Clinical and laboratory parameters associated with anemia in Rheumatoid Arthritis Patients.

Quteiba Nuseir MD, Faraj Al-Hzymeh* MD, Ra'ed Jaradat **MD, Mohammad Al Bakhit** MD, Mohammad Obeidat***MD.*

ABSTRACT

Objective: To describe the causes of anemia associated with Rheumatoid Arthritis and to assess the relationship of anemia with a set of parameters covering clinical and serological status.

Methods: This is a retrospective study from January 2016 to June 2016. Adult patients diagnosed with Rheumatoid Arthritis (RA), who were treated in outpatient department at both Rheumatology/Rehabilitation and General Medicine clinics at Prince Rashid hospital in Irbid – Jordan, were included. The collected data of study were gender, age at diagnosis, duration of disease, level of disease activity, medication history and lab investigations (including full hematologic indices, Chemistry, and serological markers for rheumatoid arthritis). In anemic patient's further investigation were done to reveal the cause and type of anemia. The WHO definition of anemia was used.

Results: A total of 87 patients with RA were included in the study, 72(82.75%) were females and 15(17.25%) were males with a ratio of (5:1).The average duration of disease before the beginning of our study was 11 years. The mean value for the Disease Activity Score 28 (DAS28) was 4.2 ± 1.64 which puts most patients in the moderate to severe group of disease activity. patients had mean hemoglobin level of 11.67 (SD±1.8 g/dl) with females having a mean haemoglobin of 11.4 (SD±1.58 g/dl), and 12.86(SD ±2.38 g/dl) in males. The prevalence of anemia was 56% (49 patients). Anemia among female patients were more frequent than in male patients (61% vs. 33%, p=0.04). Characteristics of anemic patients were: being female, having longer history of the disease, higher number of disease modifying anti-rheumatic drugs use, Lower B12 level and higher Disease Activity Score . The mean ESR, CRP, Creatinine levels were significantly increased in the anemic when compared with the non-anemic group.

Conclusion: Anemia in RA has many causes and complete evaluation is necessary for diagnosis and therapeutic management. Treatable causes were commonly identified. Our study clearly illustrates that more than half of patients with RA had anemia and anemia of chronic diseases (ACD) was the most common type. It is also concluded that patients with anemia tend to have more severe disease than patients without anemia.

Keywords: Anemia, Disease activity, Inflammation, Rheumatoid arthritis.

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Introduction

Rheumatoid arthritis (RA) is the most common inflammatory arthritis; it affects nearly 1% of population worldwide.[(1)] The natural history of RA is chronic symmetrical synovitis which mostly affects the small joints of hands and feet that ultimately leads to joint destruction, deformity and loss of function.[(2)] There are many extra articular manifestations (EAM) in RA that carry a negative impact to patients and are associated with greater morbidity and premature death.[(3)] Anemia in rheumatoid arthritis is the most common extraarticular feature, being

From the department of:
*Medicine, King Hussein Medical Center
**Rheumatology and Rehabilitation. King Hussein Medical Center
*** Medicine/Hematology and Oncology. King Hussein Medical Center
Correspondence should be addressed to Dr Qutaiba Nusseir: E-mail: qutaiba@hotmail.com
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perceived to reflect the degree of systemic inflammation. It develops in 30-70% of patients. [4] Anemia of chronic disease (ACD); also termed "anemia of inflammation" (AI) is the most common type of anemia in RA as documented in many studies [5]. A range of factors play an important role in the pathogenesis of ACD like Shortened red blood cell life span, impaired reticuloendothelial iron release and increased production of inflammatory cytokines (e.g., tumor necrosis factor) that lead to decrease in erythropoietin response in the bone marrow, thus leading to inadequate erythropoiesis.[6] Other types of anemia documented in RA are iron deficiency anemia secondary to gastrointestinal blood loss associated with the use of nonsteroidal anti-inflammatory agents, megaloblastic anemia, hemolytic anemia, myelodysplastic syndrome or anemia induced by medications such as methotrexate.[7] Rheumatoid anemia is usually mild to moderate, normochromic,normocytic or, less often, microcytic, and aregenerative (no increase in circulating reticulocytes).[6] The objective of this study is to describe the causes of anemia associated with RA and to assess the relationship of anemia with a set of parameters covering clinical and serological status.

