Myelodysplastic/myeloproliferative disorders

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Most patients with myelodysplastic syndromes present with anemia, while neutropenia, thrombocytopenia, or both may be found initially or may appear later.[1] Therefore cytopenia, frequently pancytopenia (i.e., reduced counts of red blood cells, white blood cells and platelets in peripheral blood), represents one of the hallmarks of these syndromes. The pathophysiological mechanism leading to peripheral cytopenia is ineffective hematopoiesis, i.e., the excessive apoptosis of hematopoietic precursors within the bone marrow.

Philadelphia-negative chronic myeloproliferative disorders (polycythemia vera, essential thrombocythemia, primary myelofibrosis) are characterized by various combinations of erythrocytosis, leukocytosis and thrombocytosis, i.e., the opposite of cytopenia. These conditions are typical clonal disorders of hematopoietic stem cells. The occurrence of a mutation of *JAK2*[2-5] or *MPL*[6-8] in a multipotent stem cell generates a myeloid clone that expands to replace hematopoietic cells without the mutation.[9] This clone is more efficient in the production of mature blood cells, at least initially, and this results in increased peripheral blood cell counts.

Although myelodysplastic syndromes and myeloproliferative disorders appear to have entirely different pathophysiological mechanisms, the existence of conditions with overlapping features is well established. The World Health Organization (WHO) classification of the myeloid neoplasms[10] introduced the category of myelodysplastic/myeloproliferative diseases, which includes myeloid disorders that have both dysplastic and proliferative features at the time of initial presentation and that are difficult to assign to either the myelodysplastic or myeloproliferative group of diseases. The following disorders belong to this category: chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia, juvenile myelomonocytic leukemia, and *myelodysplastic/myeloproliferative disease, unclassifiable (MDS/MPD, U)*.

The sideroblastic anemias are a heterogeneous group of inherited and acquired disorders characterized by anemia of varying severity and the presence of ringed sideroblasts in the bone marrow.[11] Ringed sideroblasts are erythroblasts with iron-loaded mitochondria, visualized by Prussian blue staining as a perinuclear ring of blue granules. Most of the iron deposited in these perinuclear mitochondria of ringed sideroblasts is present in the form of mitochondrial ferritin.[12] The presence of ringed sideroblasts in the bone marrow (15% or more) is a marker of the myelodysplastic syndromes defined as refractory anemia with ringed sideroblasts (RARS) and refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS).[10] In addition, they are also a typical feature of the condition defined as *refractory anemia with ringed sideroblasts associated with marked thrombocytosis (RARS-T)*, which has been included as a provisional entity in the category MDS/MPD, U.

In 2002, Schmitt-Graeff and co-workers[13] published an interesting study on 38 patients showing both thrombocytosis in peripheral blood and ringed sideroblasts in the bone marrow, a condition that was at that time defined as *essential thrombocythemia with ringed sideroblasts (ET-RS)*. Findings of this study provided evidence that ET-RS includes a wide spectrum of conditions ranging from myelodysplastic syndromes in the strict sense to myeloproliferative disorders (essential thrombocythemia, prefibrotic primary myelofibrosis).

The association of ringed sideroblasts with thrombocytosis was partly clarified following the identification of the unique mutation (V617F) of *JAK2* in myeloproliferative disorders.[2,3] Szpurka and co-workers[14] studied 57 patients with myelodysplastic/myeloproliferative disease, and found that 11 of them carried *JAK2* (V617F). In particular, this mutation was detected in six of the patients with RARS-T, and the authors concluded that RARS-T constitutes another *JAK2* mutation-associated form of myeloproliferative disease.

Several other studies including mutation analysis of *JAK2* and *MPL* in myelodysplastic/myeloproliferative diseases have been published in the last 2 years,[15-21] and their findings are summarized in Table 1. In this issue of the journal, Schmitt-Graeff and co-workers[22] report their findings in a study evaluating *JAK2* (V617F) status in 23 patients with RARS-T by allele-specific polymerase chain reaction analysis. The mutation was detected in 11/23 patients, and in six RARS-T patients the allelic ratio of *JAK2* (V617F) was above 50%, indicating the presence of cells homozygous for the mutation. Very interestingly, in two of these latter patients a transition from *JAK2* (V617F) heterozygosity to homozygosity was documented, and this was accompanied by rising platelet counts in sequential samples. The *MPL* (W515L) mutation was detected in one *JAK2* (V617F)-negative patient.

This study clearly indicates that RARS-T has several features of myeloproliferative disorders in addition to overproduction of platelets, including striking megakaryocytic proliferation, leukocytosis, abnormalities of chromosomes 8 and 20, vascular events, and marrow fibrosis.[22] The authors correctly raise the question of what

Table 1. Findings of studies on mutations of *JAK2* and *MPL* in patients with myelodysplastic/myeloproliferative disorders.

