Splenomegaly in Patients with Sideropenic Anemias: Clinical and Hematologic Significance

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ABSTRACT

Background, Objectives: Sideropenic anemias (SAs) are a group of hypoproliferative anemias characterized by hyposideremia. Although they run an insidiously started slowly progressive course, they are a pointer for an underlying serious disease. Fortunately, in most cases, management of SAs is available, effective and relatively inexpensive. Splenomegaly was reported in patients with SAs with variation in Hackett's grading and hematological profile. Etiopathogenesis of splenomegaly in SAs was mainly explained as related to the underlying pathologic process of anemia or as a component of the rarely occurring Paterson-Kelly syndrome. Apart from the etiopathogenesis of splenomegaly of SAs it is still a fruitful point for current research. The aim of the present study was to assess splenomegaly in patients with SAs in terms of frequency, clinical and hematological profile of splenomegaly in SAs. Another aim was to assess prognostic significance and to assume etiopathogenesis of splenomegaly in SAs.

Methods: A prospective study was conducted on 83 patients with SAs and 25 normal sex and age matched healthy controls. Patients' demographics, clinical and hematologic data were collected through thorough history and clinical examination. Splenomegaly was assessed with clinical examination of the study subjects and was graded with Hackett's clinical grading, then confirmed with ultrasonographic examination. Patients were treated as per the published guidelines for treatment of SAs. Those with splenomegaly were subjected to a strict follow up plan.

Results and Conclusion: Analysis of the collected data showed that splenomegaly is of robust clinical and hematologic significance in patients with SAs.

Key words: Sideropenic anemias, splenomegaly, Clinical significance.

1. Introduction

Sideropenic anemia is a hematologic term referred to anemias with reduced serum iron levels; the term includes iron deficiency anemia (IDA), and anemia of chronic disease (ACD), or a dimorphic anemia of IDA and ACD. SAs are the most prevalent types of anemias worldwide, firstly IDA and secondly ACD. (1-3)

In vitro and in vivo studies demonstrated reduced serum iron in patients with chronic inflammatory conditions, infections and malignancies. Inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor-alpha are the main trigger for hypoferemia; other bone morphogenetic proteins 2, 4, 6, & 9 produce the same effect in patients with malignancy. These effects were mediated through hepcidin. (4-6)

The differentiation between IDA and ACD is quiet difficult, nevertheless in ACD there is confounding evidence of chronic infectious, inflammatory, or malignant disease causing the anemia. Furthermore in ACD the RBCs indices are usually normal (MCV from 80- 100fl, MCHC from 32-36 gm/dl and RDW 12.0-14.6%), while in IDA all RBCs indices are below normal except the RDW which is commonly raised. Total iron binding capacity (TIBC) was found raised in IDA and reduced in ACD, however serum hepcidin levels were considered the most important difference between IDA and ACD. Unfortunately, laboratory assay of serum hepcidin is difficult, expensive and not widely available. Soluble transferrin receptor (sTfR) was found to be a good differential test between IDA and ACD; it was found raised in patients with IDA however standardization of the test was difficult. (7-9)

Hepcidin is a hepatic protein that is found to be raised in patients with ACD and reduced in IDA. Inflammatory cytokines are the most important triggers for hepcidin production. Hepcidin affects iron homeostasis by inhibition of a divalent iron transporter protein-1, that in turn hinders enteral iron absorption; and blocking a ferroprotin that inhibits release of iron from iron stores. Both cause sideropenia and raised iron levels in the reticulo-endothelial tissues. (9,10)

Splenomegaly was reported in patients with SAs; in IDA splenomegaly was described with Paterson-Kelly syndrome, and hypopituitarism whereas in ACD it is a diagnostic feature of the underlying disease. The classic triad of Paterson-Kelly syndrome is retropharyngeal dysphagia, eosophageal web, and iron deficiency anemia. (11-14)

This study was conducted to evaluate the frequency, and clinical significance (diagnostic/prognostic) of splenomegaly in patients with SAs, also to assess the association between different grades of splenomegaly and both clinical and hematological profiles of patients.

2. Materials and Methods

2.1. Study design and subjects

A prospective longitudinal study was conducted at the Department of Internal Medicine, Assiut University Hospital over a period of 6 months. Three groups of patients were enrolled in the study, patients with IDA patients with ACD, and another group of gender and age matched healthy volunteers was included as controls. Patients were recruited among those who were admitted or attending the outpatient clinics of Internal Medicine Department, while controls were among students, staff and co-workers. Consent of patients and controls were obtained before enrollment in the study. However, as mentioned before, splenomegaly in ACD is related to the underlying etiology, accordingly the study focused on patients with IDA. Hence the study participants were grouped into three groups 1: patients with IDA, group 2: sideropenic control (patients with ACD), and group 3: normal controls.

