Clinical and Molecular features of the patients with Idiopathic Erythrocytosis

CARATTERISTICHE CLINICHE E MOLECOLARI DEI PAZIENTI CON ERITROCITOSI IDIOPATICA

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Background: Polycythemia Vera (PV) is typically caused by *JAK2*V617F or exon 12 JAK2 mutations. Little is known about polycythemia cases where no *JAK2* variants can be detected and no other causes of primary or acquired erythrocytosis can be identified. This condition is defined as Idiopathic Erythrocytosis (IE).

Material and methods: We evaluated clinical-laboratory parameters of a cohort of 56 IE patients (pts), regularly followed up at the Hematology Unit of our Institution, between 1999 and 2021. We determined their molecular profile using a high-depth targeted oncopanel on peripheral blood coupled with paired blood/buccal-DNA exome-sequencing. Concerning the treatment, all pts were managed with phlebotomies, to maintain hematocrit below 50%. No cytoreduction was used at onset, only low dose aspirin in pts with concomitant risk vascular factors.

Results: Principal clinical-laboratory features of IE pts at diagnosis are showed in Tab. 1A. Compared to PV (Randi, 2015), IE pts were mostly males, younger and presented normal/higher serum erythropoietin levels. Interestingly, ferritin levels were higher in our cohort (median 115 ng/ml) than we expected in PV pts (Ginzburg, 2018). According to molecular profiling (Tab. 1B), we identified 17 Low Mutation Burden somatic variants in 13 (23.2%) pts, principally involving *DNMT3A* and *TET2*. Notably, a large part of the cohort (76.8%) showed no evidence of clonal hematopoiesis (CH). These findings opened-up the possibility of an underlying genetic disorder functionally connected with congenital erythrocytosis but characterized by adult onset and limited penetrance. By using ad hoc statistical analyses, we identified recurrent germline variants in 43 (76.8%) pts occurring mainly on JAK/STAT, Hypoxia and Iron metabolism pathways (Tab. 1C). In particular, a high fraction of pts (50%) resulted HFE mutated.
After a median follow-up of 7.7 years, 6 (10.7%) thrombotic events were reported during follow-up. Eight (14.3%) pts required introduction of cytoreduction. Only 2 (3.6%) myelofibrotic evolutions was observed. No pts presented leukemic transformation.

Conclusion: Our data suggest that IE are, in large part, genetic disorders with few pts showing evidence of low burden CH. In most IE we identified recurrent germline variants occurring mainly on JAK/STAT, Hypoxia and Iron metabolism pathways. To validate our data, the generation of cellular models is ongoing.

Attachment:

Table 1: Clinical and molecular profile of Idiopatic Erytrocytosis