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Original Article

Anaemia of Chronic Disease; A Study of Cases in a Tertiary Care Hospital

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Abstract

Background: **Anaemia of chronic disease (ACD) is the second most prevalent type of anaemia. Causes can be chronic infections, autoimmune diseases, malignancies and is characterized by pathologic iron homeostasis, impaired erythropoiesis and blunted erythropoietin response.**

Materials and Methods: **This retrospective case series study was conducted in Department of Pathology, Benazir Bhutto Hospital Rawalpindi where all the consecutive cases of ACD diagnosed by peripheral blood smear and bone marrow slide examination, presented during 2014-2016 were studied. The presenting complaints, physical examination findings, complete blood count, bone marrow biopsy, and provisional diagnosis were noted. Patients with other types of anaemia were excluded.**

Results: **In our study of 51 cases, 27(52.9%) were males and 24(47%) were females. Median age was 35 years. Most common age group involved was 8-25 years (25.39%). Fever was the commonest complaint (68.6%) followed by weight loss (37.2%). Commonest physical examination finding was pallor (90.2%) and hepatomegaly (37.2%). Severe anaemia (Hb≤8g/dl) was present in 43.1% cases. RBCs were microcytic hypochromic in 43.1% of patients. Thrombocytopenia (platelets <150,000/mm3) was a finding in 49% of patients. Hemophagocytes were present in 49% of cases. Aetiology was undiagnosed in 68.6% of cases. 45.09% patients had a previous history of blood transfusion.**

Conclusion: **Fever is the commonest presenting complaint. Most of the cases have unknown aetiology. A high number of patients with severe anaemia is not in accordance with ACD as a disease of mild anaemia. This reflects inappropriate recognition of ACD.**

Introduction

Anaemia is a global disorder. It is defined as reduction of total circulating red cell mass below normal limits. Multifactorial in origin, Anaemia of chronic disease (ACD) is the commonest type of anaemia after iron deficiency anaemia and is most frequently encountered anaemia in hospital settings. As its name implies it is due to chronic diseases which can be infections (bacterial, viral and fungal), cancers(hematologic and solid tumours) and autoimmune disorders(systemic lupus erythematous, rheumatoid arthritis and inflammatory bowel disease).Interleukin-1(IL-1), Interleukin-6(IL-6) and Tumour Necrosis Factor-alpha (TNF-α) are mainly involved in its pathogenesis which induce the formation of hepcidin, an acute phase protein which impairs the function of ferroportin ,hence blocking the export of iron from macrophages[1,2] .Interleukin-10(IL-10) increases the formation of transferrin receptors hence increasing the uptake of iron in the monocytes. It is a paradoxical condition in which body is not deficient of iron but due to accumulation and entrapment in the macrophages cannot be used for erythropoiesis. Anaemia of chronic disease is characterized by pathologic iron homeostasis, impaired erythropoiesis and blunted erythropoietin response. Laboratory findings which differentiate it from iron deficiency anaemia are increased ferritin levels and decreased total iron binding capacity. There is also increase in the cytokines level in this type[1]

Anaemia of chronic disease is a hypo proliferative type of anaemia primarily occurring in response to inflammatory cytokines which are TNF-α, IL-1 and IL-6. There is also shortening of life of RBCs[3,4]. There is low serum iron, decreased serum transferrin and transferrin saturation. There is increased erythrocyte free protoporphyrin and iron absorption is reduced. Iron given intravenously is sequestered in reticuloendothelial system[4]. Iron used alone causes growth of microorganisms and tumour cells[5]

Anaemia of chronic disease can be diagnosed on the basis of bone marrow biopsy. On iron staining there is presence of increased iron in bone marrow histiocytes with the absence in sideroblasts and siderocytes[6].

Treatment options mainly include treatment of the underlying cause, blood transfusions in cases of severe anaemia (Hb≤8g/dl), erythropoietic agents[1] and anti-interleukin-6 treatment[7]. Blood transfusions causes iron overload which has shown to increase the mortality over years[8]. Introduction of Recombinant human erythropoietin has resulted in decreased blood transfusions in hospital settings[9].

The objective of our study was to assess the clinical presentations, laboratory findings and etiological factors of Anaemia of chronic disease.