Authors	*Proportion of cases that were found to be positive for* JAK2 *(V617F)*	MPL *mutations*
Szpurka *et al.*[14]	6/9 RARS-T 3/26 MDS/MPD, U 2/22 CMML	Not studied
Remacha *et al.*[15]	6/9 RARS-T	Not studied
Wang *et al.*[16]	6/12 RARS-T with platelet count ≥600 x 10^9/L 0/19 RARS-T with platelet count < 600 x 10^9/L 0/11 MDS/MPD, U	Not studied
Boissinot *et al.*[17]	5/16 RARS-T (5/8 RARS-T with features of ET)	Not studied
Ceesay *et al.*[18]	4/6 RARS-T	Not studied
Renneville *et al.*[19]	5/7 RARS-T 2/15 CMML	Not studied
Gattermann *et al.*[20]	9/10 RARS-T	Not studied
Schnittger *et al.*[21]		*MPL* (W515) mutation in a case with features of both ET and RARS-T
Schmitt-Graeff *et al.*[22]	11/23 RARS-T	*MPL* (W515) mutation in one JAK2 (V617F)-negative patient with RARS-T

CMML = chronic myelomonocytic leukemia; ET = essential thrombocythemia; MDS/MPD, U = myelodysplastic/myeloproliferative disease, unclassifiable; RARS-T = refractory anemia with ringed sideroblasts associated with marked thrombocytosis.

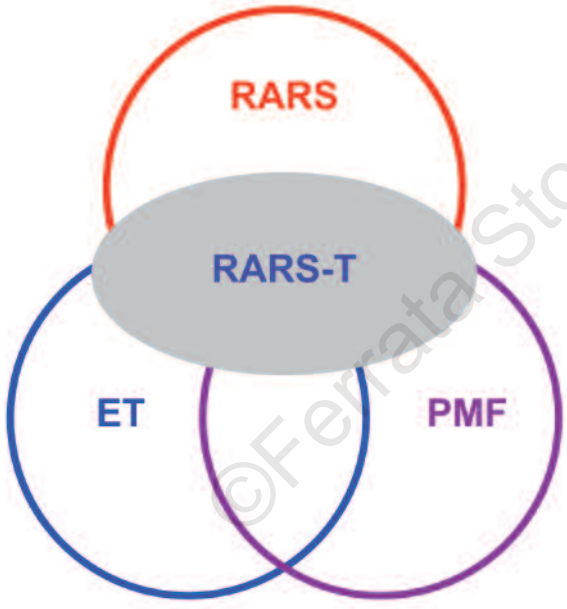

Figure 1. Schematic representation of the hypothetical relationships between refractory anemia with ringed sideroblasts (RARS), essential thrombocythemia (ET), primary myelofibrosis (PMF), and the provision entity defined as refractory anemia with ringed sideroblasts associated with marked thrombocytosis (RARS-T). The acquisition of a mutation in *JAK2* or *MPL* in a RARS patient might lead to the development of thrombocytosis, and change the clinical phenotype from RARS to RARS-T. Alternatively, the occurrence of a mutation in an unknown gene, capable of causing mitochondrial iron loading and ineffective erythropoiesis, in a patient with ET or PMF may result in a myelodysplastic/myeloproliferative phenotype (RARS-T).

mechanism may be responsible for anemia in a *JAK2* (V617F)-positive disorder, taking into account that this mutation is normally associated with erythrocytosis. In order to answer this question properly, it should be first considered that the casual combination of ringed sideroblasts and *JAK2* (V617F) mutation is highly improbable, considering the low prevalence of both refractory anemia with ringed sideroblasts and essential thrombocythemia in the general population. This means that this combination cannot be simply coincidental. Thus, there must be a pathophysiological mechanism that predisposes RARS patients to acquire *JAK2* (V617F), or alternatively patients with *JAK2* (V617F)-positive myeloproliferative disorder to develop mitochondrial iron loading and ineffective erythropoiesis. Further studies are required to elucidate which of the two mechanisms is more likely.

Diagnostic criteria for RARS-T need to be better defined, as this disorder currently appears to represent a condition that is borderline to RARS, essential thrombocythemia and primary myelofibrosis (Figure 1). A better diagnostic definition may in fact have relevant prognostic implications. Schmitt-Graeff and co-workers[22] report that patients with RARS-T carrying *JAK2* (V617F) have a better outcome than those with RARS-T wild-type *JAK2*. While this is interesting, it should not be forgotten that patients with RARS-T have a worse outcome than those with essential thrombocythemia.[13,23] In particular, RARS-T patients are more likely to develop acute myeloid leukemia, and therefore a correct diagnosis is of fundamental importance for defining the prognosis of the individual patient. As a practical recommendation, we believe that Perls' staining on a bone marrow aspirate should be performed in patients with myeloid neoplasm and thrombocytosis whether or not they carry mutations of *JAK2* or *MPL*.

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