Myeloid sarcoma

Sonali Sadawarte
Definition

‘Is a pathologic diagnosis for extramedullary proliferation of blasts of one or more myeloid lineages that disrupts the normal architecture of the tissues in which it is found’
History


• **FAB classification (1976)** – does not specify

• **WHO classification (2001)** – Included under ‘AML not otherwise categorized’

• **WHO Classification (2008)** – separate entity in classification of AML

• **Other**
  - Leukemia cutis
  - Meningeal leukemia
  - Extramedullary myeloid tumour
  - Myeloblastoma
Clinical presentation

• Median age – 45-55 years
• Male: Female – 1.5-2:1
• Median time from previous diagnosis to MS – 2.9 months
• Median time to develop AML – 5-10 months
Types of presentation

• De novo – 27%
• Concurrent with AML, MPD or MDS – 35%
• Previous H/O AML, MDS, MPN – 38%
  - Initial manifestation of relapse in AML in remission
  - Evolution to AML in known MDS or MDS/MPN
  - Blast transformation in MPN
Sites of involvement

- Parotid gland: 0% (Breccia et al), 8% (Pilleri et al)
- Medstium: 0% (Breccia et al), 17% (Pilleri et al)
- CNS: 3.3% (Breccia et al), 25% (Pilleri et al)
- Bone: 0% (Breccia et al), 3.3% (Pilleri et al)
- Gastrointestinal: 6.5% (Breccia et al), 8% (Pilleri et al)
- Genitourinary: 6.5% (Breccia et al), 8% (Pilleri et al)
- Lymph node: 17% (Breccia et al), 16.3% (Pilleri et al)
- Skin: 17% (Breccia et al), 28.2% (Pilleri et al)
Morphology

WHO 2001 / Nieman et al

- Differentiated / Well differentiated
- Immature / Poorly differentiated
- Blastic

No practical relevance in recently published studies
<table>
<thead>
<tr>
<th>Histological classification</th>
<th>Morphology</th>
<th>IHC</th>
<th>Borislav et al (n=13)</th>
<th>Pileri et al (n=92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immature granulocytic sarcoma (IGC)</td>
<td>&gt;90% blast</td>
<td>CD43, CD117, Lysozyme, MPO&lt;10%</td>
<td>2</td>
<td>49</td>
</tr>
<tr>
<td>Differntiated GS (DGS)</td>
<td>&gt;10% more mature (neutrophils)</td>
<td>CD43, MPO, CD15, Lysozyme, CD117</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Monoblastic sarcoma (MBLS)</td>
<td>&gt;80% monoblast</td>
<td>CD43, Lysozyme, CD68, CD163, neg CD34</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Monocytic sarcoma (MCS)</td>
<td>More mature monocytes</td>
<td>CD43, Lysozyme, CD68, CD163, variable MPO</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Myelomonocytic sarcoma</td>
<td>Both myeloid and monocytic</td>
<td></td>
<td>3</td>
<td>20</td>
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</tbody>
</table>

Diagnostic Pathology 2007, 2:42
Pitfalls of conventional light microscopy

Confused with

- Haematopoietic – Lymphoblastic, Burkitts, Diffuse large B cell Lymphoma
- Non haematopoietic – small round cell tumour (neuroblastoma, rhabdomyosarcoma, Ewing sarcoma/PNET, medulloblastoma)
- Undifferentiated carcinoma

Immunophenotyping is mandatory
Misdiagnosed 50% of the times if IPT not done
Immunophenotypic features of Myeloid sarcoma

• Poorly recognized
• Confused with other malignant neoplasm
• Concordance of the immature myeloid cells in MS with those in bone marrow?
• Positive staining with some antibodies (anti-S-100 and MB2) – misdiagnosis of histiocytic neoplasm, melanoma or malignant lymphoma
Pileri et al (n=92)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>CD68/KP1</td>
<td>100%</td>
</tr>
<tr>
<td>MPO</td>
<td>83.60%</td>
</tr>
<tr>
<td>CD117</td>
<td>80.40%</td>
</tr>
<tr>
<td>CD99</td>
<td>54.30%</td>
</tr>
<tr>
<td>CD68/PG-M1</td>
<td>51%</td>
</tr>
<tr>
<td>CD34</td>
<td>43.40%</td>
</tr>
<tr>
<td>tdt</td>
<td>31.50%</td>
</tr>
<tr>
<td>CD56</td>
<td>13%</td>
</tr>
<tr>
<td>CD61</td>
<td>2.20%</td>
</tr>
<tr>
<td>CD30</td>
<td>2.20%</td>
</tr>
<tr>
<td>CD4</td>
<td>1.10%</td>
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</tbody>
</table>
IPT – For Lineage Differentiation and Maturation

• Chang et al (n=17)
• Most sensitive markers for myeloid origin in MS – MPO (88%) and CD68 KP1(94%)
• KP1 – better marker than MPO for myeloid origin (p=0.059)
• PG-M1 – More specific than KP1 for monocytic differentiation in bone marrow (86% vs 25%, p<0.02)

Am J Clin Pathol 2000;114:807-811
• CD56 positivity in GS strongly correlated with monocytic differentiation in bone marrow. (Adhesion molecules enables circulating blast to home extramedullary sites)