Patients and Methods

This retrospective case series study was conducted in the Department of Pathology, Benazir Bhutto Hospital, Rawalpindi from January 2014 – December 2016. All consecutive cases of Anaemia of Chronic Disease, which were 51 in number, presented during this time period were included in this study.

Anaemia of Chronic Disease was diagnosed on the basis of peripheral blood smear staining along with bone marrow aspirate staining. Patients specifically having increased iron in bone marrow histiocytes and decreased iron in siderocytes and sideroblasts were included. Patients having any other type of anaemia were excluded.

Blood sample was taken from all the patients in the morning. Complete blood count was assessed by an automated blood analyser. The haemoglobin levels, red blood cell count, white blood cell count and platelet count were noted. A thin smear blood slide was made, stained with Giemsa stain, and seen under light microscope for peripheral blood picture. Reticulocytes were assessed using new methylene blue (NMB) stained slide.

Bone marrow aspiration of all the patients was done from anterior superior iliac spine. Two slides from a single aspirate were made. Giemsa staining was performed to assess the status of myelopoiesis, erythropoiesis, cellularity, and the presence of megakaryocytes and hemophagocytes [Figure I]. The second slide was stained with Prussian Blue stain for iron and was used to assess the iron status in histiocytes, siderocytes and sideroblasts [Figure II]. Males having haemoglobin less than 13g/dl and females less than 11g/dl were considered anaemic. World Health Organization criteria for anaemia severity was used to categorize the patient's haemoglobin levels, according to which haemoglobin ≥9.5g/dl is classified as mild, haemoglobin 8-9.5gdl as moderate and hemoglobin≤8g/dl as severe anaemic. The presenting complaints of the patients were noted and physical examination findings, including generalized appearance, any swellings, lymphadenopathy and liver and spleen palpation was performed and noted. History of blood transfusion, if any, was noted along with the provisional diagnosis of the patients from the referring department. The data was entered in Microsoft Excel 2007 and descriptive statistics were calculated.

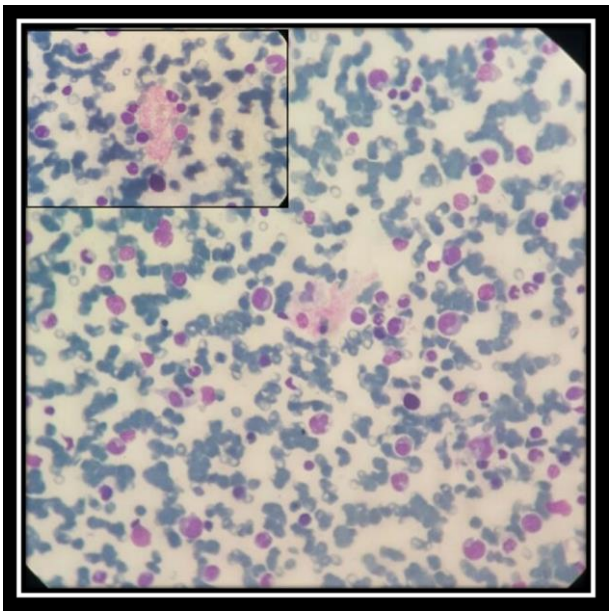

Figure 1: A hemophagocyte is engulfing the RBCs. In our study 49% patients had hemophagocytosis. Giemsa stain 40X. inset 100X

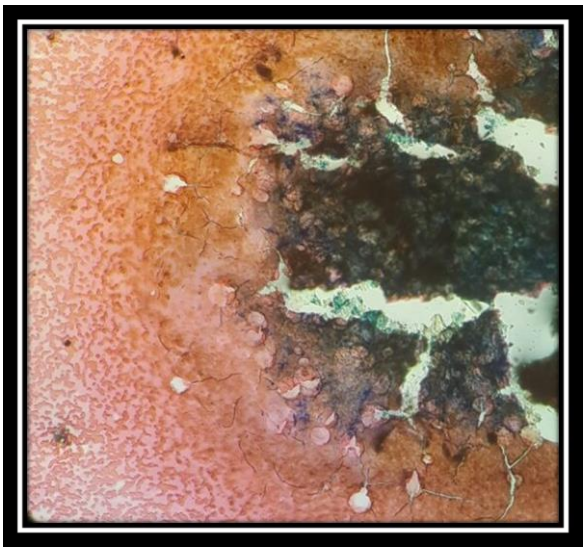

Figure 2: Iron increased in the bone marrow fragments (blue). Prussian blue stain 40X

