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Original Article

Anemia of Chronic Diseases

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Abstract

Objective: To evaluate the etiology and clinicohematological profile of patients with anemia of chronic disease.

Patients and Method: Patients with anemia of chronic disease were included. All underwent bone marrow examination, and bone marrow trephine biopsy, where required. Etiology was elucidated on the basis of clinical history and relevant investigations. Diagnosis of anemia of chronic disease was based on increased iron in fragments with decreased or absent siderocytes and sideroblasts

Results: Definitive cause of anemia was not ascertained in 57.1%. In the rest of the cases tuberculosis (17.1%) was the commonest. Majority of the patients (54.3%) were more than 60 years of age. Fever (51.4%) was the commonest complaint. Severe anemia was found in 25.8%. Bone marrow iron stain revealed increased iron in stores with absent siderocytes and sideroblasts

Conclusion: A high number of unexplained cases (57.1%) highlights the need to characterize the causes of anemia of chronic disease as treatment of underlying disease will actually improve the hemoglobin concentration in these patients.

Key words: Anemia, chronic infection, microcytic hypochromic blood picture, SLE, tuberculosis, rheumatoid arthritis

Introduction

Anemia of chronic disease (ACD) is a hypoproliferative anemia that develops in response to systemic illness or inflammation. It was first described in the 1930s and was more fully characterized by Cartwright and Wintrobe in the 1950s.[1] Amongst microcytic hypochromic anemias, ACD is the second most prevalent anemia only after iron deficiency. Unfortunately, it is commonly under diagnosed in clinical practice, and is frequently misunderstood and managed inappropriately. Significant gaps remain in comprehension of the true prevalence or consequences of ACD. Different diseases are found to be associated with ACD. Infections (Tuberculosis, bacterial, parasitic, fungal and viral infections, including human immunodeficiency virus infection), cancers, autoimmune diseases, chronic renal diseases and inflammations are most commonly incriminated.[2]

ACD is characterized by inadequate erythrocyte production in the setting of low serum iron, low iron binding capacity, low transferrin, but normal or high serum ferritin with a preserved or even increased macrophage iron stores in the bone marrow, with absence of siderocytes and sideroblasts. Iron is very much available in stores but paradoxically is unavailable for hemoglobin synthesis (Reticuloendothelial block).The erythrocytes are usually normocytic and normochromic, but long standing anemia can give rise to microcytic and hypochromic blood picture.[3-5]

In the pathogenesis of ACD different cytokines play important role. Cytokines along with the cells of reticuloendothelial system induce changes in iron homeostasis, affect the proliferation of erythroid progenitor cells, down-regulate erythropoietin production and decreases the life span of red cells. All of these then contribute to the pathogenesis of anemia. The invasion of microorganisms, the emergence of malignant cells or autoimmune dyrsregulation leads to activation of T cells (CD3+) and monocytes. These cells induce immune effector mechanisms, thereby producing cytokines such as interferon-γ, tumor necrosis factor-α (TNF-α) and interleukin-1. Interkeukin-6 and lipopolysaccharide stimulate the hepatic expression of the acute phase protein hepcidin, which inhibits duodenal absorption of iron. Interferon-γ, lipopolysaccharide, or both increase the expression of divalent metal transporter-1 on macrophages and stimulate the uptake of ferrous iron (Fe2+). The anti-inflammatory cytokine interleukin-10 upregulates transferrin receptor expression and increases transferrin receptor-mediated uptake of transferrin-bound iron into monocytes. This increased uptake and retention of iron within cells of the reticuloendothelial system leads to diversion of iron from the circulation into storage sites of the reticuloendothelial system, subsequently leading to the limitation of availability of iron for erythropoiesis. Interferon-γ and lipopolysaccharide down-regulate the expression of the macrophage iron transporter ferroprotein-

1. Ferroportin is a transmembrane exporter of iron, i.e., it is responsible for the transfer of absorbed ferrous iron from duodenal enterocytes to the circulation. At the same time, TNF-α, interleukin-1, interleukin-6 and interleukin-10 induce ferritin expression and stimulate the storage and retention of iron within macrophages. Finally, all these mechanisms lead to a decreased iron concentration in the circulation and thus to a limited availability of iron for erythroid cells. TNF-α, and interferon-γ inhibit the production of erythropoietin in the kidney. TNF-α, interferon-γ and interleukin-1 directly inhibit the differentiation and proliferation of erythroid progenitor cells.[6,7]

Identification of hepcidin is an important finding in ACD. IL-6, released during inflammatory process, induces hepcidin expression. Hepcidin excess causes the endocytosis and degradation of the sole known cellular iron exporter, Ferroportin, a 12-transmembrane segment protein. Ferroportin is found in all tissues that export iron to blood plasma. This inhibition and depletion of ferroportin from the cellular membranes progressively inhibits iron efflux from duodenal eneterocytes, macrophages and other cells involved in iron export to erythroid cells.[8,9] Another protein involved in ACD is lactoferrin. Lactoferrin is similar to transferrin, in respect to its size, shape and affinity for binding iron. Lactoferrin competes transferrin, get hold of the iron and traps it back to macrophages, making it unavailable for hemoglobin synthesis.[10] Several mechanisms independently contribute to ACD. The relative contribution of these mechanisms is uncertain. The occurrence of several independent processes, each contributing in concert to the reduction of hemoglobin, suggests a process of evolutionary adaptation.11Patients have microcytic hypochromic or normocytic normochromic anemia. Determination of cause of anemia holds a significant importance as treatment strategies vary with diagnosis. The present study was aimed to look into various causes of ACD in patients with anemia referred for bone marrow biopsy.