2.2. Methods

2.2.1. Data collection

Demographic and clinical data of the study groups were obtained through detailed medical history and clinical examination, with particular stress on dietary habits and nutritional history, also detailed menstrual history was obtained in females. Hematological profiles were obtained from results of laboratory investigations.

Patients with splenomegaly were asked for regular follow up at the outpatient clinic every 2-weeks, in each follow up visit patients' splenic sizes were reassessed clinically together with laboratory assessment of anemia.

2.2.2. Diagnosis of SAs in the study groups

Diagnosis of SAs was accomplished by presence of general symptoms and signs suggestive of anemia. Specific signs such as smooth tongue, flattened nails, angular cheilitis, and koilonychias were suggestive of IDA. (15) Presence of chronic infection, inflammation, or malignancy was suggestive of ACD. Diagnosis of SAs was ascertained by laboratory detection of blood hemoglobin level < 11.8 gm/dl in females and < 13.8 gm/dl in males.

Hematologically, presence of microcytosis (MCV< 80 fl0, hypochromia (MCHC< 32 gm/dl), sideropenia (serum iron < 50 mcg/dl) and impaired reticulocytic response to anemia were diagnostic of SAs in the study subjects. Normocytic, normochromic anemia and reduced TIBC were diagnostic of ACD, while raised TIBC were present in IDA. Blood film with target cells or pencil shaped poikilocytes was highly suggestive of IDA. Patients with dimorphic blood film were excluded from the study.

In patients with microcytic hypochromic anemia and splenomegaly hemoglobin electrophoresis was performed to exclude thalassemia minor or trait. Bone marrow aspirate was performed in selected cases to exclude hypersplenism and differentiate IDA from ACD. In presence of reticulocytosis direct antiglobulin test was done.

2.2.3. Diagnosis of the etiology of SAs in the study patients

Various laboratory, radiological and histopathological investigations were performed in a trial to verify the underlying etiology of SAs in the study groups. These included thorough nutritional history, stool and urine analyses, ESR, C-reactive protein, KFT and LFT. Abdominal or pelvic ultrasound, upper or lower endoscope were also performed as indicated.

2.2.4. Assessment of splenomegaly in patients with sideropenic anemias

Splenomegaly was assessed in the study groups by thorough clinical history and examination. On detailed clinical examination splenomegaly was considered by detection of dull Traube's area or palpable spleen either in supine or Rt. Lateral positions. In our practice clinical examination of patients attending the outpatient clinics or admitted in the ward usually takes place early in the morning before patients have their breakfast, however some of the patients had their breakfast before examination. All patients were examined by the hematology resident in charge, before the researcher. Grading of splenomegaly was mainly based on the WHO proven Hackett's clinical grading as following. (16)

Class 0: Impalpable spleen,

Class 1: Just palpable spleen only with deep inspiration.

Class 2: Palpable spleen but not below a horizontal line passing half way between the costal margin and umbilicus.

Class 3: Palpable spleen but not below a horizontal line passing through the umbilicus.

Class 4: Palpable spleen but not below a horizontal line between the umbilicus and pubic symphysis.

Class 5: Palpable spleen beyond class (4).

Splenomegaly was diagnosed mild, moderate or massive if it is Hackett's class 1&2, 3, 4&5, respectively.

Confirmation of presence or absence of splenomegaly was done with the least hazardous radiographic assessment tool, abdominal U/S.

Abdominal US was performed using an Ultrasound System (GE, LOGIQ 3 Color Doppler) for all patients using 3.5-5.0MHz convex transducer. The splenic size was measured (in cm) with the probe in the left upper quadrant. The largest superior- inferior dimension of the spleen was identified and measured. US scoring system was by evaluating the edge, surface and parenchymal texture of the spleen. Score 0 means normal and score 2 means Splenomegaly, that was defined as an anteroposterior dimension >13 cm, without any abnormality of the structure. (17)

2.2.5. Treatment of the study groups

Treatment of SAs included treatment of the underlying etiology of SA; those with IDA received ferrous fumarate tablets 200 mg Tds immediately after meals together with vitamin C supplementation and were advised regarding consuming iron rich diets. In ACD erythropoietin and iron supplementation were provided. Intravenous iron and packed RBCs transfusions were used to treat those with severe anemia and those intolerant to oral iron supplements. (18-22) Anemia was considered mild if Hb>10g/dl, moderate if Hb7-10g/dl and severe if Hb<7g/dl.