Results

Out of the 51 cases presented in 3 years span (2014-16), 27(52.9%) were males and 24(47%) were females with a male to female ratio of 9:8 The age of the patients ranged from 8 years to 90 years with 41.17% patients below the age of 25 years. Median age was 35 years [Table no. I].

Table no.1 Demographic Details of Patients (n=51)

Parameter	No. (%)
Gender	
Male	27(53)
Female	
Age(Years)	
Less than 25	21(41.17)
25-50	19(37.25)
Above 50	11(21.56)

Fever was the commonest presenting complaint (68.6%) followed by weight loss (37.2%) and abdominal pain (29.4%) [Figure III]. On physical examination, 90.1% patients were pallor, 37.2% had hepatomegaly and 23.5% had splenomegaly. [Figure IV]

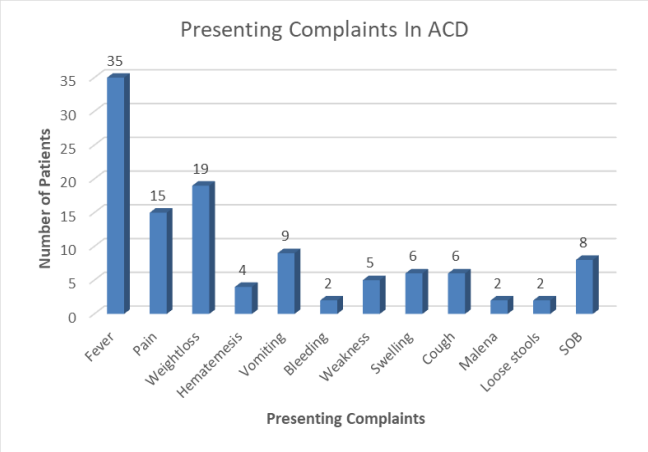

Figure III: Presenting Complaints of Patients with ACD

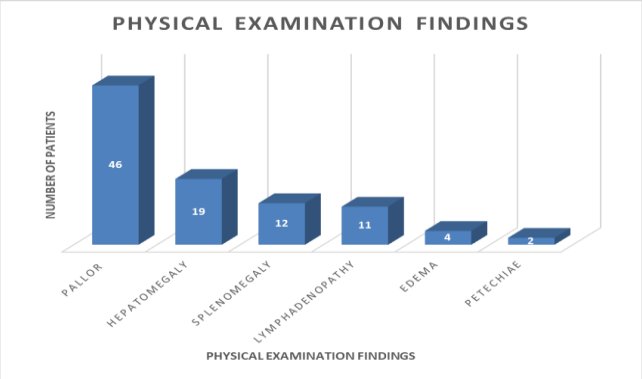

Figure IV: Physical Examination Findings in patients of ACD

Haemoglobin was assessed from complete blood count reports. Mild anaemia (Hb>9.5g/dl) was present in 31.3% of patients.25.4% had moderate anaemia (Hb 8-9.5g/dl) and severe anaemia (Hb<8g/dl) was found in 43.1% of patients. Mean haemoglobin was 8.4 ± 1.8 g/dl. Red blood cell morphology was normocytic normochromic in 56.9% and microcytic hypochromic in 43.1% of patients. On peripheral blood giemsa staining, 43.1% patients had reticulocytopenia (reticulocytes<0.5%). 45.09% patients had a history of blood transfusion. Leucocytopenia (leukocytes<4000/mm3) was present in 29.4% of patients. Thrombocytopenia (platelets< 150,000/mm3) was obvious in 49% of patients. Bone marrow aspirate giemsa staining results showed that 42.8% had normocellular 33.3% bone marrows. Erythropoiesis was normal in 68.2% patients. Hemophagocytes were present in 50.7% of cases. [Table II]

