Anaemia of chronic disease

Anaemia of chronic diseases is a common condition.

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Anaemia of chronic disease (ACD) is a multifactorial anaemia often coexistent with iron deficiency. Worldwide, anaemia of chronic disease is the second most common anaemia. Diagnosis generally requires the presence of chronic infection, inflammation, or cancer; marginal normocytic and later microcytic anaemia; and abnormal values for iron studies. The major issue is that the bone marrow erythroid mass fails to expand appropriately in response to anaemia. Treatment is to reverse the underlying disease and, if the disease is irreversible, to give erythropoietin.

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Definition

ACD is a mild-to-moderate anaemia associated with chronic infections, chronic non-infectious inflammatory diseases, and malignancies (Table I). The anaemia develops after a month or two of active disease. Its severity is related to that of the underlying disorder, but it may also be asymptomatic or a coincidental finding. This type of anaemia is usually normocytic-normochromic (Fig. 1), but it may also be normocytic-hypochromic or microcytic-hypochromic when it is associated with concomitant iron deficiency.

Table I. Underlying cause of anaemia of chronic disease[1]

Associated diseases	Prevalence
Infections (acute and chronic)	20 - 95%
Viral, including HIV	
Bacterial	
Parasitic	
Fungal (usually deep seated)	
Cancer	30 - 77%
Haematological and solid tumours	
Autoimmune	10 - 70%
Rheumatoid arthritis	
SLE	
Vasculitis	
Sarcoid	
Inflammatory bowel disease	
Solid organ transplant rejection	10 - 70%
Chronic kidney disease	25 - 50%

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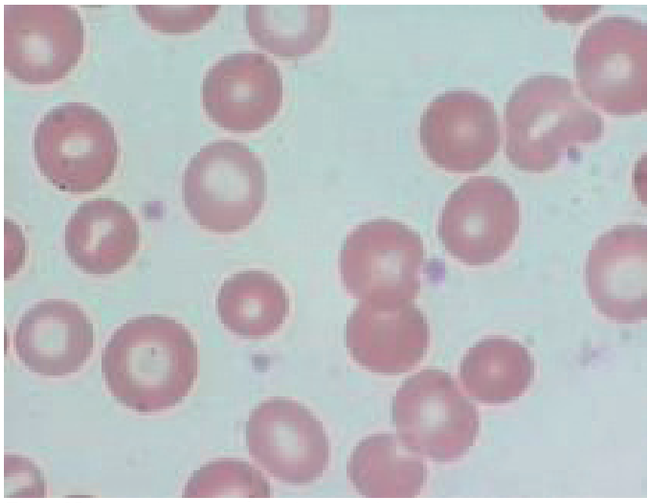

Fig. 1. Normocytic-normochromic anaemia.

Pathophysiology

ACD is immune driven where inflammatory cytokines and cells of the reticuloendothelial system (RES) induce changes in iron homeostasis, the proliferation of erythroid progenitor cells, the production of erythropoietin (EPO), and the life span of the red cell.[2]

Iron homeostasis

In the setting of inflammation and/or infection there is an increase in uptake and retention of iron within cells of the RES; this results in a diversion of iron from the circulation into storage sites of the RES. Hepcidin, an iron-regulated acute-phase protein, is induced by pro-inflammatory cytokines (TNF-α, IL-6, and lipopolysaccharide). This protein decreases intestinal iron absorption and blocks iron release from macrophages seen in ACD.[3] Iron is thus not available for the production of new erythrocytes in the marrow, with subsequent iron-restricted erythropoiesis.

Impaired proliferation of erythrocyte precursors

Cytokines of inflammation (interferon-α, β and TNF-α) inhibit the proliferation and differentiation of erythroid burst-forming units and erythroid colony-forming units which are the precursors to mature red blood cells.[4] Such inhibition is reflected by reduced haemoglobin concentrations and low reticulocyte counts.

Overall EPO production is also reduced in ACD and the provision of exogenous recombinant EPO may improve erythrocyte proliferation.

