Session 4: Genetic testing in the diagnosis of myeloid neoplasms (excluding acute leukemia)

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## Disease categories discussed in Session 4

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<th>Disease Category</th>
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<tr>
<td>Myeloproliferative neoplasms (MPN)</td>
<td>4 &amp; 6</td>
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<tr>
<td>Mastocytosis</td>
<td>4 &amp; 6</td>
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<td><strong>Myeloid/lymphoid neoplasms with eosinophilia and gene rearrangement</strong></td>
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<tr>
<td>(PDGFRA, PDGFRB, FGFR1 or PCM1-JAK2)</td>
<td>4 &amp; 6</td>
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<tr>
<td>Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)</td>
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<tr>
<td>Myelodysplastic syndromes (MDS)</td>
<td>4 &amp; 6</td>
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<tr>
<td>Blastic plasmacytoid dendritic cell neoplasm (BPDCN)</td>
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Ineffective hematopoiesis
Intact maturation

Effective hematopoiesis
Intact maturation

MDS/MPN
MLN-Eo

MDS

MPN
MLN-Eo

Mastocytosis

AML
MLN-Eo

B-ALL
MLN-Eo

T-ALL

MLN-Eo

BPDCN

Myeloid lineage
Arrested maturation

Lymphoid lineage
Arrested maturation

Intact maturation

Arrested maturation
Diagnostic hematopathology 2017

Dysplasia
Cellularity
Differential counts
CBC
Clinical history
Immunophenotype

Karyotype/FISH
NGS panels
- mutation spectrum
- variant frequencies
- germline variants
- VUSs
- CHIP/CCUS
- prognostic significance
- targeted therapies

Diagnosis
NGS panels: General trends in mutation patterns

- MDS – spliceosome genes (SF3B1, SRSF2), ASXL1, RUNX1, EZH2
- MPNs – JAK2, CALR, MPL, CSF3R
- MDS/MPN
  - Atypical CML- ASXL1, TET2, SETBP1
  - CMML – SRSF2, TET2, CBL, ASXL1
  - MDS with ring sideroblasts and thrombocytosis – JAK2 + SF3B1
  - JMML – RAS pathway mutations (PTPN11, KRAS/NRAS)
- CHIP – TET2, DNMT3A, ASXL1
General issues addressed in this session

• Newly defined entities in the WHO Classification system
  – Myeloid neoplasm with *PCM1-JAK2*

• Are there any truly specific molecular genetic abnormalities?
  – Yes: ex. *t(8;21);RUNX1-RUNX1T1*
  – But not these: ex’s. *CSF3R* p.T618I or *JAK2* p.V617F
  – And certainly not in these genes: *DNMT3A, TET2*

• How helpful are ‘typical’ mutation patterns in supporting a particular diagnosis?
  – “Oligomonocytic” chronic myelomonocytic leukemia

• What about ‘atypical’ patterns?
  – Atypical CML with mutated *CSF3R*
General issues addressed in this session

- Establishing clonality using NGS panels
  - Diagnosis of CEL, NOS with “molecular genetic” abnormalities
  - Beware of CHIP

- Variants of uncertain significance (VUSs)
  - Germline or somatic?

- Finding unexpected mutations that change the diagnosis
  - Detection of a *KIT* D816V mutation led to an unanticipated diagnosis (systemic mastocytosis)

- Synthesizing morphologic and molecular genetic findings
Oral presentation cases

- #124 – Dr. John Goodlad: Atypical chronic myeloid leukemia
- #351 – Dr. Madhu Menon: Chronic myelomonocytic leukemia-0
- #156 – Dr. Jeffrey Craig: Systemic mastocytosis with associated hematologic neoplasm (CMML-0)
- #171 – Dr. Shunyou Gong: Juvenile myelomonocytic leukemia
- #376 – Dr. Magdalena Czader: Myeloid neoplasm with PCM1-JAK2
- #300 – Dr. Geetha Jagannathan: Chronic eosinophilic leukemia, NOS
- #314 – Dr. Habibe Kurt: Blastic plasmacytoid dendritic cell neoplasm