fibrosis</td>
<td>• Usually fibrosis</td>
</tr>
<tr>
<td>• Polymorphous</td>
<td>• Monotonous</td>
</tr>
<tr>
<td>• T- &gt; B-cells</td>
<td>• B- &gt; T-cells</td>
</tr>
<tr>
<td>• Normal phenotype</td>
<td>• Aberrant phenotype</td>
</tr>
<tr>
<td>• Polyclonal IGH/TCR</td>
<td>• Monoclonal IGH/TCR</td>
</tr>
</tbody>
</table>
Lymphoma infiltration in the bone marrow

- Primary diagnosis (lymphoma classification)
- Staging
- Follow-up investigation
  - response assessment (immune therapy, chemotherapy, allo/auto SCT)
  - Side effects
Flow-cytometric algorithm of mature B-cell neoplasms

Monoclonal B-cells

CD5

CD23

CLL

MCL

CD10

FL

other Lymphoma
# Phenotype of mature B-cell lymphoid neoplasia

<table>
<thead>
<tr>
<th>Antigen</th>
<th>CLL</th>
<th>MCL</th>
<th>FL</th>
<th>HCL</th>
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<tr>
<td>CD20</td>
<td>+</td>
<td>+++</td>
<td>++</td>
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<tr>
<td>CD19</td>
<td>+</td>
<td>+</td>
<td>dim</td>
<td>+</td>
</tr>
<tr>
<td>CD5</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<tr>
<td>CD23</td>
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<tr>
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<td>CD103</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>FMC7/CD22</td>
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<tr>
<td>CD79b</td>
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<td>+</td>
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<tr>
<td>sIg</td>
<td>dim</td>
<td>+</td>
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</table>
B-CLL /small lymphocytic lymphoma

- Very frequent bone marrow involvement
- Mixed pattern (nodular, interstitial and diffuse)
- Small lymphocytes / Prolymphocytes
- Fibrosis only focal
- CD20+ (DIM), CD79a positive, CD5 positive, CD23 positive, CD43 positive, Cyclin D1 negative
Bone marrow: CLL infiltration

H&E

CD20

CD5

CD23
Mantle cell lymphoma

- 50-90% BM-infiltration
- Mixed infiltration pattern including paratrabecular
- CD20+, CD5+, CD23-, CD43+, Cyclin D1+, Sox11+, p27-
- 3 subtypes based on cytomorphology
  - Classic
  - Bastoid
  - Pleomorphic
- Cytogenetics t(11;14)
Follicular lymphoma

• 50-60% bone marrow infiltration
• Paratrabecular infiltration pattern
• Fibrosis (Cave aspirate and FCM)
• CD20+, Bcl2+, CD5-, Cyclin D1-, CD23-/+ (Bcl6+, CD10+-/−)
• Reactive T-cells grading frequently not possible
• 30-40% “discordant lymphoma”
Follicular Lymphoma
Hairy cell leukemia

- 90-100% bone marrow infiltration
- Splenomegaly, cytopenia, dry tap
- Monocytopenia
- Interstitial infiltration, clear cytoplasm (“fried egg”)
- Diffuse fibrosis
- CD20+, CD25+, Trab+, DBA44+, CD103+, Cyclin D1+/-, AnexinA1+, CD103+, CD5-, CD23-
- Molecular genetics: B-RAF mutation
Marginal zone lymphoma

- Nodal
- Extranodal (MALT-lymphoma)
- Splenic
Splenic marginal zone lymphoma

- Splenomegaly, PB-lymphocytosis (+/- villous lymphocytes)
- Frequent bone marrow infiltration
- Infiltration pattern nodular, interstitial and intrasinusoidal
- IHC mandatory if suspected
- CD20+, CD5-, CD43-, CD23-, Cyclin D1-, Annexin1-
- DD: Polyclonal B-cell lymphocytosis
BM: Splenic marginal zone lymphoma

 Courtesy of S. Pileri
Lymphoplasmocytic lymphoma/
Waldenström Macroglobulinaemia

- Frequent bone marrow infiltration (90-100%)
- Interstitial, diffuse and paratrabecular pattern
- Increase in mast cells
- Frequent fibrosis
- CD20+ (small B-cells, CD79a+, CD138+ (mature plasma cells), Cyclin D1-, CD5-, cig+ (IgM)
- MYD88+ (95%)
- DD: B-CLL, MZL, MM
- If bone marrow infiltration with IgM-paraprotein: Waldenström Macroglobulinaemia
Summary

• Lymphoid aggregates in the bone marrow are common
• Benign vs reactive
• Morphology (pattern, extent, cytology) – phenotype – genotype
• Lymphoma: Primary diagnosis – staging – follow-up
• Interdisciplinary approach