2.2.6. Follow up for the study groups

Patients with evident splenomegaly were asked for regular follow up at the Hematology outpatient clinic firstly after 10-days and then every two weeks until hemoglobin reached near normal values within 2-3 months. In the first visit assessment of response to treatment was evaluated by the rising reticulocyte count. In each visit patients were re-assessed clinically, and with laboratory investigations. Abdominal U/S was repeated in the last follow up visit. Data were recorded in a hand written follow up file available at the clinic for each patient. Patients with IDA were advised to continue treatment for 6 months after hemoglobin reached normal values to replenish iron stores.

2.2.7. Ethical considerations

The study aims and methodology were discussed with patients and controls; furthermore they were consistent with the World Medical Association (WMA) declaration of Helsinki for ethics in medical research. (23) Consent for participation in the study was obtained from both patients and controls. Patients were asked to feel free to withdraw from the study at any time.

2.2.8. Statistical analysis

Data were collected then introduced into a personal computer substituting patients' names with code numbers. The collected data were analyzed with Graphpad Prism V5, Italy and SPSS V. 17 software (SPSS Inc. Chicago, TL, USA). Quantitative variables were expressed as mean ±SD, median, and range while qualitative variables were expressed as percentages from the total number. The one-way ANOVA and Tukey's multiple comparison tests were used to compare means while the chi-square test was used to analyze differences among qualitative variables among the study groups.

3. Results

3.1. Characteristics of the study population

3.1.1. Demographic and clinical characteristics of the study groups

A total of 108 participants were included in the study. Among these 53 were with IDA (group 1), 30 sideropenic controls (group 2) and 25 healthy controls (group 3), the means of their ages were 30.89±13.39, 31.21± 15.15 and 31.01± 14.01 respectively, P=0.912. Gender analysis showed female predominance in the study patients with male to female ratio 1:1.1 in IDA and 1: 1.5 in sideropenic controls. The vast majority of the study participants were from Assiut governorate, 56.5%. Due to perfect matching there were no significant differences in age, gender and residential distribution among the study groups. SAs were commoner in rural residents compared with urban residents (59.3% vs 39.8 %). 47.2% of patients with IDA were singles while 83.3% of sideropenic controls were parents. IDA was commoner in students and housewives, 28.3% and 26.4% respectively.

The most common presenting complaints were dizziness in those with IDA (98.2%), while non hematological manifestations were commoner in sideropenic controls (60%). One patient with IDA (1.8%) presented with delayed puberty. More than two thirds (69.8%) of group 1 patients were excessive drinkers of tea vs 50% and 36% in groups 2&3, respectively. Malnutrition was documented in 22.6% and 20% of groups 1&2 patients respectively. Specific features of IDA as angular stomatitis and koilonychia were present in 45.3% and 32.1%, of group 1, respectively. 3.8 % of patients of groups 1 or 2 had hepatomegaly. Table 1 shows demographic and clinical characteristics of the study groups.

3.1.2. Hematologic and disease characteristics of the study groups

Expectedly, hypochromia, microcytosis, thrombocytosis and raised TIBC were present in group 1 patients. On the contrary normocytic normochromic anemia with decreased TIBC and raised ESR and C-reactive protein were the most common features of group 2. Sideropenia was the unique feature of all the study patients. There was no significant difference in WBCs count among the study groups. There were significant differences in Hb, Plts, MCV S .iron and TIBC between group 1 patients and the controls. Group 2 differences were significant in Hb, retic., S.iron, TIBC, ESR and C-reactive protein as depicted in tables 2 & 3. 47.2%, 52.8% and 0 % of group 1 patients had severe, moderate and mild anemia, vs 13.3%, 80%, and 6.7% in group 2 respectively. Interestingly mild anemia was detected in 20% of the healthy controls with a minimum hemoglobin level of 11.5g/dl as in Table 4.

3.2. Underlying etiology of sideropenic anemia in the study patients

The most prevalent causes of IDA were menorrhagia, hemophilia, unknown etiology and occult bleeding while those for ACD were CRF, rheumatoid arthritis, malignancy and systemic lupus erythematosus in descending order. Benzidine test was positive in 9.4 % of patients with IDA denoting occult blood in stools as in figure 1.