• CD34 expression – Infrequent in GS (38%) More in cases associated with CML or MDS than AML (83% vs 10%, p=0.003)

• HLA-DR – positive in all but 2 of the 14 tested

Am J Clin Pathol 2000;114:807-811
H&E ×100

KP1 ×100

PG-M1 ×150.
Cytogenetics

• Initial reports – t(8;21) and inv(16) – recurrent aberrations in MS
• Mainly in children and orbital presentation.
• Adult studies –
  Abnormal karyotype – about 50% (almost all with AML/MPD/MDS)
  Denovo MS – Normal cytogenetics
  Trisomy 8, Inv(16)
FISH and karyotyping in analysis of Myeloid sarcoma – Pileri et al (n=92)

- Monosomy 7 10.8%
- Trisomy 8 10.4%
- MLL splitting 8.5%
- Inv(16) 4.5%
- Trisomy 4 4.4%
- Monosomy 16 2.3%
- 16q-, 5q-, 20q-
- Trisomy 11

- No correlation with age, sex, histotype, denovo, previous h/o AML/MDS/MPN
- Inv(16), t(8;21), t(15;17) – younger and had denovo MS
- MLL rearrangement – always associated with BM involvement
- All patients with cytogenetic abnormality have died irrespective of other factors
### NPM1 mutations and Myeloid sarcoma

Anti-NPM1 antibodies – aberrant cytoplasmic expression of NPM by immunohistochemical detection

<table>
<thead>
<tr>
<th></th>
<th>NPMc- 147/173(85%)</th>
<th>NPMc+ 26/173(15%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous CMPD/MDS</td>
<td>39.6%</td>
<td>0%</td>
<td>0.001</td>
</tr>
<tr>
<td>CD34 positivity</td>
<td>47.85%</td>
<td>12%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normal karyotype</td>
<td>19%</td>
<td>85.7%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Leukemia (2007)21, 1566-1570
H&E

Wild type NPM

Mutated NPM
Pathogenesis

• Significant correlation between extramedullary involvement and coexpression of MCP-1/CCR2
  Expressed by M4/M5 blasts*

<table>
<thead>
<tr>
<th></th>
<th>M0-M1(n=8)</th>
<th>M4-M5 (n=12)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCP-1 (pg/mL)</td>
<td>61+60</td>
<td>1587+398</td>
<td>0.0050</td>
</tr>
<tr>
<td>MDC (pg/mL)</td>
<td>0+0</td>
<td>2165+554</td>
<td>0.0059</td>
</tr>
</tbody>
</table>

• Possible role of neural adhesion molecule CD56 in extramedullary invasion.

*Experimental haematology 31 (2003) 495-503
Treatment

• No definite guidelines
• Complex issue – depends on type of presentation
• Various modalities
  - Surgery
  - Radiotherapy
  - Chemotherapy
    Anti-AML therapy/ less intense /more intense therapy?
  - Combined therapy
Treatment

- **MD Anderson group** – EFS and OS of the MS patients vs AML patients matched for age, PS, Cytogenetics, time of treatment.
- Both received cytarabine containing induction therapy
- Statistically significant result – 99% probability that EFS and OS are longer in MS than AML

Better outcome?
Earlier stage disease with less tumour burden
May not die till develop AML?
Lead time advantage
Need to treat MS with AML therapy

Cancer. 2008 September 15;113(6):1370-1378
Chemotherapy Vs combined modality?

MD Anderson group
• 20 patients with non leukemic GS
• 16 - Chemotherapy (IA, FLAG, CAT-G, Dauno and Ara C)
• 3 - Chemotherapy+radiotherapy (with CNS disease)
• 1 - radiotherpay (skin disease)

Results:
• CR – 13 (65%)
• PR – 1 (15%)
• NR - 6
• Median time to achieve CR- 28 days
• CR - 50% with chromosome 8 abnormalities and 64%with other cytogenetics

Leukemia (2003) 17, 1100-1103
• 45% of treated patients still alive
• 83% with chromosome 8 abnormalities died compared with 50% with other cytogenetics- Survival difference not significant
• OS prolonged with combined chemo radiotherapy
• Although CR rates high, FFS short
• Median time to progression – 5 months
• GS with abnormal BM karyotype - ? Non leukemic disease.
Outcome after treatment

• Pilleri et al (n=92)
• 150 months median follow up
  - Died - 89.5%
  - Alive / CR - 10.5%
• Survivors (7) – all achieved CR after first line therapy
  - 6/7 – Allo-BMT
  - 1/7 – several courses of conventional chemotherapy
• Overall survival at 48 months with / without BMT – 76% vs 0% (p=0.0000)
Mean survival time

- BMT: 52.5 months
- Chemotherapy: 7.1 months
- Imatinib: 5.6 months
- Surgery: 36 days
- Radiotherapy: 1 week
To summarise...

• Denovo Myeloid sarcoma – rare presentation
• Diagnosis often missed initially
• Importance of immunophenotyping in diagnosis
• Need to further evaluate cytogenetics and molecular studies for prognosis
• Need for intensive AML like therapy.