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CASE REPORT

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A presumed case of Darbepoetin-induced myocardial infarction in the patient with MDS-RARS

Aneeqa Ahsan Zafar[1] | **Peter Kouides**[2]

[1]Internal Medicine, Rochester General Hospital, Rochester, NY, USA

[2]Lipson Cancer Center, Mary M Gooley Hemophilia Center, Rochester General Hospital, Rochester, NY, USA

Correspondence
Aneeqa Ahsan Zafar, Department of Medicine, Rochester General Hospital, 1425 Portland Avenue, Rochester, NY 14621, USA.
Email: Aneeqa.zafar@rochesterregional.org

Abstract

Our case is only the 2nd such reported case of atherothrombosis from ESAs and highlights the increased risk of cardiovascular events in patients receiving erythropoietin-stimulating agents specially patients with underlying MDS where targeting a lower hemoglobin goal and optimizing other cardiovascular risk factors might be beneficial in preventing future cardiovascular mortality.

KEYWORDS

acute coronary syndrome, anemia with ringed sideroblasts, clonal hematopoiesis of indeterminate potential, erythropoietin-stimulating agents, myelodysplastic syndromes

Acute coronary syndrome secondary to use of erythropoietin-stimulating agent in a patient with myelodysplastic syndrome anemia with ringed sideroblasts with negative CHIP mutations.

A 60-year-old man with a past medical history of MDS—refractory anemia—with ringed sideroblasts (RARS) presented to the ED with substernal chest pain. He was diagnosed 26 years ago and had been managed with amifostine for 6 months as well as chloroquine. He was given a trial of erythropoietin with no appreciable response. Darbepoetin was FDA approved in September 2001, and our patient was restarted on Epogen 40 000 units weekly in September 2003 and was switched to darbepoetin 4 months later and has been on it since then with a baseline Hct of 32%-34% (Hb 11.4-12 g/dL). Iron profile revealed a serum iron of 235 μg/dL (65-175 μg/dL), ferritin 308 ng/mL (22-322 ng/mL), iron sat 89% (15%-55%), and TIBC 264 μg/dL (250-450 μg/dL). Vit B-12 and folate were within normal limits. He had no prior history of arterial or venous thrombosis. Admission laboratories revealed macrocytic anemia with Hb/Hct 12.4 g/dL /37% (13-18 g/dL/40%-52%) and a troponin of 15.65 ng/mL (0.00-0.09 ng/mL) with no EKG changes. Patient was started on aspirin, statin, beta blocker, and heparin for acute coronary syndrome. He underwent coronary angiography which showed normal coronaries except for a mild LAD territory distal wall motion abnormality identified on ventriculogram. Transthoracic echocardiography postangiography did not suggest any wall motion abnormality, and the LV function was within normal limits. Ultimately, a cardiac MRI confirmed hypokinesis of a focal area of the apical lateral segment as well as abnormal transmural delayed enhancement consistent with prior myocardial infarction of the apical lateral segment consistent with in situ thrombosis. It was noted that his Hb had been above 12.0 g/dL on three different occasions (12.1, 12.1, and 12.4 g/dL, respectively) within a month of his presentation to the Emergency Department (Figure 1). Typically, ESA is held for Hb ≥ 12 g/dL and/or Hct ≥ 36% but our patient was on home injections and had not followed this guideline strictly in the past year. Based on recent data suggesting MDS patients carrying certain mutations which confer a higher risk of cardiovascular disease, he underwent next-generation sequencing testing which was negative for TET-2, DNMT3A, JAK-2, and AXSL2. Post-MI, he agreed to lengthen out darbepoetin therapy to every month to target Hb of 10 g/dL. Ideally, he can be switched

to luspatercept, once it is FDA approved, since has shown to reduce transfusion dependence in RARS-MDS patients.[1]

Refractory anemia with ringed sideroblasts is a clonal hematopoietic neoplasm which falls under the category of low-grade MDS.[2] These patients typically have single lineage dysplasia with anemia which is managed with regular infusions of erythropoietin-stimulating agents to maintain a target Hb level to prevent symptoms and avoid transfusion dependency. Previous meta-analysis has shown an increased risk of all-cause mortality, hypertension, and arteriovenous thrombosis in ESA patients with a higher Hb target of 12-15 g/dL vs a lower target of 9.5-11.5 g/dL.[3] Our patient had been receiving once weekly darbepoetin infusions without complications as far back as 1993 and had maintained his Hb/Hct < 12 g/dL except for three occasions within a month of his presentation where his Hb was slightly above threshold. Other than his age and gender, our patient did not have any of the typical cardiovascular risk factors.

