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Study of RBC Indices and Bone Marrow Iron Stores in Anaemia of Chronic Disease and comparison with Serum Ferritin

Authors:
Dr Manisha Kakkar MBBS, MD Pathology[1], Dr Nikhil Mahajan MBBS, MD Medicine[2]
[1]Medical Officer, Postgraduate Department of Pathology
Government Medical College, Jammu

Abstract
Anaemia observed in patients with infectious, inflammatory or neoplastic diseases that persist for more than 1 or 2 months is called anaemia of chronic disease. The purpose of this study was to study the various morphological types of anaemia in Anaemia of chronic disease and to correlate bone marrow iron stores and serum ferritin in these patients. This study was conducted in Post Graduate Department of Pathology ASCOMS, Sidhra, Jammu for a period of one year. It was concluded from the study that normocytic normochromic anaemia was the most common type of anaemia and there exists a positive correlation between serum ferritin and bone marrow iron stores in patients of Anaemia of chronic Disease.
Keywords: *RBC Indices, bone marrow iron stores, anaemia of chronic disease, rheumatoid arthritis, tuberculosis, malignancy, serum ferritin.*

Introduction

Anaemia of chronic disease was established as a distinct entity in 1962 after studies on anaemia associated with the three big clinical causes: infection, inflammation (including connective tissue disorders) and neoplasia, which account for 75% of cases. Though the chronic disease that leads to anaemia is usually easily identified, this is not always so, and occult disease must be considered in every case of unexplained anaemia[1]. Anaemia often observed in patients with infectious, inflammatory or neoplastic diseases that persist for more than 1 or 2 months is called anaemia of chronic disease.

Anaemia appears to be caused not by changes in iron metabolism, but, rather by the effect of a number of suppressor cytokines. Tissues injured by infections, inflammation or neoplastic cells release cytokines such as Interleukin-1, Tumor Necrosis Factor, Interferon gamma, known to reduce the production of erythropoietin in the kidney and impair its action in the marrow. The anaemia of chronic disorders is characterised by a slightly shortened red cell life span, disturbed iron metabolism, and impaired erythropoietin stimulated red cell production. Characteristic features of the anaemia of chronic disease characterised by disordered iron metabolism manifest as a low serum iron, decreased serum transferrin, decreased transferrin saturation, increased serum ferritin, increased reticuloendothelial stores, increased erythrocyte free protoporphyrin and reduced iron absorption[2].

In anaemia of chronic disease, anaemia is normocytic normochromic in 60% to 70% of cases and microcytic hypochromic in 30% to 40% of cases. Hypochromia is more common than microcytosis. Hypochromia may be observed even though the hematocrit remains within normal limits. Microcytosis in anaemia of chronic disease is usually not as striking as that commonly associated with iron deficiency anaemia, values for MCV below 72 fl are rare.

Hypochromia precedes microcytosis in anaemia of chronic disease. Slight anisocytosis and poikilocytosis may be detected. The absolute reticulocyte count is within the normal range or slightly elevated. Changes in the blood cell count or platelet count are not consistent and depend exclusively on the underlying disorders. Measurement of serum ferritin is often recommended as a useful estimate of iron stores or of iron deficiency. Normally 1 microgram/liter serum ferritin roughly corresponds to about 8 mg of storage iron. However, ferritin is also an acute phase protein; fever and infections increase its synthesis and produce inappropriately high serum levels. Therefore, especially in chronic disease, measurement of ferritin is not reliable for estimating bone marrow iron deficiency or overload. Apart from inflammation, liver cell damage can also increase the ferritin concentration and in some malignancies very high ferritin concentrations have been measured, which are obviously not related to the body iron stores. Consequently it has been suggested that only a serum ferritin level in excess of 60microgram/liter should be considered as reflecting normal or increased iron stores. Serum ferritin concentrations if corrected for the acute phase response could still be used to estimate the iron stores in bone marrow even in patients with anaemia of chronic disease[3]. The purpose of the study was to study Red Blood Cell Indices and Peripheral Blood film for various morphological types of anaemia in Anaemia of Chronic Disorder. Also, to correlate bone marrow iron stores and serum ferritin in Anaemia of Chronic Disorder.

Material and Methods

Study Design: The present study was a prospective, single centre, hospital based study conducted in the Post Graduate Department of Pathology, Acharya Shri Chander College of Medical Sciences (ASCOMS) and Hospital, Sidhra, Jammu (J&K) for a period of one year i.e. from 1st November 2012 to 31st October 2013.

Inclusion criteria: Patients who presented with anaemia and suffering from chronic infection or chronic inflammation or malignancy were taken up in the study.

