Anemia of Chronic Disease
Making the Right Call

Benjamin H. Chen, MD, CM, CCFP, FRCPC; and Sonal Gandhi, Hon. BSc

Physicians frequently see patients with anemia, an increasingly prevalent problem as the population ages. The prevalence of anemia among men over 85 has been reported to be 44.4%.

Of the numerous causes, anemia of chronic disease (ACD) is the most common cause of anemia in the elderly and the second most common cause of anemia worldwide (after iron-deficiency anemia [IDA]).

Making the diagnosis of ACD

The diagnosis of ACD begins with a clinical suspicion of anemia, whether due to the patient’s risk factors and/or the patient’s symptoms or signs. The presence and severity of any symptom or sign depends on several factors, including:

- the degree of anemia,
- the speed with which the anemia developed,
- the existence of co-morbid diseases, and
- the physician’s clinical skills.

On this last point, it is interesting to note that a Toronto-based study concluded the presence of conjunctival pallor upon physical examination is highly predictive of a hemoglobin < 110 g/L. Of course, the absence of conjunctival pallor does not exclude significant anemia, especially if there is clinical suspicion based on risk factors, symptoms, or other signs.

While ACD typically presents as a normocytic...
anemia on blood testing, with a normal mean corpuscular volume (MCV) of 80 fL to 100 fL, it can also present as a microcytic anemia (MCV < 80 fL). The bone marrow’s response to ACD is inadequate, so the reticulocyte production index (RPI) is usually well below two (Figure 1). The serum iron is low, and so are the total iron binding capacity and transferrin saturation, but the ferritin level is usually high.

Mary’s Tests

Blood tests confirm that Mary has anemia with a hemoglobin of 105 g/L, mean corpuscular volume of 82 fL, and reticulocyte production index of 0.9. Additional results include: ferritin of 120 ug/L, creatinine of 90 umol/L, and thyroid stimulating hormone of 3.5 mU/L.

Differential diagnoses

Other potential causes of normocytic anemias with a RPI < 2, include:

- nutritional deficiencies,
- renal failure,
- endocrine dysfunction,
- drugs and toxins,
- infections,
- multiple myeloma and other infiltrative diseases, and
- nutritional deficiencies (Table 1).

Iron-deficiency anemia is the main differential diagnosis, as microcytosis may be present or absent in either disorder. Table 2 summarizes key laboratory differences between these two most common causes of anemia.

Serum ferritin is the most useful test; a level < 15 ug/L confirms the diagnosis of IDA, whereas a level > 100 ug/L practically rules out IDA. Serum ferritin levels between 15 ug/L and 100 ug/L are more difficult to interpret, since ferritin can also act as an acute-phase reactant and, thus, be spuriously elevated with infection or inflammation.
Survey Says

Mary’s physician clinically diagnosed her with anemia on the basis of conjunctival pallor. It is a normocytic anemia with a low-normal MCV and an inadequate reticulocyte response. Her medications place her at risk for upper GI bleeding, however the ferritin level rules out an iron-deficiency anemia.

Causes of ACD

The pathophysiology of ACD is not fully understood, but inflammation appears to play a key role. While chronic inflammatory conditions have been traditionally linked to ACD, it now appears diabetes mellitus, congestive heart disease, and “acute” illnesses can also cause ACD (Table 3).

Treatment

Treatment of ACD focuses on the management of underlying causes. Although there is no specific treatment for ACD, one exception is erythropoietin, which has been given to some patients with cancer or HIV with plasma erythropoietin levels < 500 IU/mL; the results are promising. If a concomitant iron deficiency is suspected due to an intermediate ferritin level, a therapeutic trial of iron supplementation may help delineate between ACD and IDA.

Where To Go From Here

As for other differential diagnoses, Mary’s renal function is good, and she is not hypothyroid. Therefore, she probably has an anemia of chronic disease, so she should be assessed for the possibility of an underlying infectious, inflammatory, or neoplastic disease (note her smoking history). If no such disease is found, then she might have ACD secondary to her diabetes.

Take-home message

- Anemia can be diagnosed at the bedside by inspecting for conjunctival pallor.
- The many causes of anemia can be classified based on the erythrocyte morphology (MCV) and on the marrow’s response (RPI).
- Serum ferritin is useful in distinguishing ACD from IDA.
- Apart from the traditional infectious, inflammatory, or neoplastic etiologies, ACD is also associated with diabetes mellitus and certain acute illnesses.
- As in patients with renal failure, erythropoietin might be useful in certain patients with ACD, cancer, HIV, and a low plasma erythropoietin level.

Table 3

Conditions associated with ACD

- Infections
- Inflammatory (e.g., rheumatoid arthritis, vasculitis)
- Malignancies
- Others (e.g., diabetes, congestive heart disease)
- Acute variant (e.g., surgery, major trauma, myocardial infarction, sepsis)

References