Earlier studies have highlighted the effect of erythropoietin (EPO) on thrombopoiesis including a transient rise in platelet count as well as enhanced endothelial activation and platelet reactivity as demonstrated by increased levels of circulating P- and E-selectins in the blood of patients receiving EPO infusions.[3] These molecular markers have also been described as predictors for atherosclerosis and severity of coronary heart disease and their presence in erythropoietin-dependent patients highlights the role of increase platelet activation in promoting thrombogenesis. Given the normal coronaries and identification of a small area of hypokinesis in the apical area, we postulate that his myocardial infarction was the result of hyperviscosity induced by the relative polycythemia and increased platelet activation and reactivity from regular darbepoetin infusions leading to acute intracoronary thrombosis which then spontaneously improved and resolved with endogenous fibrinolysis and consequent dual agent anti-platelet therapy.

Patients receiving ESA agents are at increased risk of iron overload and our patient's iron stores were above normal limits at the time of presentation; however, the association of iron overload with cardiovascular mortality remains controversial and much debated. Moreover, iron overload cardiomyopathy is associated with biventricular dilation with restrictive physiology and evidence of iron deposition in the myocardium on MRI, neither of which were present in our patient.[4]

MDS confers an independent risk of myocardial infarction in otherwise healthy patients without a history of prior cardiovascular comorbidities.[5] In fact, after 5 years, patients with lower risk MDS have an equal or higher risk of dying from cardiovascular causes than dying from MDS-related events.[5,6] The increased risk comes from recurrent mutations targeting genes regulating DNA methylation, transcription regulation, RNA spliceosome machinery, signal transduction, and post-translational chromatin modification which can be found in 10%-30% of MDS patients as well as in patients with clonal hematopoiesis of indeterminate potential (CHIP) in the absence of a confirmed myeloid disorder.[6] Pathogenesis is unclear but may involve augmented expression of inflammatory cytokines leading to increased atherogenesis.

Our patient tested negative for TET2, DNMT3A, ASXL2, and JAK-2 which are the most common mutations identified in these patients and confer the highest risk of atherosclerotic adverse events.[6] Not surprisingly, in light of the pre-existing diagnosis of RARS, a missense somatic mutation of SF3B1 was identified in our patient, which is among the 15 most commonly mutated genes seen in myeloid disorders and clonal hematopoiesis of indeterminate significance and is particularly prevalent (>80%) in patients MDS with ringed sideroblasts.[7]

Our patient presented with an acute coronary syndrome on the background of no cardiovascular risk factors except a history of low-grade MDS requiring regular darbepoetin infusions. Other than his age of 60 years and his male gender, our patient did not have any other known risk factors for coronary artery disease. Our patient has a normal BMI and nonsmoker with no premature family history of coronary artery disease. He does not have any other comorbidities including hypertension or diabetes that may increase his cardiac risk.

We believe that his MI was the result of relative hyperviscosity induced by a slightly higher than target hemoglobin and hematocrit as well as increased platelet activation and reactivity while his underlying long-standing MDS may have contributed toward his overall risk. Of course, he was not substantially above target and does not carry the MDS mutations with the highest risk of atherosclerotic

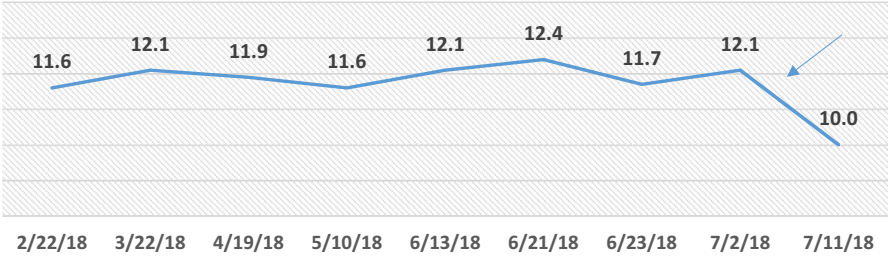

FIGURE 1 Graph showing trend of hemoglobin preceding hospital admission. Note that hemoglobin was above 12 g/dL on three occasions a month prior to admission (arrow pointing to the time of admission)

heart disease. Our case highlights the increased risk of cardiovascular events in patients receiving erythropoietin-stimulating agents specially patients with underlying MDS where targeting a lower hemoglobin goal and optimizing other cardiovascular risk factors might be beneficial in preventing future cardiovascular mortality. Above all, our case questions whether these patients should have a lower hemoglobin cutoff in holding an ESA than currently recommended.

1 | CONCLUSION

The association of darbepoetin as the incriminating agent for this patient's presentation is a relatively weak one, but this conclusion was reached after eliminating all other contributing risk factors such as history of obesity, smoking, hypertension, diabetes, and family history. We also ruled out any possible contribution from specific clonal hematopoietic mutations which, if present, would have increased his cardiac risk as well. In the absence of other risk factors, we conclude that presumably a higher than baseline, darbepoetin was the likely culprit and cause of this patient's presentation.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

AZ: involved in writing the manuscript and subsequent revisions. PK: involved in writing and revision of the manuscript.

ORCID

Aneeqa Ahsan Zafar https://orcid.org/0000-0002-6009-3945

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