Review of: "Potential limitations of diagnostic standard codes to distinguish polycythemia vera and secondary erythrocytosis"

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In their report entitled, *"Potential limitations of diagnostic standard codes to distinguish polycythemia vera and secondary erythrocytosis"*, Barrios-Ruiz and colleagues perform a service for hematologists regarding the diagnostic difficulties involved in distinguishing polycythemia vera from secondary causes of erythrocytosis. These difficulties are, of course, self-inflicted, because 20 years ago most hematologists understood that the peripheral blood hematocrit does not correlate with the total body hematocrit[1]. This is because the distribution of plasma and red cells is not equivalent in the smaller blood vessels in the body due to the faster passage of the axially (centrally) flowing red cells as compared to the centrifugally-located plasma which is pushed by the axial red cells closer to the blood vessel wall[2]. As a consequence, the presence of true erythrocytosis as opposed to pseudo-erythrocytosis due to plasma volume contraction, cannot be assumed from a peripheral blood hematocrit value unless it is greater than 59 %[3].

Thus, only by doing measurements of both the red cell mass (RCM) using ^{51}Cr, and the plasma volume (PV) using ^{131}I-albumin, can the actual total body hematocrit (based the red cell mass and plasma volumes) be determined. Fortunately, both tests can be done in the patient simultaneously[4]. Considered a historical curiosity today, the development of an accurate technique to determine the true total body hematocrit was a scientific challenge in the last century, which was solved by the work of several Noble Laureates. The test's importance can be gauged by the fact that using both RCM and PV measurements, the diagnosis of polycythemia vera could be established with 99 % accuracy[5], whereas today, using the current WHO MPN diagnostic criteria[6], the diagnosis of PV will be missed in 25-38% of patients[7].

This is because the WHO experts reasoned that using the newly discovered *JAK2* gene mutations together with a serum erythropoietin assay and bone marrow histology[8], polycythemia vera could be distinguished from secondary erythrocytosis as well as from essential thrombocytosis and primary myelofibrosis. They were misled by the erroneous contention that RCM/PV measurements relied on a simultaneously measured peripheral blood hematocrit[9], which by definition they do not[10]. Even worse, the proposed WHO hematocrit and hemoglobin levels were never prospectively validated and were to be proven erroneous[11], as was the use of the serum erythropoietin assay[12][13] and bone marrow histology[14] as clues to polycythemia vera. Subsequently, the WHO lowered its estimated diagnostic hematocrit and hemoglobin levels in an attempt improve diagnostic accuracy but as usual, never prospectively validated these either[6].

This clumsy, unscientific diagnostic approach increased the risk of the false-positive diagnosis of polycythemia vera, while ignoring the essential facts that in contrast to secondary forms of erythrocytosis involving increased erythropoietin production where plasma volume contraction is the rule, in polycythemia vera, the serum erythropoietin level is not increased, and, as the hematocrit increases, the plasma volume also increases[15]. Stated differently, when polycythemia vera is a consideration, a “normal” hematocrit cannot be considered normal, particularly in women, in whom hepatic vein thrombosis is most common[16]. As corollary, it is not surprising that in this clinical situation hydroxyurea has been a therapeutic failure[17], because, unless the red cell mass is first reduced by phlebotomy, nitric oxide scavenging by the increased red cell mass antagonizes this drug.

It is also worth noting, that contrary to the WHO contention, the hemoglobin level is not a useful measurement in polycythemia vera because hemoglobin is a red cell product whose synthesis is affected by the available iron supply, it correlates poorly with the red cell mass and not at all with blood viscosity. On the other hand, red cell number and, in particular, microcytic erythrocytosis, is a hallmark of polycythemia vera[18], though the WHO MPN diagnostic criteria do not mention this[6].

With this background in mind, we can return to the important contributions of Barrios-Ruiz and colleagues. They conducted a chart review of the ICD9/10 diagnostic codes for polycythemia vera (D45) and secondary erythrocytosis (D75.1) over a ten year period at their respective institutions, and compared the accuracy of diagnostic coding with the actual diagnostic evaluation. From 1092 patients with a consistent ICD diagnostic code for one or both disorders, they identified 578 adults who also had a *JAK2* mutation assay. Of these, 450 were classified as having polycythemia vera; 67 (11.5%), had secondary erythrocytosis; and, remarkably, 16 (11%) were classified as having both polycythemia vera and secondary erythrocytosis.

Importantly, after chart review and recoding, of the 450 patients thought to have polycythemia vera, only 427 did, 49 had secondary erythrocytosis and 4 were normal. Of the 67 with secondary erythrocytosis, 2 had polycythemia vera and 2 were normal; of the 61 who had both diagnoses, 5 had polycythemia vera, 54 had secondary erythrocytosis and 2 were normal.