The samples of blood and bone marrow aspiration were done after proper counselling and consent. The relevant history and clinical details of the patients was recorded. Haematological and biochemical investigations done were recorded.

Haemoglobin Estimation was done using the auto-mated cell counter/ cynmethaemoglobin method.

Peripheral blood film: It was stained using Leishmans stain[4].

Red cell indices comprising of mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC) shall be estimated using automated cell counter. (Daice & Lewis).

Bone marrow aspiration was done from posterior superior iliac spine under complete aseptic conditions using Salah's aspiration needle. Smears were stained with Leishman/ Giemsa stain for assessment of cellularity and morphological details. Perls' Prussian blue staining was done on one slide for estimation for estimation of marrow iron stores[5].

Serum ferritin estimation was done using ELISA method.

Results

In the present study, 73 patients of rheumatoid arthritis, tuberculosis and malignancy with anaemia were included and evaluated.

Demographic data: Almost two third (60.3%) of the patients were in the age group 31-50 years. Males constituted 54.8% of the patients as compared to 45.2% females.

PBF: In the current study, 64.4% of the patients had normocytic normochromic anaemia followed in frequency by microcytic hypochromic anaemia in 20.6% of patients.

RBC Indices: Mean MCV was 86.7fl, mean MCH was 28.4pg and mean MCHC was 32.9gm/dl.

Haemoglobin (Hb): In the present study majority (n=39) of the patients had Hb in the range of 9-9.9 gm/dl. Mean Hb was 9.1gm/dl.

Serum Ferritin and Bone marrow Iron stores (BMIS): A positive correlation existed between serum ferritin and BMIS in the present study for the entire group (point biserial correlation coeffient=0.571, p=0.000).

In the current study, 34 patients (46.6%) had rheumatoid arthritis. A positive correlation existed between serum ferritin and BMIS in this group (point biserial correlation coefficient=0.539; p=0.001).

In our study, 24 patients (32.9%) had tuberculosis. A positive correlation existed between serum ferritin and BMIS in this group (point biserial correlation coefficient=0.540; p=0.006).

In the present study, 15 patients (20.5%) had malignancies. A positive correlation existed between serum ferritin and BMIS in this group (point biserial correlation coefficient =0.715; p=0.003).

Table 1: Distribution of Cases According to the Age

Age in years	N	%
<30	4	5.5
31-40	20	27.4
41-50	24	32.9
51-60	19	26
61-70	6	8.2

Table 2: Distribution of Cases According to Type of Anaema

Type of Anaemia	N	%
Normocytic Normochromic	47	64.4
Microcytic Hypochromic	15	20.6
Macrocytic Normochromic	9	12.3
Dimorphic Anaemia	2	2.7

Table 3: Distribution of Cases According to the Disease

DISEASE	N	%
TUBERCULOSIS	24	32.9
MALIGNANCY	15	20.5
RHEUMATOID ARTHRITIS	34	46.6

Table 4a: Distribution of cases according to BMIS

Bone marrow iron stores grade	T.B.	R.A.	MALIGNANCY	TOTAL
DECREASED	5	5	3	13
NORMAL OR INCREASED	19	29	12	60

Table 4b:

Bone marrow iron stores grade	TB	RA	MALIGNANCY	N(%)
Grade 0	4	4	2	10 (13.7)
Grade 1	1	1	1	3 (4.1)
Grade 2	4	6	2	12 (16.4)
Grade 3	3	6	2	11 (15.1)
Grade 4	4	5	2	11 (15.1)
Grade 5	6	8	5	19 (26)
Grade 6	2	4	1	7 (9.6)

Table 5a: Relationship between Serum ferritin and BMIS grade.

Bone Marrow iron stores grade	Serum Ferritin(ng/ml)			Total
	Reduced <20	Normal 20-500	Raised >500	
Grade 0	6	4	0	10
Grade 1	0	3	0	3
Grade 2	1	10	1	12
Grade 3	0	5	6	11
Grade 4	0	4	7	11
Grade 5	0	3	16	19
Grade 6	0	1	6	7
Total	7	30	36	73

Table 5b:

Bone marrow iron stores grade	Serum ferritin(ng/ml)			Total
	Reduced <20	Normal 20-500	Raised >500	
Reduced	6	7	0	13
Normal or Increased	1	23	36	60
Total	7	30	36	

Table 6: RBC Indices.

Indices	Mean	Standard Deviation
MCV(fl.)	86.7	7.2
MCH(pg.)	28.4	1.9
MCHC(gm/dl)	32.9	1.7

Discussion

Most patients suffering from chronic infections, chronic inflammations, or various malignancies develop a mild to moderate anaemia. This anaemia, designated anaemia of chronic disease, is characterized by a low serum iron level, a low to normal transferrin level, and a high to normal ferritin level. However, the anaemia appears to be caused, not by these changes in iron metabolism, but, rather, by the effect of a number of suppressor cytokines.