3.3. Splenomegaly in patients with IDA compared with the sideropenic and healthy control subjects

Splenomegaly was present in 11.3%, 40 % and 0 % of groups 1, 2 & 3, respectively. In IDA half most of the patients had Hackett's G1 (9.4%) and only 1.9% had G2, also in ACD G1 comprised 33.3% followed by grade 0 (16.7%) and lastly grade 2 (6.7%). However splenomegaly was sonographically proven only in 5-patients of group 1 (9.4%), and 10 patients in group 2 (33.3%). Table 1 shows distribution of splenomegaly in the study groups, and Table 5 shows diagnostic performance of US variables in predicting splenomegaly among groups 1 & 2.

Splenomegaly in patients with IDA was commoner in males 4(80%) and rare in those from urban community (20%). Their medical history denoted insufficient dietary intake of iron, and they had pica and malnutrition. They were excessive drinkers of tea (100%) with angular stomatitis (80%), and koilonychias (100%). Hepatomegaly was associated with splenomegaly in 0 % & 90% of patients of IDA and sideropenic controls, respectively.

When we correlated hematological parameters with grading of splenomegaly in patients with IDA they were negatively associated with HB, MCV, and reticulocytes, and all patients had severe anemia (Hb ranged from 3.2-6 g/dl). Table 6 showed factors associated with splenomegaly in patients with IDA.

The stool analyses showed Giardia lamblia cysts in 2-patients with IDA and splenomegaly, hookworm ova in 1 patient and occult bleeding in 1 patient. The possible etiology of IDA in the other patient was unknown, however the defective dietary intake of iron was marked in all patients and was continuous for many years.

Follow up of patients with SAs and splenomegaly after treatment revealed gradual progressive reduction of splenic size with increase in hemoglobin. After 3-months follow up spleen was nearly impalpable in those with grade 1 Hackett's however dullness at Traube's area was still detected in patients with grade 2. Splenomegaly was still sonographically detected in 2 patients. These findings were noted in patients with IDA (group 1). On the contrary splenic size remained stable in the sideropenic control patients (group 2).

Table 1. Demographic and clinical characteristics of the study groups (total n = 108).

Variable	Group 1 (n = 53)	Group 2 (n = 30)	Group 3 (n =25)	P value
Demographics				
-Age				
Mean ±SD	30.89±13.39	31.21± 15.15	31.01± 14.01	0.912
- Gender				
Male	25(47.2%)	12 (40%)	11 (44%)	0.818
Female	28 (52.8%)	18 (60%)	14 (56 %)	
- Residence				
Urban	16(30.2%)	17 (56.6%)	11 (44%)	0.105
Rural	37(69.8%	13 (43.4%)	14 (56%)	
-Governorate				
Assiut	37 (69.8%)	13 (43.3%)	11 (44%)	
Qena	3(5.7%)	11 (36.7%)	2 (8%)	
Sohag	0 (0%)	6 (20%)	0 (0%)	0.000**
Luxor	5 (9.4%)	0 (0%)	8 (32%)	
Al Menia	6 (11.3%)	0 (0%)	0 (0%)	
Aswan	2(3.8%)	0 (0%)	4(16%)	
-Occupation				
Housewife	14 (26.4%)	9 (30.0%)	0(0%)	
Farmer	9(17%)	2(6.7%)	0(0%)	0.000**
Employed	9 (17%)	10 (33.3%)	16 (32.4%)	
Unemployed	6(11.3%)	0(0%)	0(0%)	
Student	15 (28.3%)	4 (13.3%)	9 (36%)	
Retired	0(0%)	5(16.7%)	0(0%)	
- Family				
Married	8 (15.1%)	4 (13.3%)	3 (12%)	0.001*
Parent	20(37.7%)	25(83.3%)	14(56%)	
Single	25 (47.2%)	1 (3.3%)	8 (32%)	
Main complaint				
- Pallor , dizziness	52 (98.2%)	5 (16.7%)	0 (0%)	
- Repeated vomiting	0 (0%)	7 (23.3%)	0 (0%)	0.000**
- Non-hematological	1 (1.8%)	18 (60%)	0 (0%)	
- Asymptomatic	0 (0%)	0 (0%)	25(100%)	
Nutritional history				
- Drinking tea				
Excessive	37(69.8%)	15(50%)	9(36%)	0.013
Mild	16(30.2%)	15(50%)	16(64%)	
- Malnutrition				
Not present	41(77.4%)	24(80%)	0 (0%)	0.037
Documented	12(22.6%)	6(20%)	0 (0%)	
Signs				
- Pallor	53 (100%)	28 (93.3%)	0 (0%)	
- Angular cheilitis	24 (45.3%)	2 (6.7%)	0 (0%)	0.000**
- Koilonychia	17 (32.1%)	0 (0%)	0 (0%)	
-Liver				
Impalpable	53(100%)	17(56.7%)	25(100%)	0.000**
Hepatomegaly	0(0%)	13(43.3%)	0 (0%)	
-Spleen				
No Splenomegaly	47 (88.7%)	18 (60%)	25(100%)	
Grade 0	0 (0%)	6 (20%)	0 (0%)	0.000**
Grade 1	5 (9.4%)	6 (20%)	0 (0%)	
Grade 2	1 (1.9%)	0 (0%)	0 (0%)	
- Ultrasound score				
Score 0	48(90.5%)	20(66.7%)	25(100%)	0.000*
Score 1	5(9.4%)	10(33.3%)	0 (0%)	

Data were presented as mean± SD, or as percentage from the total number.

