Anemia of Inflammation
A Review

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KEYWORDS

• Anemia • Inflammation • Hepcidin • Ferroportin • Interleukin-6 • Erythroferrone • Iron • Cancer

KEY POINTS

- In anemia of inflammation, proinflammatory cytokines suppress erythropoiesis, cause iron sequestration via effects on the iron regulatory hormone, hepcidin, and promote alteration in the erythrocyte cell membrane leading to shortened red blood cell survival.
- In the setting of critical illness, severe anemia is associated with increased mortality.
- Advanced age, cancer, rheumatologic diseases, chronic infection, and kidney failure are also associated with anemia of inflammation.
- Experimental therapies reverse the effects of anemia of inflammation in animal models, but have not been approved for human use.

EPIDEMIOLOGY

Inflammation is one of the most common causes of anemia in the elderly and chronically ill. In the National Health and Nutrition Examination Study (NHANES III), anemia of inflammation was defined as a low serum iron level (<10.74 μM or <60 μg/dL) without evidence of low iron stores, that is, transferrin saturation greater than 15%, serum ferritin greater than 12 ng/mL, or erythrocyte protoporphyrin concentration greater than 1.24 μM.[1] Other features of anemia of inflammation include inappropriately low levels of erythropoietin, and elevated measures of inflammatory markers, such as C-reactive protein.[2] In the NHANES III, investigators discovered that about 1 million Americans greater than the age of 65 exhibit anemia related to inflammation.

Anemia in Critical Illness

Anemia of inflammation can occur in the setting of acute or chronic inflammation. The CRIT study of anemia and blood transfusion in the critically ill was an observational

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cohort analysis of 4892 patients in intensive care units across the United States.[3] The CRIT study revealed that anemia of inflammation develops in critically ill patients even within 30 days. The mean hemoglobin levels in critically ill individuals decreased over a 30-day period despite the administration of blood transfusions. The CRIT study also demonstrated that severe anemia, hemoglobin less than 9 g/dL, is an independent predictor of increased mortality and length of stay in critically ill patients.

Anemia in the elderly is frequently linked to inflammatory conditions. In a recent study of 191 consecutive hospitalized elderly patients with anemia, 70% of the patients were found to have anemia related to inflammation. Sixteen percent of the patients with anemia of inflammation had concomitant chronic renal failure.[4] Of the patients with inflammatory anemia, 71% were suffering from an acute infection, 12% had cancer, and 16% had a chronic infection, such as a pressure ulcer, or a chronic autoimmune inflammatory disease.[4]

Anemia in Obesity

As the prevalence of obesity is increasing in the United States, more attention is being paid to the potential effect of obesity on erythropoiesis. Obese patients exhibit higher plasma levels of proinflammatory cytokines and acute phase reactants as well as higher rates of iron-restricted erythropoiesis that can result in anemia.[5] Functional iron deficiency is defined as inappropriately low iron stores, despite the presence of inflammation, that is, a normal serum ferritin (12–100 ng/mL for women or 15–100 ng/mL for men) and a serum C-reactive protein greater than 3 mg/L.[6,7] A recent cross-sectional study of 947 obese patients under evaluation for bariatric surgery revealed that 52.5% exhibited functional iron deficiency. Most obese patients with functional iron deficiency appear to have sequestration of iron as manifest by a serum transferrin saturation less than 20%.[6] Weight loss has been associated with an increase in transferrin saturation in overweight individuals,[8] which supports the hypothesis that obesity causes iron sequestration.

Anemia in Cancer

Anemia of inflammation is a common manifestation of advanced cancer. A recent prospective, observational study of 888 patients with a variety of carcinomas revealed that 63.4% of the patients were anemic.[9] The prevalence and severity of anemia correlated with the stage of cancer.[9] The prevalence of increased mean plasma levels of markers of inflammation, including C-reactive protein, fibrinogen, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), IL-1β, ferritin, hepcidin, erythropoietin, and reactive oxygen species, was significantly increased in advanced stage compared with patients with early stage cancer. Supporting a role for inflammation in iron sequestration, serum iron levels were significantly reduced in advanced stage patients.[9]

PATHOPHYSIOLOGY

Recent discoveries indicate that both iron sequestration and impaired erythropoiesis cause anemia of inflammation. Erythroid progenitors mature to erythrocytes through a series of stages that require coordination of iron acquisition and cell proliferation. As erythroid progenitors mature to the polychromatophilic stage, transferrin receptor 1 expression on the surface of the red cell membrane increases.[10] Macrophages export iron via ferroportin (fpn). The carrier protein, transferrin, binds free iron with high avidity. Transferrin-bound iron attaches to transferrin receptor 1. In an acidified vacuole, the iron is released from transferrin and exported to the cytoplasm by divalent metal transporter 1, whereas transferrin receptor is recycled to the cell surface (reviewed