The present study was prospective in nature and was carried out in post graduation department of pathology, Acharya Shri Chander College of Medical Sciences and Hospital Sidhra, Jammu over a period of one year.

In the present study, 73 male patients of rheumatoid arthritis, tuberculosis and malignancy, with anaemia were studied.

Age: In the present study, almost two third (60.3%) of the patients were in the age group 31-50 years.

Sex: In the present study, males constituted 54.8% of the patients as compared to 45.2% females.

PBF: Iron deficiency anaemia may be difficult to distinguish from microcytic hypochromic anaemia found in patients with anaemia of chronic disease in whom serum iron concentration and transferrin saturation are reduced but in whom iron stores are normal or increased[6]. In the present study, 64.4% of the patients had normocytic normochromic anaemia followed by microcytic hypochromic anaemia in 20.6% of patients.

This observation was in concordance with M.D. Joseph M.Cash et al 1989[6]. He studied 90 patients with anaemia of chronic disease. The anaemia was usually normocytic but 21% of patients had MCV <80 fl. This observation was in concordance with Frank H. Wians, Jr et al 2001[7] who observed normocytic normochromic anaemia in 60% to 70% of cases and microcytic hypochromic in 30% to 40% of cases.

Serum Ferritin and BMIS: In normal subjects, serum ferritin concentration correlates well with iron stores. The relationship of serum ferritin concentration, in the present study, indicates a similar association with body stores (point biserial correlation co-efficient= 0.571; p=0.000). A positive correlation between serum ferritin and BMIS existed for the entire group. This observation was in concordance with Baynes et al 1986[8], Bartels et al 1978[9], Porter et al 1994[10].

There are a number of advantages in using serum ferritin concentration as an index of storage iron. The visual grading of iron has a considerable observer error when six grades were used. There are also clinical advantages in a quantitative technique over a subjective assessment and in addition to this a blood test is more likely to be acceptable to the patient than marrow aspiration.

However, in some cases normal serum ferritin values were found when no stainable iron could be detected in marrow. This is because ferritin is also a so called positive acute phase protein and fever and infections increase its synthesis and produce inappropriately high serum levels.

Rheumatoid Arthritis: In our study 34 patients (46.6%) had rheumatoid arthritis. A positive correlation existed between serum ferritin and BMIS in this group (point biserial correlation coefficient = 0.539; p=0.001). The observation was in concordance with Shroff K et al 1991[11]. He conducted a prospective and controlled study for iron status with special reference to serum ferritin in a group of 30 patients with rheumatoid arthritis. The serum ferritin levels in the iron depleted rheumatoid arthritis patients were significantly lower in comparison to patients with normal to increased marrow iron stores. There was a strong correlation between serum ferritin level and marrow iron stores (r=+0.08, p<0.001).

Tuberculosis: In our study, 24 patients (32.9%) had tuberculosis. A positive correlation existed between serum ferritin and BMIS in this group (point biserial correlation coefficient = 0.540; p= 0.006). This observation was in concordance with Baynes et al 1986[12]. He conducted a study on 59 patients with active pulmonary tuberculosis. He concluded from his study that there was a good correlation between the serum ferritin and the

concentration of iron in the marrow as assessed chemically on trephine biopsies (r=0.78, p<0.0001) and histologically on aspirated and biopsied material (r=0.78, p<0.0001 and r=0.68, p<0.0001, respectively).

Malignancy: In the present study, 15 patients (20.5%) had malignancies. A positive correlation existed between serum ferritin and BMIS in this group (point biserial correlation coefficient =0.715; p=0.003). This observation was consistent with Jakobsen E et al 1982[13]. He evaluated serum ferritin and Bone marrow haemosiderin in 306 patients with malignancies, mostly lymphomas and in 46 healthy controls. There was a good correlation between serum ferritin and BMIS both in patients (r=0.67) and in the controls (r=0.77).

Conclusion

From the current study, it was concluded that the most common morphological type of anaemia in Anaemia of Chronic Disease is normocytic normochromic anaemia, seen in 64.4% of the patients.

Also it is concluded that there exists a positive correlation between serum ferritin and BMIS in patients of Anaemia of Chronic Disease. Measurement of serum ferritin is often recommended as a useful estimate of iron stores or of iron deficiency. Normally, 1 mc/l serum ferritin roughly corresponds to about 8 mgs of storage iron.

However, ferritin is also an acute phase reactant. Serum ferritin concentration if corrected for the acute phase response could still be used to estimate the iron stores in bone marrow even in patients with Anaemia of Chronic Disease.

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