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Mimicry of inherited red cell disorders: the result of somatic mutations in a clonal myeloid disease

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Authors' contributions

MAL and ANJ each reviewed the relevant literature and both contributed to the writing of the letter

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The mutations resulting from a clonal myeloid disease, usually a myelodysplastic syndrome, can lead to an abnormality of the red cell membrane, heme or globin synthesis or an enzyme pathway. These events can result in a syndrome that simulates the erythropoietic effects of a germline mutation.[1,2] The result can be a more complex cause of anemia than the disorder of erythropoiesis intrinsic to the chronic myeloid neoplasm itself. These acquired syndromes are shown in Table 1 and include hemoglobinopathies and hemolytic anemias. A superimposed protoporphyria syndrome may result from somatic mutation of the ferrochelatase gene (*FECH*) and another type of porphyria from an unidentified mutation. These effects may require therapy in addition to that used for the neoplasm. Whereas clonal hematopoiesis of indeterminate potential is, usually, a preclinical syndrome without a phenotype, in rare cases, the mutations may result in an acquired clinical disorder of the red cell that simulates a germline mutation, resulting in a phenotype, in this case the simulation of hereditary spherocytosis. (Table 1) The (i) advanced age at presentation of the syndrome or (ii) the absence of any earlier laboratory or clinical evidence of the syndrome or both should heighten suspicion of such a somatic mutation.

This brief note provides a list of the reported phenotypes and the molecular abnormalities that should raise consideration of an acquired red cell disorder. The loci 8p11, 11p15, 14q23, 16p13, 18q21, Xq21 and Xq28 are noteworthy. In a few cases, the implicated genes were identified by next generation sequencing in the absence of cytogenetic clues. The red cell alterations pointing to such a syndrome may be admixed with other red cell changes resulting from the clonal myeloid disease and not appreciated by the physician's focus, understandably, on a life-threatening neoplasm making the diagnosis more difficult. In some cases, the mutations were considered secondary (passenger) mutations, but the high variant allele frequency mimicked that found in the germline-mutation-induced inherited disease.[14]

The hematopathologist and hematological oncologist should consider acquired syndromes described here when alterations of the genes and/or chromosome loci noted in Table 1 occur in association with a chronic myeloid neoplasm or when the red cell morphology has features that are unusual, such as a heightened frequency or dominance of ovalocytes or spherocytes.

A clonal myeloid disease, especially a myelodysplastic syndrome, may also result in a profound disorder of erythropoiesis that leads to "red cell anarchy".[18] The latter is defined by an exaggerated combination of anisocytosis, anisochromia and poikilocytosis. Red cell anisocytosis (elevated red cell distribution width) predicts for a poor prognosis in acute myelogenous leukemia[19] and in myelodysplastic syndrome.[20] Elevated red cell distribution width is also a risk factor for progression of age-related clonal hematopoiesis in otherwise healthy persons to acute myelogenous leukemia.[21]

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Table 1. Somatic Mutations in Chronic Myeloid Neoplasms Leading to Acquired Red Cell Syndromes Simulating Germline Mutations

Red cell Abnormality	Acquired Phenotype	Somatic mutation (gene)	Chromosome location of gene	Patient Cytogenetic Finding	References
Deficient α-Globin Chain Synthesis	α-thalassemia (Hemoglobin H disease)	*ARTX*	Xq21.1		2,3
Deficient α-Globin Chain Synthesis	α-thalassemia (Hemoglobin H disease)	α-globin chain gene complex	16p13.3	del(16p)	4
Deficiency of β-Globin Chain Synthesis	β-thalassemia	β-globin chain gene cluster	11p15.5	Abnormalities of chromosome 11p15.5	5
Abnormal Heme Synthesis	Erythropoietic protoporphyria	*FECH*	18q21.31	Various abnormalities of chromosome 18q	6,7
Abnormal Heme Synthesis	Erythropoietic Uroporphyria	?	?	?	8-10
Membrane Protein Abnormality	Elliptocytosis	?	?	Frequent del(20q)	11
Membrane Protein Abnormality	Spherocytic Hemolytic Anemia	*SPTB* *ANK1*	14q23.3 8p11.21	del(14q23.1–24.2) Not examined	12,13 14
Glycolytic Enzyme	Pyruvate Kinase Deficiency	*PKLR*	1q22	?	15,16
Hexose Monophosphate Shunt Enzyme	Glucose-6-Phosphate Deficiency	*G6PD*	Xq28	?	17

ARTX mutation causes downregulation of the α-thalassemia gene locus

Reference 14 reports the acquired spherocytosis syndrome in a patient with what was designated by the authors as age-related clonal cytopenia (ARCH) and in another patient designated as clonal hematopoiesis of indeterminate potential (CHIP). Thus, these usually subclinical clonal disorders had a phenotype, not characteristically a part of their features.