Patients and Methods

This retrospective study was conducted in the department of pathology, District Head Quarters Hospital, Rawalpindi, from January 2010 to December 2011. All the cases diagnosed as anemia of chronic disease (n 35) on the basis of bone marrow findings and iron staining pattern (increased iron in histiocytes with absence of sideroblasts and siderocytes) during the study period were included. Demographic data (Age, sex), the available clinical data (duration of illness, presenting complaints, symptoms, history of blood transfusion and provisional diagnosis) and blood as well as bone marrow findings were recorded. The patients were categorized as having severe anemia (Hb <8.0 g/dl), moderate anemia (Hb 8.1- 9.5 g/dl) and mild anaemia (Hb >9.6/dl and less than 11.0 g/dl in females and <13.0 g/dl in males).

The Giemsa and iron-stained bone marrow smears and H & E stained trephine sections, if available, were studied, and data were recorded. The data were analyzed for frequencies, where ever applicable.

Results

Table 1 details the demographic and available clinical & laboratory data of our patients. Males comprised 60% of cases; male: female ratio was 3: 2. Majority of patients was >60years of age. About three fourth of the patients had been symptomatic for > 6 months. Fever was a prominent symptom in about half of the patients. Anemia was the most consistent feature; it was severe (Hb< 8.0 g/dl) in 25.7%, and moderate (Hb between 8.1 and 9.5 g/dl) in 45.7% patients. Nearly half of the patients had been transfused red cell concentrates before they were referred to us.

Table 1: Demographic, clinical and laboratory features (n=35)*

Parameter	No (%)
Sex	
Male	21(60)
Female	14 (40)
Age (Yrs)	
18-45	06 (17.1)
46-60	10 (28.6)
>60	19 (54.3)
Duration of Illness (months)	
<6	09 (25.7)
>6 to 12	18 (51.4)
> 12	08 (22.9)
History of Fever	18 (51.4)
History of Blood Transfusion	17 (48.6)
Degree of Anaemia (Hb g/dl)	
Severe (≤ 8)	09 (25.7)
Moderate (8 to 9.5)	16 (45.7)
Mild (> 9.5)	10 (28.6)
Red Blood Cells Morphology	
Normocytic & Normochromic	23 (65.7)
Microcytic & Hypochromic	12 (34.3)
Bone Marrow	
Haemophagocytosis	10 (28.6)

*All cases showed Increased Iron in bone marrow macrophages with absent or decreased siderocytes and sideroblasts

As shown in table 2, a diagnosis of chronic disease was manifest, before bone marrow biopsy was performed, in only 15 (42.9%) cases. Tuberculosis was the commonest already diagnosed underlying chronic disorder, followed by other infections (typhoid, respiratory infections, etc), chronic liver disease, systemic lupus erythematosus, and chronic renal disease, respectively.

In the remaining patients (57.1%), who were referred to us

for bone marrow biopsy with an attempt to investigate for anemia, other cytopenias(s), or fever, the findings indicated chronic underlying disorder. In these patients, there was no previous clinical suspicion of any chronic disease. Red cell morphology was normocytic normochromic in two thirds and microcytic hypochromic in the remaining one third of the cases. On bone marrow smears, iron overload with absence of siderocytes and sideroblasts & siderocytes was a consistent feature; haemophagocytosis was a prominent feature in 28.6% of cases.

Table 2: Anaemia of Chronic Diseases-Causes (n 35)

Cause	No (%)
Tuberculosis	6 (17.1)
Chronic Liver Disease	3 (8.6)
Systemic Lupus Erythrmatosus	2 (5.7)
Typhoid	1 (2.9)
Chronic Renal failure	1 (2.9)
Chronic Infections	2 (5.7)
No Chronic disease suspected before bone marrow biopsy	20 (57.1)

Discussion

ACD is a hypoproliferative anemia that accompanies chronic inflammatory, infectious, or neoplastic disorders. The anemia of chronic disease is primarily an anemia due to underproduction of red cells, with low reticulocyte production, and is most often a normochromic, normocytic anemia. However, in 30% to 50% of patients, the red cells are hypochromic and microcytic and, most often, the serum iron, total iron-binding capacity, and transferrin saturation are reduced in the presence of adequate iron stores.[12]

In comprehensive population-based studies, precise estimates of prevalence are difficult to ascertain because many patients with anemia are not investigated sufficiently to establish the cause. Moreover, no consensus research criteria exist for the diagnosis of anemia of chronic disease, and patients may have multifactorial causes for anemia, wherein ACD is only a part.[10] According to the World Health Organization (WHO) mild anemia corresponds to a Hb 9.5 g/dl, moderate anemia to a Hb 8 g/dl but <9.5 g/dl, and severe anemia to a Hb <8.0 g/dl. Anemia of chronic disease is usually patients have mild to moderate.[13] Our results also showed that most of patients diagnosed as ACD (74.5%) had mild to moderate degree of anemia. Majority of our patients (54%) were more than 60 years age. This is also important because such patients do not respond to treatment unless underlying disease is diagnosed and treated. Bone marrow examination also differentiates these cases of ACD from refractory anemia (MDS) which is suspected in elderly patients not responding to treatment.