Table 2: Laboratory and hematologic characteristics of the study groups (total no = 108)

Parameter	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
				Lower Bound	Upper Bound		
WBCs x10³/dl Group 1	6.27	2.576	.354	5.56	6.98	3	12
- Group 2	8.55	3.281	.599	7.32	9.78	4	15
- Group 3	7.32	2.824	.565	6.15	8.49	4	12
Hb(g/dl) -Group 1	7.579	2.0649	.2836	7.010	8.148	3.2	10.0
- Group 2	8.387	1.2412	.2266	7.923	8.850	6.5	11.0
- Group 3	12.63	1.0319	.2064	12.206	13.058	11.5	14.5
Plts x10³/dl -Group 1	447.1	193.356	26.559	393.84	500.43	210	923
- Group 2	279.6	79.079	14.438	250.10	309.16	155	400
- Group 3	227.2	59.636	11.927	202.62	251.86	165	380
MCV(FL) -Group 1	67.38	10.367	1.424	64.52	70.23	44	78
- Group 2	86.33	4.943	.903	84.49	88.18	77	94
- Group 3	86.04	4.087	.817	84.35	87.73	76	92
Retic(%) -Group 1	1.840	1.0454	.1436	1.551	2.128	.7	3.8
- Group 2	.950	.5625	.1027	.740	1.160	.2	2.0
- Group 3	1.728	.3221	.0644	1.595	1.861	.8	2.5
S. iron Group1	24.68	1.554	.213	24.25	25.11	22	28
- Group 2	28.80	4.838	.883	26.99	30.61	22	40
- Group 3	97.52	22.664	4.533	88.16	106.88	50	135
TIBC(mcg/dl) -Group 1	389.2	41.963	5.764	377.70	400.83	300	480
- Group 2	210.2	46.024	8.403	193.01	227.39	13	280
- Group 3	319.8	42.346	8.644	301.99	337.76	230	380
Duration of SA(ms)							
-Group 1	5.25	7.746	1.064	3.11	7.38	1	36
- Group 2	5.97	1.771	.323	5.31	6.63	2	9
- Group 3	.00	.000	.000	.00	.00	0	0
ESR-Group 1	22.17	6.345	.872	20.42	23.92	13	36
- Group 2	84.70	38.896	7.101	70.18	99.22	27	135
- Group 3	11.44	3.743	.749	9.90	12.98	5	18
C reactive P.							
-Group 1	1.950	3.1043	.4264	1.094	2.805	.0	11.0
- Group 2	23.33	5.8329	1.0649	21.155	25.511	13.0	34.0
- Group 3	1.752	2.4324	.4865	.748	2.756	.0	8.0

N.B. WBCs= white blood cells, Hb= hemoglobin, MCV= mean corpuscular volume, Plt= platelet, Retic= reticulocyte count, ESR= erythrocytic sedimentation rate, C reactive P= C reactive protein. Duration of anemia in months. Data were presented as mean± SD. P value was significant at 0.05 level.

Table 3: Tukey multiple comparison test of quantitative variables of patients with SAs compared with the controls (total no=108)

Table 3. Tukey multiple comparison test of quantitative variables of patients with SAs compared with the controls (total no=108).

Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
WBCs $x10^3$/dl	group 3	group 1	1.050	.690	.285	-.59	2.69
		group 2	-1.230	.770	.251	-3.06	.60
Hb mg/dl	group 3	group 1	5.0528*	.4046	.000	4.091	6.015
		group 2	4.2453*	.4516	.000	3.172	5.319
Plts $x10^3$/dl	group 3	group 1	-219.892*	35.206	.000	-303.59	-136.19
		group 2	-52.393	39.294	.380	-145.81	41.03
MCV FL	group 3	group 1	18.663*	1.938	.000	14.06	23.27
		group 2	-.293	2.163	.990	-5.44	4.85
Retic%	group 3	group 1	-.1116	.1960	.837	-.577	.354
		group 2	.7780*	.2187	.002	.258	1.298
S.iron mcg/dl	group 3	group 1	72.841*	2.713	.000	66.39	79.29
		group 2	68.720*	3.029	.000	61.52	75.92
TIBC mcg/dl	group 3	group 1	-69.389*	10.633	.000	-94.67	-44.11
		group 2	109.675*	11.835	.000	81.53	137.82
Duration of SA(ms)	group 3	group 1	-5.245*	1.342	.000	-8.44	-2.06
		group 2	-5.967*	1.497	.000	-9.53	-2.41
ESR mm/hr	group 3	group 1	-10.730	5.095	.094	-22.84	1.38
		group 2	-73.260*	5.687	.000	-86.78	-59.74
C-reactive protein	group 3	group 1	-.1976	.9559	.977	-2.470	2.075
mg/dl		group 2	-21.5813*	1.0669	.000	-24.118	-19.045

*. The mean difference was significant at 0.05 level.

N.B. WBCs= white blood cells x103, Hb= hemoglobin g/dl , MCV= mean corpuscular volume FL, Plts= platelets x103, Retic= reticulocyte count%, ESR= erythrocytic sedimentation rate mm/hr, C reactive P= C reactive protein mg/dl , TIBC= total iron binding capacity mcg/dl, S. iron= serum iron.

Table 4: Degree and treatment modalities of SAs in the study patients (total n = 83)

Variable	Group 1(n = 53)	Group 2 (n = 30)	P value
Degree of anemia			
- Non anemic	0 (0%)	0 (0%)	0.000**
-Mild	0 (0%)	2 (6.7%)	
- Moderate	28 (52.8%)	24 (80%)	
- Severe	25(47.2%)	4 (13.3%)	
Treatment			
- No ttt	0 (0%)	9(30%)	0.000**
- Parenteral iron	11 (20.8%)	0 (0%)	
- Oral iron	40(75.5%)	8(26.7%)	
- Blood transfusion	2(3.8%)	5(16.7%)	
- Oral iron+ erythropoietin	0 (0%)	8(26.7%)	

Table 5: Diagnostic performance of US variables in predicting splenomegaly among groups 1&2

Splenomegaly**	sensitivity (95% CI)	Specificity (95% CI)	positive predictive value (95% CI)	negative predictive value (95% CI)	P value
Group1 (n=53)	83.33%(0.364,0.991)	95.74%(0.843.,0.993)	71.43%(0.302,0.948)	97.82%(0.870,0.998)	0.48
Group2 (n=30)	83.33%(0.509,0.970)	100%(0.0781,1)	100%(0.655,1)	90%(0.668,0.982)	