Phenotypically, both the polycythemia vera and secondary erythrocytosis patients were largely male and both had a mean age in the mid to late fifties. The mean serum erythropoietin level in the secondary erythrocytosis group was 19.3 mU/mL (range 8.8-22.6); no data were provided for the polycythemia vera patients. Only 2 of the secondary erythrocytosis group had a positive PCR assay for *JAK2* V617F but no quantitative allele burden was provided. So, it is unclear whether the mutation was associated with the erythrocytosis, since normal individuals can express this mutation at a low level[19]. The authors state that these two patients did not have marrow morphology compatible with polycythemia vera, but it is a misconception that *JAK2* V617F expression is always associated with abnormal marrow morphology, particularly when the quantitative mutation allele burden is low.

More importantly, 5 of the secondary erythrocytosis patients had other *JAK2* gene variants, some germline, which might have predisposed to erythrocytosis. Not surprisingly, 41 % of the secondary erythrocytosis patients had no determined etiology, but tobacco use was not recorded. A large percentage of the secondary erythrocytosis patients had an underlying solid tumor but this unusual diagnostic skewing probably reflects ascertainment bias, since all the patients were seen at tertiary cancer referral centers. Finally, five of the secondary erythrocytosis patients had a plasma volume contraction syndrome.

The authors epidemiologic results are similar to those of Ruggeri et al. before the discovery of *JAK2* gene mutations. These investigators studied the rate of progression to polycythemia vera or essential thrombocythemia of a large cohort of normal individuals[20]. They found that out of a cohort of 10,000 citizens in a single town, one had polycythemia vera and 88 had a high hematocrit. After 8 months, 2 additional cases of polycythemia vera were diagnosed but only 33 of the other 86 still had erythrocytosis. After 5 years, 11 of these 33 had idiopathic erythrocytosis, of the rest, 18 were smokers, 2 had congenital heart disease and 2 had polycystic kidney disease. Taken together with the observations of Barrios-Ruiz et al., it is clear that isolated erythrocytosis is neither a static nor always a permanent diagnosis.

The data of Barrios-Ruiz et al. serve warning that epidemiologic studies using ICD 10 diagnostic codes alone can lead to misleading results. The data of Barrios-Ruiz et al. also highlight something even more important and disturbing: *the current inability to distinguish polycythemia vera from secondary erythrocytosis*. In large part this is due to current lack of ability to measure the RCM and PV, because the first question when a high hematocrit is identified clinically, is whether this is due to too many red cells, plasma volume contraction or both? Obtaining a serum erythropoietin level and a bone marrow biopsy will not help diagnostically here because they both can be normal. Obtaining an assay for a *JAK2* mutation will not be helpful unless a quantitative allele burden is obtained, and even then, some polycythemia vera patients do not express a *JAK2* mutation; the assay is also not inexpensive and isolated erythrocytosis is a rare presentation for polycythemia vera, a point ignored by the WHO.

The main source of the problem is, of course, the WHO MPN diagnostic criteria, which depict polycythemia vera as a disease of the red cells, and essential thrombocytosis as a disease involving only the platelets. When in fact, all the MPN are disorders of the hematopoietic stem cell[21], which is not only pluripotent but also has as a default mechanism when stressed, to increase the production of megakaryocytic stem cells, since HSC only express the thrombopoietin receptor. Thus, isolated thrombocytosis could represent a response to infection, inflammation, cancer or an MPN mutation, but isolated (true) erythrocytosis can be due to many causes, of which polycythemia vera would be rare, because the MPN are rare diseases. Polycythemia vera is a panmyelopathy, which actually starts commonly as isolated thrombocytosis or with elevation of the leukocytes, platelets and red cells or various combinations of these, and not erythrocytosis alone[22][23]. Thus, the observation by Barrios-Ruiz et al. of the overlap of ICD 10 diagnoses of polycythemia vera and secondary erythrocytosis confirms how serious the problems inherent to the WHO MPN diagnostic criteria really are.

These problems have, unfortunately, been compounded by a recent publication entitled, *"JAK2 unmutated erythrocytosis:*

current diagnostic approach and therapeutic views."[24]. This title implies that when confronted with isolated erythrocytosis, a *JAK2* mutation analysis should be performed. Not only has the diagnostic utility of this approach (like the WHO MPN diagnostic criteria) never been validated but it also contradicts the American Hematology Society's clinical agenda of "Choosing Wisely".

In summary, polycythemia vera is a clonal HSC malignancy in which blood oxygenation is normal, plasma volume expansion is the rule, cure requires bone marrow transplantation and in which there is a thrombotic diathesis due an elevated red cell mass that can only be alleviated by adequate phlebotomy therapy to a sex-specific hematocrit; hydroxyurea is not an appropriate option Secondary erythrocytosis is a nonclonal disorder that involves only red cells, which can be congenital or acquired, and when acquired, can be alleviated by correcting the underlying condition causing tissue hypoxia, while thrombotic risk is low and a substantial reduction in the red cell mass is not required.[25] Given all that we know about both conditions, there is no excuse for confusing them clinically in 21st century.

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