The blood in systemic disease

Barbara Bain

Abstract

Systemic disease has protean manifestations. Most frequently observed is anaemia of chronic disease, anaemia can also be autoimmune, microangiopathic, mechanical or caused by haematinic deficiency, bone marrow replacement or pure red cell aplasia. The platelet count can be increased or decreased. The number of neutrophils, eosinophils, monocytes and lymphocytes can be increased, but neutropenia, eosinopenia and lymphopenia can also occur. Leucocytes can appear activated. Systemic disease can lead to thromboembolism, haemorrhage or disseminated intravascular coagulation. Lymphoma can occur as a result of viral infection, immune deficiency or the treatment of systemic disease.

Keywords Anaemia of chronic disease; autoimmune disease; cancer; eosinophilia; haematinic deficiency; haemolysis; heart failure; infection; liver disease; renal disease

Key points

- Anaemia of chronic disease can result from infection, inflammation or cancer
- Haematinic deficiency can result from a systemic disease or its treatment
- Hepatic and renal diseases are often lead to haematological abnormalities of diverse types
- Eosinophilia is more often a feature of a systemic disease than of a haematological disorder

Introduction

Non-haematological diseases can have prominent haematological manifestations affecting all lineages. Haematological features can be cytokine-mediated in chronic infection, inflammation or malignancy, or can result from haematinic deficiency or bone marrow or splenic infiltration. In addition, in the case of autoimmune disorders, the blood and bone marrow can be one target of more generalized disease.

Anaemia of chronic disease

The anaemia of chronic disease, sometimes called the anaemia of inflammation, is a common feature of infection, inflammation and malignant disease.[1] It is mediated by cytokines, particularly interleukin (IL) 6. There is resultant increased hepatocyte synthesis of hepcidin, which binds and internalizes ferroportin in macrophages and enterocytes, leading to its ubiquitination and degradation; iron export from enterocytes and macrophages is thus reduced (Figure 1). The plasma iron concentration falls, and there is reduced availability of iron for haemoglobin synthesis. There is a concomitant blunted erythropoietin response, mediated by IL-1 and tumour necrosis factor-α (TNF-α). There is some degree of dyserythropoiesis, ineffectiveness of erythropoiesis and shortening of red cell lifespan.

The term 'dyserythropoiesis' indicates cytologically abnormal or dysplastic erythropoiesis, while 'ineffective erythropoiesis' indicates that the production of mature cells is less than expected for the cellularity as a result of increased intramedullary death of precursors; the two often occur together. It has been postulated that anaemia of chronic disease is a defence mechanism in infection as bacteria can be deprived of iron.

The anaemia that occurs is initially normocytic and normochromic, but when the condition is more severe it becomes microcytic and hypochromic. The low serum iron is associated with a reduced transferrin concentration and saturation. This is in contrast to iron deficiency anaemia, when transferrin concentration is increased. Serum ferritin is high in the normal range or increased, this being mediated by IL-1, IL-6, IL-10 and TNF-α. Concomitant features often include an increased erythrocyte sedimentation rate and increased rouleaux formation. When anaemia of chronic disease and iron deficiency coexist, the situation is more complex; transferrin may be neither reduced nor increased, and ferritin tends to be in the low-normal range.

Treatment is ideally directed at the underlying disease. When this is not sufficiently effective, recombinant erythropoietin with supplementary oral or intravenous iron can be of benefit. Tocilizumab, an antibody to the IL-6 receptor, can improve the haemoglobin concentration.

Haematinic deficiency

Haematinic deficiencies can be the direct result of a disease process or be attributable to the treatment of a systemic disease.

Iron deficiency anaemia can result from malabsorption (atrophic gastritis, gastric atrophy, *Helicobacter pylori* infection, pancreatic insufficiency, coeliac disease), blood loss (use of corticosteroids or non-steroidal anti-inflammatory drugs, ulcerative colitis, Crohn's disease, diverticulitis), chronic urinary loss of iron (mechanical haemolytic anaemia caused by a defective prosthetic valve) or sequestration of iron in pulmonary macrophages (idiopathic pulmonary haemosiderosis).

Folic acid deficiency can result from malabsorption (coeliac disease, tropical sprue) or increased need (extensive skin disease).

Vitamin B_{12} deficiency can result from malabsorption (occasionally coeliac disease but typically total gastrectomy or, in pernicious anaemia, autoimmune gastric atrophy; also *H. pylori* infection). Rarely, vitamin B_{12} deficiency results from Crohn's disease, but more often it is a feature of treatment of this condition by resection of the terminal ileum. Vitamin B_{12} deficiency can result from tropical sprue.