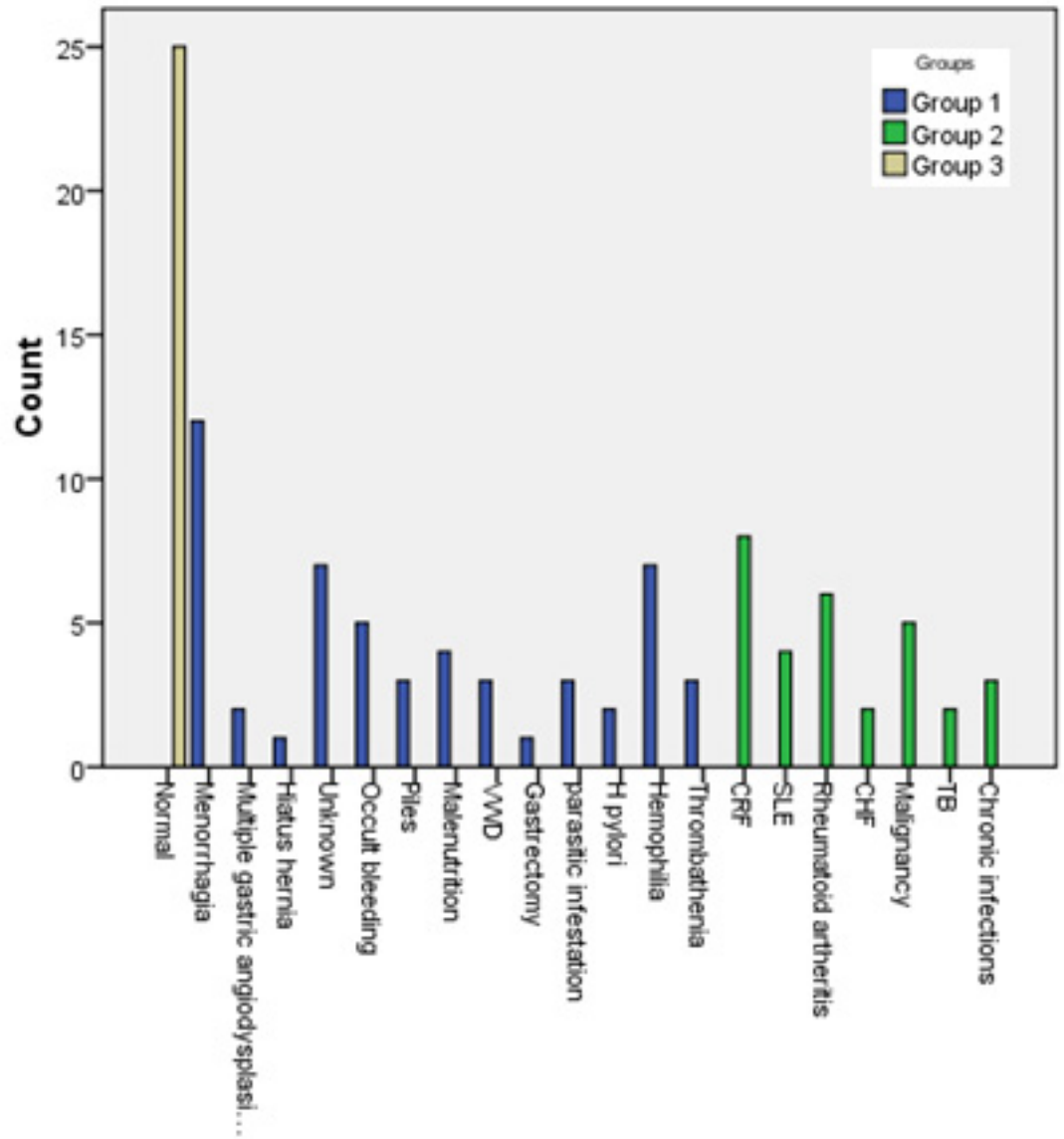
*P value <0.05 , ** No splenomegaly found in group 3.

Table 6: Factors associated with splenomegaly in patients with IDA (total no = 53)

Variable	No splenomegaly 48 (90.6%)	Splenomegaly 5 (9.4%)	P value
- Gender			
Male	21(43.7%)	4(80%)	0.060
Female	27(56.3%)	1 (20%)	
- Residence			
Urban	15(31.2%)	1 (20%)	0.595
Rural	33(68.8%)	4(80%)	
Nutritional history			
- Drinking tea	32(66.7%)	5(100%)	0.405
Excessive	16(33.3%)	0(0%)	
Mild			
Malnutrition			0.000**
Not present	41(85.4%)	0(0%)	
Documented	7(14.6%)	5(100%)	
Signs			
- Angular cheilitis			0.060
Present	20(41.7%)	4(80%)	
Absent	28(58.3%)	1(20%)	
- Koilonychias			0.000**
Present	11(22.9%)	5(100%)	
Absent	37(77.1%)	0(0%)	
-Liver			0.000**
Impalpable	53(100%)	5(100%)	
Hepatomegaly	0(0%)	0(0%)	
Degree of anemia			
-Mild	0(0%)	0(0%)	0.000**
- Moderate	28(58.3%)	0(0%)	
- Severe	20(41.7%)	5(100%)	

N.B. P value was significant at 0.05 level.

Figure 1: Causes of sideropenic anemias in the study patients



4. Discussion

SAs are hypoproliferative anemias that are caused by iron deficiency and/or decreased erythropoietin (EPO) production and/or reduced response to EPO, the latter due to resistance of target cells to EPO action or reduced number of cells. (24) This study was conducted to elucidate splenomegaly in patients with SAs in terms of occurrence, clinical and hematological profile and the effect of treatment on splenomegaly. The study focused on IDA while ACD was used as a sideropenic control.

In this study SAs were commoner in females; IDA was more prevalent in rural residence while urbanization was obvious in sideropenic controls. Furthermore IDA was commoner in students and housewives while ACD in those who did regular office work. These expected results were explained by increased prevalence of iron deficiency and chronic inflammatory diseases in females and higher number of vegans in rural communities. (25, 26)

This study confirmed a direct relationship between excessive intake of tea and incidence of IDA. A common custom in Egypt is to drink nearly 2gms/250 mls of red tea right after each meal particularly after lunch. Numerous studies reported that tea hinders iron absorption and advise tea drinkers to have their cups at least 1 hour after a meal. (27-29)

Manifestations of tissue iron deficiency were much higher than that in comparable studies; this could be explained by the longer duration of iron deficiency in our patients. However results of this study were accordant with others in showing positive association between the degree of tissue iron deficiency and severity of IDA besides revealing that angular cheilitis was more prevalent than koilonychias. Both angular cheilitis and koilonychias were explained by deficiency of iron based enzymes in the mucosal and epithelial tissues. (30,31)

In accordance with other studies, reduced Hb, MCV, MCHC, and thrombocytosis were the CBC features of IDA; on the contrary normocytosis and normochromia were evident in sideropenic controls. (32) An interesting finding was laboratory detection of mild anemia in asymptomatic controls with the

minimum hemoglobin 11.5g/dl in females. This finding denoted that the lower cut of value of hemoglobin should be tailored for each population specifically.

