Anemia of Inflammation

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KEYWORDS

- Anemia of chronic disease • Hepcidin • Ferroportin • Cytokines
- Erythropoiesis-stimulating agents

KEY POINTS

- Anemia of inflammation results from hepcidin-induced hypoferremia combined with cytokine-mediated suppression of erythropoiesis and decreased lifespan of erythrocytes.
- Treatment of the cause of inflammation improves the anemia.
- Treatment with erythropoiesis-stimulating agents and/or intravenous iron is rarely necessary.

CLINICAL PRESENTATION

- Mild to moderate anemia (hemoglobin rarely <8 g/dL)
- Occurring in a setting of infection, inflammatory disease, or malignancy
- Low serum iron
- Systemic iron stores not depleted

Definitions

Anemia of inflammation (AI, formerly also called anemia of chronic disease or anemia of chronic disorders) is usually a mild to moderately severe anemia (hemoglobin rarely lower than 8 g/dL) that develops in the setting of infection, inflammatory disease, or malignancy.[1] The defining biochemical features of AI include low serum iron despite adequate systemic iron stores. The concentration of serum transferrin is also decreased during chronic inflammation but this is a lagging indicator because of the long half-life of transferrin (about 8 days) compared with iron (about 1.5 hours).[2] The erythrocytes are usually of normal size and have normal hemoglobin content but are reduced in number (normocytic, normochromic anemia). In some cases, particularly if the inflammatory disease is longstanding, the red cells are mildly decreased in size and hemoglobin content.

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Related Conditions

Anemia of critical illness presents with a similar pattern of findings but develops within days in patients who are hospitalized in intensive care units with infections, sepsis, or other inflammatory conditions.[3] Anemia of critical illness may be exacerbated by frequent diagnostic phlebotomies or increased gastrointestinal blood loss as is common in such settings. Anemia of aging[4] is a chronic anemia similar to AI but often occurring in the elderly without a specific diagnosis of a predisposing underlying disease. The prevalence of this anemia increases with age, and detailed studies often detect evidence of inflammation, including increased serum C-reactive protein or other biomarkers of inflammation. Anemia of chronic kidney disease is commonly attributed to erythropoietin deficiency but accumulating evidence favors a more complex pathogenesis with a large component of AI whose exacerbations may be manifested as "erythropoietin resistance".[5]

Diagnosis

The traditional gold standard for the diagnosis of AI was anemia with hypoferremia or with low transferrin saturation, despite the presence of Prussian blue stainable iron in bone marrow macrophages. The main confounding diagnostic entity that also presents with anemia and hypoferremia is iron deficiency anemia where there is no stainable iron in the marrow macrophages. This gold standard has been challenged not only because of the invasive nature of the marrow sampling procedure but also because of findings that bone marrow iron readings are qualitative and not always consistent between evaluators and in multiple specimens[6,7] and that iron therapy may cause marrow iron deposition in a poorly bioavailable form, which cannot be used by iron-deficient patients.[8] The marrow iron stain has largely been replaced by serum ferritin determinations. Low serum ferritin (less than 15 ng/mL for general population, with some laboratories using age and gender-specific norms) is highly specific for iron deficiency[9] (genetic deficiency of L-ferritin is an extremely rare exception[10]) and effectively rules out AI. AI is diagnosed when anemia and hypoferremia are accompanied by serum ferritin that is not low. Serum ferritin is increased by inflammation, in part reflecting direct inflammatory regulation of ferroportin synthesis[11,12] and in part because serum ferritin originates in macrophages where its synthesis is increased by iron sequestration[13] that takes place during inflammation. Iron deficiency is presumed to coexist with AI when ferritin is insufficiently elevated for the intensity of inflammation. Serum ferritin is also increased by tissue injury, especially to the liver.

Diagnostic Challenges

The determination of what constitutes "inappropriately low" ferritin may be difficult in practice because even patients with very high serum ferritin levels may respond to intravenous iron therapy by increasing hemoglobin.[14] In principle, the limitations of serum ferritin could be circumvented by assaying additional markers of iron deficiency less affected by inflammation, most prominently soluble transferrin receptor.[15–17] However, the relevant assays have not been standardized, the added value of such studies has not yet been convincingly demonstrated,[18] and none have been widely adopted. When the anemia is clinically significant and a component of iron deficiency is suspected in a patient with AI, it may be reasonable to perform a therapeutic trial of intravenous iron. Current intravenous iron preparations are quite safe, but the very rare reactions to their administration and the possibility of exacerbating an existing or occult infectious process should be included in the risk-benefit analysis.[19]