Blunted erythropoietin response

Central erythrocyte proliferation is regulated to a large extent by EPO, which is produced mainly in the kidney. The expression of EPO is inversely related to tissue oxygenation and haemoglobin levels and in ACD the EPO response to the anaemia is inadequate for the degree of anaemia.[5] Overall EPO production is also reduced in ACD and the provision of exogenous recombinant EPO may improve erythrocyte proliferation.

Laboratory evaluation

The anaemia associated with chronic disease is typically normocytic and normochromic and mild to moderate (Hb 9.5 - 8 g/dl). As mentioned, the reticulocyte is also typically low, suggesting a blunted production of red blood cells. Assessment of total body iron status is also in the setting of ACD as iron deficiency (IDA) is a common accompaniment of ACD (Table II). In both conditions serum iron and transferrin saturation (TSAT) are low, suggesting absolute iron deficiency in IDA and unusable iron on the RES in ACD. Furthermore, the low TSAT in ACD is a reflection of the decreased levels of serum iron.

An active search for the cause of any iron deficiency should be entertained when reflected on the serum results.

Why treat the anaemia of chronic disease?

Chronic anaemia can add to the co-morbidity of a chronic disease and certainly induces a compensatory increase in cardiac output to maintain systemic oxygen delivery. Elderly patients and those with concomitant end-organ pathology (ischaemic heart disease or heart failure, pulmonary disease or renal failure) require aggressive correction of the anaemia in its own right. Furthermore, anaemia imparts a poorer outcome in patients with the aforementioned conditions added to by the chronic disease that is causing the anaemia. In patients with malignant conditions and those with chronic kidney disease correction of anaemia to a level of 11 - 12 g/dl seems most appropriate.

Treatment strategies

Logic would dictate that aggressive treatment of the underlying condition should improve the anaemia of chronic disease, and this is especially so in inflammatory conditions such as rheumatoid arthritis.[6] In those patients with HIV infection and ACD treatment with highly active antiretroviral therapy may have a positive impact on reducing the prevalence of such anaemia. In the setting of HIV infection anaemia has been shown to be a predictor of decreased survival, and treatment plays an important role in improving patients' survival and quality of life (e.g. fatigue and dementia). Erythropoietin therapy has been considered a first-line treatment, and blood transfusions should be limited to situations requiring immediate correction of haemoglobin levels.[7] Other therapeutic options should be entertained in those conditions were treatment of the underlying disease is not possible (Table III).

Blood transfusion

Use of blood transfusion should be reserved for those patients who have severe symptoms relating to ACD, including symptoms of heart failure, extreme lethargy or in those with active haemorrhage.[8]

The inherent risks of transfusion including immune reactions, infections, immunosuppression and sensitisation to HLA antigens preclude its everyday use. Furthermore, the cost of transfusion is also not insignificant.

Iron therapy

Patients with ACD and absolute iron deficiency should receive supplemental iron therapy. Oral iron supplements with high oral bioavailability such as iron polymaltose should be used while monitoring haemoglobin response. However, in those patients with ferritin levels of >300 ng/ml iron supplementation is not recommended as supplementation in this setting may increase the risk of developing bacteraemia and, in the setting of long-term immune activation, may increase hydroxyl radical production with an increase in cardiovascular events.

Erythropoietic agents (EPO)

Conditions such as myeloma,[9] rheumatoid arthritis, inflammatory bowel disease[10] and chronic kidney disease respond well to the use of EPO given subcutaneously, where the therapy counteracts antiproliferative cytokines, stimulation of iron uptake, and stimulation of erythrocyte precursors. In South Africa two agents are available, namely erythropoietin α and β. These agents should be prescribed by practitioners versed in their usage, while strictly monitoring the clinical and haemoglobin response.[11] Side-effects such as hypertension and seizures are uncommon but vigilant supervision is required.

