Diagnosis of myelodysplastic syndromes in individuals heterozygous for mutations in the α- and β-globin genes: a reminder for haematologists

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Dear Sir,

Concomitant myelodysplastic syndromes (MDS) diagnosed in individuals heterozygous for α- or β-globin gene mutations are rarely reported. However, the development of MDS in subjects carrying a globin gene mutation may result in haematological phenotypes with clinical and laboratory features that can create several diagnostic and therapeutic problems. Given the rarity of this combination of disorders, the characteristic features have not been fully elucidated[1]. We, therefore, believe that it could be useful to present our data, based on a review of our recent clinical experience, together with our considerations on this neglected topic.

From our database, we retrieved nine cases of patients with an α or β-thalassaemic trait who were diagnosed as having MDS. These patients were under our care because they had cytopenias other than the life-long microcytic anaemia related to their thalassemia trait or because their known and usual anaemic state had deteriorated without this being explainable by another secondary cause of anaemia. The nine patients had a median age of 80 years (range: 66-89 years) and six were female. Five of the nine patients were under our attention after the discovery of one or two cytopenias, other than microcytic anaemia, during a work-up for the diagnosis of MDS. The remaining four patients were well-known carriers of heterozygous α (n =1) and β (n =3) thalassaemic traits and were referred to our clinic because of worsening anaemia to the point of needing transfusion. After a comprehensive work-up, the subtypes of MDS diagnosed were refractory anaemia (RA) without sideroblasts, refractory cytopenia with multilineage dysplasia (RCMD) and refractory anaemia with excess blasts-1 (RAEB-1) in four, three and two cases, respectively. The percentages of blast cells ranged from 1% to 7%. Standard cytogenetic and fluorescence *in situ* hybridization analyses showed karyotypic abnormalities, such as Y chromosome loss (2 patients), 20q12 deletion (1 patient) and trisomy 8 (1 patient); five patients had no cytogenetically detectable genetic changes. According to the International Prognostic Scoring System[2], seven patients had low-risk MDS, while the other two patients had intermediate-1 disease. In three cases we opted for clinical observation whereas six patients were treated with recombinant human erythropoietin.

Considering the four patients who were referred to us because of progressively worsening anaemia after other secondary causes had been ruled out and the use of standard measures of treatment had failed, three had cytopenias other than anaemia whereas the only haematological abnormality in the remaining case was an important reduction of haemoglobin level. All four patients had hypercellular bone marrow with prominent erythroid hyperplasia, indicating markedly ineffective erythropoiesis probably due to increased apoptosis, together with variable megakaryocytic and granulocytic dysplasia. Three out of these four patients had a cytogenetic abnormality (one each with loss of Y chromosome, the 20q12 deletion and trisomy 8). Three had RA whereas the other had RCMD. All four patients were administered erythropoietin, given that their endogenous erythropoietin concentrations, ranging from 48 to 114 U/L, were inappropriately low for the degree of anaemia. The dose of erythropoietin was titrated according to individual targets determined from the basic α and β thalassemia trait-induced haemoglobin concentrations and the usual red blood cell counts typically recorded in each patient. All treated patients responded to erythropoietin and achieved transfusion independence, although two of these four patients had required transfusions before (1 case) or soon after the initial phase (1 case) of the treatment.

Considering all nine patients, after a median follow-up of 19 months (range, 2-36 months), no disease progression or evolution in acute myeloid leukaemia was observed. In conclusion, α and β thalassaemia traits may be an incidental finding in cytopenic patients developing MDS; on the other hand, worsening anaemia in a subject with α- or β-thalassemia trait can be accompanied by myelodysplastic changes in the bone marrow. Certainly, cytogenetic and molecular studies are crucial to define the diagnosis and all the possible factors implicated in the pathogenesis of these low grade MDS must be investigated. Further epidemiological and clinical studies, especially among populations in whom thalassaemia mutations are relatively common, should clarify the extent of this phenomenon. In addition,

different systems of prognostic stratification should be developed for these patients. In fact, we believe that the currently validated prognostic systems for MDS[2,3] are not fully suitable and applicable to this category of patients, in particular when considering the haemoglobin levels. Indeed, under normal conditions, these patients have remained asymptomatic for many years regardless of their low haemoglobin levels. The current MDS classification systems may overestimate, at least in part, the weight of the haemoglobin values which have been usual in the life course of these individuals and only partially due to the ineffective erythropoiesis induced by the MDS. For patients with α and β-thalassemia traits who develop worsening anaemia until becoming symptomatic, an evolution associated with major dyserythropoietic alterations in the bone marrow, a possible increase in apoptosis should be investigated. Whether these forms of MDS are true cases of MDS or aggravating apoptotic disease in the context of a stressed and hyperproliferative erythropoiesis remains a matter of debate. In this regard, the role of several erythropoietic stress factors, including iron overload, occult inflammation, a relative deficit in erythropoietin concentration and/or the development of intrinsic mechanisms of resistance to the stimulating effects of erythropoietin, are matters of speculation and should be the subject of specifically designed future studies.

The Authors declare no conflicts of interest.

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