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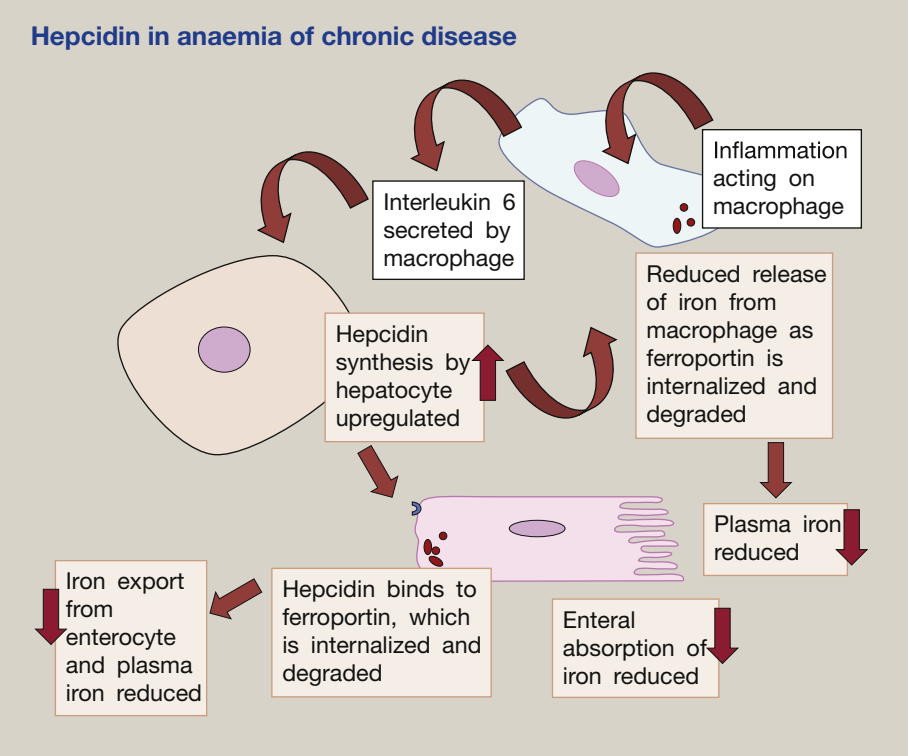

Figure 1 Role of hepcidin and disturbed iron metabolism in anaemia of chronic disease. Reproduced with permission from Bain BJ, Interactive haematology image bank, 2nd edn (DVD). Oxford: Wiley-Blackwell, 2014.

Bariatric surgery can cause haematinic deficiency if suitable supplementation is not given. In particular, it can cause iron deficiency and also copper deficiency, the latter leading to anaemia, neutropenia and vacuolation of haemopoietic cells in the bone marrow.

Autoimmune disease

Systemic lupus erythematosus serves as an archetypal autoimmune disease that often affects the blood and bone marrow. Possible haematological features are shown in Table 1.

Autoimmune diseases can have specific haematological associations. Rheumatoid arthritis can be associated with Felty's syndrome – splenomegaly and autoimmune neutropenia – which is often the result of an associated large granular lymphocyte leukaemia.

Thymoma can also be associated with autoimmune haematological complications, specifically pure red cell aplasia, pure white cell aplasia, amegakaryocytic thrombocytopenia and aplastic anaemia.

Cancer

Carcinoma and other cancers can be associated with anaemia of chronic disease, iron deficiency anaemia resulting from blood loss, microangiopathic haemolytic anaemia and disseminated intravascular coagulation. Reactive changes can include neutrophilia, monocytosis and thrombocytosis. There is an increased incidence of venous thromboembolism, this being the most common cause of death after the cancer itself. The rate of arterial thrombosis is also increased.

When the bone marrow is infiltrated, there can be a leucoerythroblastic anaemia and other cytopenias. Rarely, the spleen is infiltrated, leading to hyposplenism, or there are circulating tumour cells (carcinocythaemia).[2]

Renal disease

Acute kidney injury can be the result of a microangiopathy, and thus have microangiopathic haemolytic anaemia and thrombocytopenia as features. Responsible conditions include haemolytic–uraemic syndrome, atypical haemolytic–uraemic syndrome (caused by defects of complement components), thrombotic thrombocytopenic purpura and drug-induced microangiopathy.

Various renal conditions cause inappropriate secretion of erythropoietin with consequent polycythaemia. These include renal carcinoma (hypernephroma), Wilms' tumour, renal adenoma, renal haemangioma, renal sarcoma, renal cysts including polycystic disease of the kidney, renal artery stenosis, renal vein thrombosis, post-transplant polycythaemia, hydronephrosis, horseshoe kidney, nephrocalcinosis (including that caused by hyperparathyroidism), Bartter's syndrome, renal lymphangiectasis and perinephric lymphangioma.[3]

Chronic kidney disease is associated with a normocytic normochromic anaemia attributable to reduced erythropoietin secretion and reduced red cell survival. Hepcidin is excreted by the kidney and plasma hepcidin may be increased, with ensuing

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