In this study the most common etiology of IDA was menorrhagia while chronic renal failure was the commonest cause of ACD. This study confirmed the findings of others that IDA could retard growth and development in children and also reaffirmed that gastrointestinal tract blood loss and H-pylori infections are common causes of IDA. As reported by others, hiatus hernia was the underlying etiology of IDA in one of our patients. (33-36) Although the recommended daily requirements of iron are very small, IDA due to ineffective dietary intake was noted in our patients. This could be explained by most of them being from a rural community. Accordingly the main elements of their diets were, milk and milk products, fruits and vegetables; both are poor sources of iron.

Splenomegaly was detected in approximately one tenth of patients with IDA; this was albeit consistent and inconsistent with other studies. Unlike other studies there was no detectable splenomegaly in the control group. (37-39)

When considering the sideropenic control group splenomegaly was detected in more than half of the patients and was closely related to the underlying etiology of anemia, furthermore hepatosplenomegaly was evident in a considerable proportion of patients. However there was no association between the degree of anemia and Hackett's grading of splenomegaly in the sideropenic control group. As reported by others, treatment of the underlying etiology of anemia improved hematological profile of the patient, (18,40,41) however it did not affect splenic size. This denoted that the etiopathogenesis of splenomegaly in the sideropenic controls is not related to the anemia itself.

In this study patients with IDA and splenomegaly were mostly from a rural community and the vast majority of them were males in their late teens or early twenties. Their nutritional history denoted ineffective dietary supply of iron and pica. Parasitic infestation was detected in 3 of the patients. They were suffering from IDA for years, with periods of interrupted iron supplementation. Concomitant with other studies splenomegaly was impalpable or mild to moderate (Hackett's grades 1 & 2) in most of the patients. Furthermore the degree of splenomegaly was positively correlated with the severity of anemia. This was consistent with Hussain et al and inconsistent with Dabadghao and his coworkers. (14, 42,43) Notably this study showed reduction in splenic size with correction of hemoglobin. Another important finding was the strong association between splenomegaly and kioilonychia in patients with IDA; kioilonychia is a sign of severe long standing IDA.(30) Expectedly the degree of splenomegaly will be directly correlated with both the severity and duration of IDA; this assumption was proved with the results of the current study.

The etiopathogenesis of splenomegaly in patients with IDA is still unclear. However the most acceptable explanation is that IDA is a hypoproliferative anemia with poikilocytosis and anisocytosis both leading to splenic hyperplasia. Another explanation is extramedullary hematopoiesis. This could in turn explains the rare association of hepatomegaly and splenomegaly in patients with IDA. The latter assumption could explain the association of splenomegaly with duration and severity of IDA, furthermore it explained resolution of splenomegaly with correction of ID. Although malnutrition was detected in our patients it could not explain the occurrence of splenomegaly in IDA as it was a micronutrient malnutrition rather than a protein energy malnutrition.(44) However the presence of giardiasis in 2 of our patients could be a contributing factor for development of splenomegaly in them. (25)

5. Conclusion

In conclusion the current study demonstrated that splenomegaly had considerable clinicohematologic significance in patients with SAs. Hackett's grade 1, or 2 splenomegaly was a common finding in patients with severe, chronic IDA that was mainly caused by malnutrition. Furthermore iron supplementation and replenishment of iron stores led to gradual resolution of splenomegaly. This denoted that splenomegaly, in patients with IDA, is a very simple clinically based diagnostic/prognostic index. However every effort has to be made to exclude thalassemia in patients with microcytic hypochromic anemia and splenomegaly before prescribing iron supplementation. This was not the case in patients with ACD where splenomegaly was found to be related to the underlying etiology of anemia rather than the anemia itself.

Based on the findings of this study we recommended reducing tea drinking particularly in children and females who are already in a state of negative iron balance due to increased demands. Furthermore we advise people to avoid drinking tea after the main meal where a great proportion of iron requirements are supplied.

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