Session 5

Pre-malignant clonal hematopoietic proliferations

Chairs: Frank Kuo and Valentina Nardi
Pre-malignant clonal hematopoietic proliferations

- **Clonal LYMPHOID proliferations:**
  
  - Monoclonal gammopathy of undetermined significance (MGUS)
  
  - Monoclonal B-cell lymphocytosis (MBL)
  
  - In Situ Follicular Neoplasia (ISFN)
  
  - In Situ Mantle Cell Neoplasia (ISMCN)
Pre-malignant clonal hematopoietic proliferations

- Clonal hematopoiesis of indeterminate potential (CHIP)
- Clonal cytopenia of undetermined significance (CCUS)
- Small clones of cells with BCR-ABL1
Premalignant clonal LYMPHOID proliferations

Monoclonal gammopathy of undetermined significance

- Non-IgM MGUS (plasma cell)

- IgM MGUS (mostly lymphoid/lymphoplasmacytic) - progresses to LPL/WM, other B-cell neoplasms, or primary amyloidosis

Adapted from David P. Steensma et al. Blood 2015;126:9-16
Premalignant clonal LYMPHOID proliferations

Monoclonal B-cell lymphocytosis

- CLL-type, atypical CLL-type, non CLL-type
- Low count (<0.5 x10⁹/L) vs High count (> 0.5 x10⁹/L)

Adapted from David P. Steensma et al. Blood 2015;126:9-16
Premalignant clonal LYMPHOID proliferations

In Situ Follicular Neoplasia

"Partial or total colonization of germinal centers by clonal B cells carrying the BCL2 translocation characteristic of FL in an otherwise reactive lymph node."

Adapted from David P. Steensma et al. Blood 2015;126:9-16
Premalignant clonal LYMPHOID proliferations

In Situ Mantle Cell Neoplasia

“Presence of cyclin D1–positive lymphoid cells with CCND1 rearrangements restricted to the mantle zones of otherwise hyperplastic-appearing lymphoid tissue.”

Adapted from David P. Steensma et al. Blood 2015;126:9-16
Premalignant clonal MYELOID proliferations

Clonal hematopoiesis of indeterminate potential

CHIP

Most patients do not progress

No progression; death from unrelated causes

myeloid/lymphoid/multipotential Progenitor cell
Or
Stem cell

Progression: ~0.5-1.0% per year

MDS-associated clonal gene mutations identified in haematopoietic cells without significant dysplasia on bone marrow examination and in the absence of cytopenias.

Adapted from David P. Steensma et al. Blood 2015;126:9-16
Significance of pre-malignant clonal hematopoietic proliferations

- early involvement by a neoplasm
- precursor lesion
- inconsequential finding
Somatic mutations in CCUS and risk of progression

* Spliceosome gene mutations
* Co-mutation patterns involving DNMT3A, TET2 and ASL1

Malcovati L. et al, Blood 2017
Pre-malignant clonal hematopoietic proliferations: cases selected for oral presentation

Case 269 - Dr. Wood.
Clonal cytopenia of undetermined significance.

Case 50 - Dr. Thompson-Arildsen.
Clonal cytopenia of undetermined significance with progression to myelodysplastic syndrome with excess blasts-2.

Case 350 - Dr. Shanmugam.
Clonal cytopenia of undetermined significance with progression to chronic myelomonocytic leukemia-1.

Case 28 - Dr. Rjoop.
Occult myeloid sarcoma (in a patient with lymphoplasmacytic lymphoma).

Case 256 - Dr. Loghavi.
1. Lymphoplasmacytic lymphoma. 2. Chronic myelomonocytic leukemia-1.

Case 332 - Dr. Stuart.
Paroxysmal nocturnal hemoglobinuria.
Clonality assessment for premalignant neoplasms

- T/B cell clonality, flow cytometric analysis
- Chromosomal abnormality (karyotype, FISH, aCGH)
- Gene mutations (NGS)
  - same genes and mutations as myeloid/lymphoid neoplasms
  - variable allelic frequency (from low to high)
  - single or multiple
  - some confer higher risk of progression
## Premalignant (clonal) MYELOID proliferations

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<th><strong>CHIP</strong></th>
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Adapted from David P. Steensma et al. Blood 2015;126:9-16
Somatic mutations in CHIP

Jaiswal S., et al.


10% > age 70, 20%>age 90

DNMT3A, ASXL1 & TET2, most commonly mutated genes