In 57% of our cases there was no definitive diagnosis of an underlying disease was evident. They were referred for bone marrow biopsy to evaluate the cause of anemia and showed iron staining pattern of underlying disorder. It is important to investigate these patients for an underlying pathology. There were 6 cases of tuberculosis in our cases showing iron staining pattern of anemia of chronic disease. Multiple causes of anemia in tuberculosis have been identified. These include iron deficiency, folate deficiency (most probably because of drug therapy) decreased red cell life span, depressed erythropoiesis and defective ferrokinetics.[14] In this regard it is particularly important to differentiate anemia due to iron deficiency from that of ACD. Various tests differentiate iron deficiency anemia from ACD. These include serum iron, TIBC, Transferrin saturation, serum ferritin, serum transferrin receptors and red cell zinc protoporphyrin. However determination of iron stores by bone marrow examination remains the best method for assessment of iron stores.[15] Other tests include CRP and ESR (both braised in ACD). TB-associated anemia is usually mild and resolves with anti-TB treatment.[16] There were 2 diagnosed cases of SLE showing iron staining pattern of underlying disorder. Hematological abnormalities are very common in systemic lupus erythematosus. Anemia is found in approximately 50% of patients, with anemia of chronic disease being the most common form. Other mechanisms contributing to development of anemia in SLE include renal insufficiency, blood loss, dietary insufficiency, medications, hemolysis, infection, hypersplenism, myelofibrosis, myelodysplasia, and aplastic anemia (probably having an autoimmune pathogenesis).[17] In the absence of either symptom attributable to anemia, anemia of chronic inflammation does not require specific treatment (provided other causes mentioned above are ruled out). Some of the patients of SLE show improvement in hemoglobin concentration when treated with rEPO (Recombinant erythropoietin) ACD is considered the most frequent cause of anemia in RA; however, iron deficiency due to gastrointestinal blood loss or a combination of both. It is important to determine the cause of anemia in order to treat these patients. The most reliable characteristic for the detection of iron deficiency is stainable iron content in bone marrow aspirate. Significant increase in hemoglobin concentration in these patients has been observed in patients of Rheumatoid arthritis treated with erythropoietin.[18]

Similarly in celiac disease though major cause for anemia in deficiency of B12, Folic acid and iron, but it has been observed that in different studies ACD affects a significant portion of celiac disease patients at presentation, contributing to significant number of cases and the response of anemic patients to a gluten-free diet was not influenced by the presence of ACD.[19] This has also been observed that mean serum levels of inflammatory cytokines that contribute to ACD, including interleukin- 1b, interleukin-6, tumor necrosis factor-a, and interferon-g, are increased in active celiac disease.[20,21]

Anemia is a common association of malignant disease and may affect treatment decisions. It is important to recognize the factors leading to development of anemia and to exclude those that are treatable. The recognition that tumor-associated cytokine production is a major factor in the anemia of malignancy, and rEPO can overcome this suppression.[22]

ACD, if marked, can be a reflection of more progressive underlying disease. Treatment of underlying disease is the therapeutic approach of choice for ACD. Treatment with iron therapy is contraindicated in ACD. In general iron therapy should only be considered if there is concomitant iron deficiency and this should be with oral iron therapy. Treatment with parenteral iron therapy should be avoided due to possible aggravation of infection by large bolus of infection. Blood transfusions are helpful in the context of severe life threatening anemia. Although the positive short term effects of therapy with erythropoietic agents on the correction of anemia and avoidance of blood transfusion are well documented, few data are available on possible effects on the course of disease. The therapeutic effects of these agents primarily include the stimulation of iron uptake and heme biosynthesis in erythroid cells. Additionally they can counter act the antiproliferative effects of cytokines. The pivotal role of hepcidin in iron metabolism and in the pathogenesis of ACD could lead to development of inhibitors of hepcidin for clinical use. Future strategies, to treat ACD, may thus include the use of these inhibitors and iron-chelation therapy to induce the endogenous antagonists that overcome the retention of iron within the reticuloendothelial system, and hormones or cytokines that might effectively stimulate erythropoiesis under inflammatory conditions.[23-25] It is thus very important to determine the cause of anemia in various chronic inflammatory conditions as this would affect the treatment outcome and quality of life in these patients.

Conclusions

A high number of unexplained cases (57.1%) highlights the need to characterize the causes of anemia of chronic disease as treatment of underlying disease will actually improve the hemoglobin concentration in these patients.

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