It is imperative to rule out iron deficiency prior to using these agents, remembering too that once erythropoiesis increases the patient may require more iron to maintain normal red blood cell production. A haemoglobin level of 11 - 12 g/dl is ideal and a course of 6 - 8 weeks should ensure such a response. Failure to achieve these levels suggests resistance or non-responsiveness and the agents should be stopped.[12]

Conclusions

The anaemia of chronic disease remains prevalent and equally difficult to treat. As the pathophysiological mechanisms

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Table II. Serum levels that differentiate ACD from iron deficiency[1]

Investigation	ACD	Iron deficiency	Both
Iron	↓	↓	↓
Transferrin	↓/n	↑	↓
Transferrin saturation	↓	↓	↓
Ferritin	n/↑	↓	↓/n
Cytokine levels (not routinely tested)	↑	n	n

Table III. Treatment options for ACD[1]

Treatment	ACD	ACD + true iron deficiency
Treat underlying disease	Yes	Yes
Transfusions	Yes (short-term)	Yes
Iron supplementation	No	Yes
EPO agents	Yes	Yes (if no response to iron)

behind the condition are further elucidated new treatment strategies will emerge. At this stage aggressive management of the underlying chronic condition, together with judicious iron supplementation and possibly EPO therapy, remain the most appropriate therapies.

References

1. Weiss G, Goodnough LT. Anaemia of chronic disease. *N Engl J Med* 352; 10: 1011-1022.
2. Thomas C, Thomas L. Anaemia of chronic disease: pathophysiology and laboratory diagnosis. *Lab Hematol* 2005; 11(1): 14-23.
3. De Domenico I, Ward DM, Kaplan J. Hepcidin regulation: ironing out the details. *J Clin Invest* 2007; 117(7): 1755-1758.
4. Means RT. Recent developments in the anaemia of chronic disease. *Curr Hematol Rep* 2003; 2(2): 116-121.
5. Jelkmann W. Erythropoietin after a century of research: younger than ever. *Eur J Haematol* 2007; 78(3): 183-205.
6. Young A, Koduri G. Extra-articular manifestations and complications of rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2007; 21(5): 907-927.
7. Brokering KL, Qaqish RB. Management of anaemia of chronic disease in patients with the human immunodeficiency virus. *Pharmacotherapy* 2003; 23(11): 1475-1485.
8. Goodnough LT, Shander A. Evolution in alternatives to blood transfusion. *Hematol J* 2003; 4(2): 87-91.
9. Cornes P, Coiffier B, Zambrowski JJ. Erythropoietic therapy for the treatment of anaemia in patients with cancer: a valuable clinical and economic option. *Curr Med Res Opin* 2007; 23(2): 357-368.
10. Tsiolakidou G, Koutroubakis IE. Stimulating erythropoiesis in inflammatory bowel disease associated anaemia. *World J Gastroenterol* 2007; 13(36): 4798-4806.
11. Bihl GR. Recombinant human erythropoietin in end-stage renal disease. *S Afr Med J* 2002; 92(8): 565.
12. Macdougall IC, Cooper AC. Hyporesponsiveness to erythropoietic therapy due to chronic inflammation. *Eur J Clin Invest* 2005; 35 Suppl 3: 32-35.

In a nutshell

- Anaemia of chronic disease is a multifactorial anaemia often coexistent with iron deficiency.
- Diagnosis generally requires the presence of chronic infection, inflammation, or cancer; marginal normocytic and later microcytic anaemia; and abnormal values for iron studies.
- Treatment is to reverse the underlying disease and, if the disease is irreversible, to give erythropoietin.
- It is a mild-to-moderate anaemia associated with chronic infections, chronic non-infectious inflammatory diseases, and malignancies.
- This type of anaemia is usually normocytic-normochromic; but it may also be normocytic-hypochromic or microcytic-hypochromic when it is associated with concomitant iron deficiency.
- The anaemia associated with chronic disease is typically normocytic and normochromic and mild to moderate (Hb 9.5 - 8 g/dl).
- Elderly patients and those with concomitant end-organ pathology (ischaemic heart disease or heart failure, pulmonary disease or renal failure) require aggressive correction of the anaemia in its own right.
- At this stage aggressive management of the underlying chronic condition, together with judicious iron supplementation and possibly EPO therapy, remain the most appropriate therapies.