Table No.II: Laboratory Findings in Patients(n=51)

Parameter	**No. (%)**
Degree of Anaemia	
Severe Hb <8g/dl	22(43.1)
Moderate Hb 8-9.5g/dl	13(25.4)
Mild Hb >9.5g/dl	16(31.3)
RBC Morphology	
Normocytic Normochromic	29(56.9)
Microcytic Hypochromic	22(43.1)
History of Blood Transfusion	**23(45.09)**
Reticulocytopenia (less than 0.5%)	**22(43.1)**
Total leukocyte count	
Less than 4000/mm3	15(29.4)
4000-10000/mm3	31(60.7)
Above 10000/mm3	5(9.8)
Platelets	
Less than 150,000/mm3	25(49)
150,000-400,000/mm3	19(37.2)
Above 400,000/mm3	7(13.72)
Bone Marrow	
Cellularity	
Normocellular	23(45.09)
Hypercellular	18(35.2)
Hypocellular	10(19.6)
Erythropoiesis	
Normal	34(66.6)
Hyperplastic	14(27.4)
Depressed	3(5.88)
Myelopoiesis	
Normal	32(68.6)
Hyperplastic	19(37.25)
Hemophagocytosis	**25(49)**

Iron	
Present in Macrophages	51(100)
Absence in siderocytes and sideroblasts	51(100)

Aetiology was undiagnosed in 68.6% of cases, followed by typhoid and tuberculosis (7.8% each). [Table III]

Table No. III: Causes of Anaemia of Chronic Disease (n=51)

CAUSE	**No. (%)**
Unknown aetiology	35(68.6)
Typhoid	4(7.8)
Tuberculosis	4(7.8)
Hepatitis C	2(3.9)
Carcinoma of Head of Pancreas	1(1.96)
Gastric carcinoma	1(1.96)
Metastatic bone disease	1(1.96)
Diabetes Mellitus	1(1.96)
Renal parenchymal disease	1(1.96)
Inflammatory Bowel Disease	1(1.96)

Discussion

ACD is normocytic normochromic type of anaemia but longstanding disease can change its morphology to microcytic hypochromic type[1]. Our results showed that 43.1% cases had microcytic hypochromic blood picture which is in accordance with a study which predicted the values between 30-50%[10]. Another study indicated this value to be 39.7%. Our results showed that 68.6% patients presented with fever which is in accordance with a study conducted in Rawalpindi having 51.4% patients with fever. In our study 45% patients had history of blood transfusion which is in accordance with the same study having values of 48.6%[11]. 68.6% cases in our study have no diagnosed chronic disease at the time of their presentation which is higher than a previous study conducted in the region having values of 57.1%[11]. 4 cases of ACD had typhoid which is supported by a study which showed that anaemia and increased activity of histiocytes is associated with typhoid[12]. Tuberculosis is one of the commonest causes of ACD. Our study showed that 7.8% cases of ACD had Tuberculosis. A Korean study showed that 31.9% patients of tuberculosis had anemia[13].A study in Brazil where tuberculosis is endemic, showed that 89.2% of the patients had anemia[14].There were two cases of malignancy in our study which is in accordance with the causes of ACD mentioned before[1]. There was a case of inflammatory bowel disease (IBD) in our study. IBD is always associated with anaemia and is a combination of iron deficiency anaemia and ACD. 30 % of patients have hemoglobin below 12g/dl[15,16]. ACD is itself ameliorated on treating the underlying chronic disease although it is invariably the most difficult of all types of anaemia to treat[3,4,17,18]. Hepcidin is key acute phase protein involved in pathogenesis of ACD. It causes trapping of iron in macrophages and hepatocytes hence causing hypoferremia. Hepcidin antagonists are an emerging field of research in treating ACD[18-20].Due to lack of availability in our set-up, ferritin levels and total iron binding capacity values which are used worldwide to differentiate between ACD and iron deficiency anaemia, were not included in this study[1].

Conclusion

Fever was the commonest presenting complaint and pallor was the commonest physical examination finding. 68.6% of patients had unknown aetiology. A high number of patients with severe anaemia is not in accordance with ACD as a disease of mild anaemia. This reflects inappropriate recognition of ACD.

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