From Vaquez to Dameshek through JAK...2 much for polycythemia vera to be feared?

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Clinical practice in modern medicine is a gift that comes from afar. It comes sometimes from a lucky discovery, or sometimes from brave attempt chasing what at that time seemed crazy theories. Anyway, the gift we currently enjoy is the result of careful observation at first, and then like a sculptor with his chisel that free from marble an hidden figure, doctors and researchers carve during the years the features of many diseases.

In this number of the *Internal and Emergency Medicine Journal*, Landolfi and his co-workers [1] reviewed the principal characteristics of polycythemia vera (PV), starting from the history of the first published description by Luis Henry Vaquez in 1892 [2].

Since this first description something other than plethora and cyanosis were soon identified: the high risk of major thrombotic events potentially leading to death, both in arterial district (acute myocardial infarction, stroke or transient ischemic attack, TIA), and in venous district (deep vein thrombosis, pulmonary embolism, and splanchnic thrombosis).

The mortality rate of PV, as reassessed in the ECLAP study [3] is about 3.7/100 patients/year due not only to the vascular complications but also for a possible evolution to malignancy.

The history of PV went through the recognition of an absolute increase of blood cells, due to an abnormal

erythropoiesis as the result of a pluripotential stem cell being erythropoietin hypersensitive and independent [4]. The related clinical condition must be differentiated from secondary erythrocytosis and this exercise has challenged haematologist for decades.

So, like industrious sculptors, haematologist has learnt to use diagnostic criteria like chisels to carve for each patient the hidden truth of primary or secondary hyperglobulia. But not all sculptors are the same.

Amedeo Modigliani, the great painter and sculptor used to say that he could see at a glance what was inside a piece of marble, and that he just had to free it. In the same way, Dameshek [5] in 1951 described his vision “from outside” and speculated that PV has the same origin of essential thrombocythemia (ET), chronic idiopathic myelofibrosis (IMF) and chronic myeloid leukemia (CML). What was really inside, and Dameshek had seen, was proved more than 50 years later with the discovery of the mutation at position 617 in the JH2 domain of the Janus Kinase 2 (JAK2) cytoplasmic tyrosine kinase [6–9]. This gain-of-function mutation, recognizable in almost 90% of PV patients, is acquired and present in clonal hemopoietic stem cells and responsible for the activation of Epo-signaling pathway, leading to hypersensitivity and uncontrolled growth of cells.

The JAK2V617F mutation is also found in about 50% of patients with ET and IMF, in atypical myeloproliferative disorders, but it has been described also in some patients with CML and in patients with portal vein thrombosis but without hematological abnormalities. From these observation, recent theories and hypothesis have been explained, such as different intensity of JAK2 signaling, presence of pre-JAK2 event that will result in different myeloproliferative disorders, different host modifier polymorphisms [10], just to cite some of them.

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It was in 1967 that a first study group of expert, under the guidance of Louis Wasserman, was born with the aim to study the natural history of this disease and to design and conduct clinical trials. The Polycythemia Vera Study Group also established the diagnostic criteria that in the next years have changed so much. Nowadays in fact, the WHO diagnostic criteria for PV include the presence of JAK2 mutation or other functionally similar mutation (i.e. JAK2exon 12 mutation) as major criteria.

Polycythemia vera remains a rare disease (about 2 new cases/100,000 persons/year) mostly in people over 70 and even if life expectancy is better than in other hematological diseases, the occurrence of PV in younger people arise remarkable questions about treatment, because previous studies have demonstrated that young age is neither protective against vascular complications nor against malignant evolution.

Ruggeri and co-workers [11] provide in this number of Internal and Emergency Medicine the results of a 20 years retrospective analysis of treatment outcome in 30 adults aged less than 45 years, included in a larger cohort of patients enrolled since 1987.

The authors managed the treatment as conservative as possible, using phlebotomy in order to reduce hematocrit less than 45% and aspirin in almost all patients. The use of hydroxyurea was reserved to patients who suffered a vascular complication related to high platelet count.

As previously reported, 40% of patients have vascular complication, but 16% of all these complications occurred at presentation.

These data have to be well noted, and should be used in any clinical ward during the assessment of risk factors for both arterial and venous thrombosis especially in young patients or in case of unusual site of thrombosis (i.e., splanchnic vein thrombosis and cerebral venous thrombosis).

With respect to other previous published data [12], the rate of vascular complication is similar, but a lower incidence of evolution to malignancies in Ruggeri's cohort is noticeable, because in the latter neither acute leukemia nor myelodysplastic syndrome were described in the follow up, even in patient underwent hydroxyurea treatment. The 8.5% of progression described by Passamonti et al. [12] occurred in a cohort of patients who received in 82% of cases chemotherapy with pipobroman (73%) or hydroxyurea (6%), as compared to 40% of patients treated with hydroxyurea in Ruggeri's cohort.

Different incidence in progression might be the results of different rate of exposure to alkylating agents, even if this could not be the only explanation.

Genomic characterization of myeloproliferative disorders has just begun and if it is clear the benefit of avoiding alkylating agents in younger patients, perhaps a complete

balance of risk and benefit would be much clear when more implications of having this mutant kinase (included possible differences between having one or two copies of the mutant) or other potential affecting mechanisms will be explained.

In the meantime, as described by Landolfi, the treatment of PV with alkylating agents, interferon, or anagrelide should be tailored for each patients, while aspirin has gain its place to the sun when it was demonstrated that low dose of ASA significantly reduced major and minor thrombosis in PV patients, without excess of bleeding [13].

To this drug armamentarium for the treatment of PV, we are now waiting to add new therapeutical strategies, such as JAK2 inhibitors.

Preliminary results of in vitro and in vivo studies have shown that small molecules acting as ATP-competitive inhibitors of JAK2 kinase could be effective in controlling the hyperproliferation of hematopoietic cells in PV and ET, even if not able to erase the mutant clone [14]. Imatinib mesylate itself, another inhibitor of tyrosine kinase, has demonstrated how is it possible to change the natural history of a hematological disease and after astonishing results showed in CML, is known to act on colony growth derived from PV patients in vitro [15].

So, great expectations surrounds the treatment of PV and the other myeloproliferative disorders in these years: like smart sculptors, hematologists are now learning to sharp the right chisel for any different kind of marble. Modigliani would be proud of these fellows.

Conflict of interest None.

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