P1415 HIGH AND LOW MYELOID SKEWING IN THE GENERAL POPULATION AND THE ASSOCIATION WITH CLONAL HEMATOPOIESIS

Topic: 23. Hematopoiesis, stem cells and microenvironment

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Background:
The blood cell production represents a balance between myeloid and lymphoid progeny. During aging an increase in the absolute numbers of HSCs is observed and their differentiation potential declines. One of the hallmarks of the aging HSC is a myeloid differentiation bias and decreased lymphopoiesis. A common denominator of aging is the development of somatic mutations within the hematopoietic stem cell compartment. Clonal outgrowth of these cells is called clonal hematopoiesis (CH) and is measurable in >10% of the elderly over 60 years of age.

Aims:
We studied high myeloid skewing and low myeloid skewing in the general, population-based Lifelines cohort (n=167729). As the contribution of CH to high or low myeloid skewing is currently unknown, individuals >60 years were selected with the highest and lowest myeloid percentages, together with age and sex matched controls.

Methods:
All individuals above >18 years old with available myeloid and lymphoid peripheral blood counts were selected to study myeloid skewing (n=144676). CH was assessed in individuals above 60 years (n=21727) with the highest myeloid percentage (>99%, n=218) and lowest myeloid percentage (<1%, n=218) and age and sex matched controls (n=436). Targeted error-corrected next-generation sequencing was performed on 27 genes recurrently mutated in myeloid malignancies with a variant allele frequency (VAF) >1%.

Results:
High myeloid and low myeloid skewing is present in all age categories, and not restricted to the older population. Overall, CH was not enriched in cases with high myeloid skewing compared to matched controls. In contrast, CH was depleted in cases with low myeloid skewing. A significant enrichment of mutations involved in the spliceosome (SF3B1, U2AF1 and SRSF2) was observed in cases with high myeloid skewing (p=0.02). The VAF of detected mutations did not correspond to the number of myeloid cells for both cohorts. Cases with high myeloid skewing had a significantly worse overall survival compared to controls (HR, 2.6; 95% CI, 1.98-3.41; p=<0.001), and this was a consistent finding in all age categories >30 years old. Overall survival in cases with myeloid skewing above 60 years was significantly decreased in combination with anemia (HR, 2.27; 95% CI, 1.16-4.47; p=0.017), however, no specific mutational pattern was observed in these cases. Low myeloid skewing did not significantly affect survival, but in combination with TET2 mutations (n=15) these cases had a significantly worse overall survival (HR, 3.42; 95% CI, 1.22-9.64; p=0.02). From these, nine individuals with low myeloid skewing and a TET2 mutation carried an additional neutropenia.

Summary/Conclusion:
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High or low myeloid skewing is a common finding in the general population, and not restricted to individuals >60 years. The presence of CH is not associated with high or low myeloid skewing. Mutations in the spliceosome were enriched in cases with myeloid skewing, possibly representing cases with early oncogenic transformation. Although CH was not enriched in low myeloid skewing cases, mutations in TET2 had a negative impact on survival of these cases. In combination with neutropenia, these cases may be at risk of developing lymphoid malignancies. Overall, mutations in genes involved in myeloid malignancies are less frequently observed in cases with low myeloid skewing compared to matched controls.