Methods

This is a retrospective study from January 2016 to June 2016 of patients with RA who was treated in outpatient department at both Rheumatology/Rehabilitation and General Medicine clinics at Prince Rashid hospital in Irbid –Jordan. A total of 87 adult patients diagnosed with RA according to 1987 American College of Rheumatology (ACR) criteria for RA were included [8]. Patients were excluded if they were diagnosed of overlap syndrome with other rheumatic diseases. The collected data of study were gender, age at diagnosis, duration of disease, the level of disease activity measured by the Disease Activity Score 28(DAS28) which is calculated by counting the number of tender joints upon touching and number of swollen joints in addition to Erythrocyte Sedimentation Rate (ESR). It is not a simple formula and is calculated using an online web calculator. [9] DAS28 values range from 2.0 to 10.0. A DAS28 value >5.1 corresponds to a high disease activity and A DAS28 value < 2.6 corresponds to remission and between these two values it corresponds to mild and moderate if it is below or above 3.2 respectively. [10] Medication history included NSAIDs, Steroids, and Methotrexate with or without folic acid supplementation and other synthetic disease modifying anti-rheumatic drugs (DMARDs). Medical history included malignancy, renal failure, hemolytic anemia, blood loss, (GI bleeding, hemorrhoids and menorrhagia). Lab investigations included: Full hematologic indices that include (Hemoglobin level, PCV, WBC, PLT, MCV, MCH, MCHC) measured electronically by the SYSMEX hemotology analyzer (Sysmex XE-2100™) (Sysmex, Kobe, Japan). Kidey function test (KFT), liver function test (LFT) were measured by separation of serum by centrifugation at 3300 xg for 15 minutes and tested with chemistry analyser (Cobas C501) (Roche Diagnostics, Basel, Switzerland). C-reactive protein (CRP), Anti-Cyclic Citrullinated Peptide Antibody (ACPA), Rheumatoid Factor (RF) and ESR were measured and documented for all patients. In anemic patient's further investigation were done to reveal the cause and type of anemia :Blood film with May-Grünwald-Giemsa staining. Ferritin, B12, Folate, test were measured via immunoassay technology (Roche Diagnostics, Basel, Switzerland) Normal values are 220–1,300 ng/L for B12, 3–17 mg/ml for folate and 14–150 ng/ml for ferritin.Bone marrow aspirate and biopsy in patients with suspicion of bone marrow disease and Coombs test to rule out hemolysis.Follow up of patient was done at both clinics every one to four weeks after the start of our study to assess the cause of anemia till the end of our study. The World Health Organization (WHO) criteria was used to define anemia with hemoglobin threshold of <130 g/L for men and <120 g/L for women . [11] IDA diagnosis was made when they present with low Hb (men < 13 g/dL and women < 12 g/dL) and ferritin concentrations (< 30 ng/mL).In the presence of intermediate serum ferritin concentration (30–100 ng/ml), confirmation of IDA will be given by microcytosis (mean corpuscular volume (MCV) <80 fl). ACD was diagnosed by exclusion of other causes of anemia. The study was approved by the ethical committee of Royal Medical Services. Statistical Analysis: The statistics was done using SPSS 21 software

describing the frequency and mean ± SD. Correlation was done using Pearson's correlation test. Results were statistically significant at $p < 0.05$. Chi-square was used to determine significance among the study variables.

Results

A total of 87 patients with RA were included in the study, 78 patients from Rheumatology/Rehabilitation clinic and 9 patients from general medicine clinic. 72(82.75%) were females and 15(17.25%) were males with a ratio of (5:1). the mean age was 47.2 years (range 18 to 80 years) with a peak between 40 and 45 years of age. In females, the mean age was 44 years while in males it was 47.7. Fifty percent of the participants were under 46 years of age. The average duration of disease before the beginning of our study was 11 years; from 0 years (diagnosed at the time of enrolment) to a maximum of 45 years.) 50% of patients had the disease for more than 9 years. More details about patients' characteristics, serological values and medications are shown in Table I. The mean value for the DAS28 score was 4.2 ± 1.64. According to DAS-28, 75.8% were in the moderate and high disease activity category, 21.8 % in low activity and only 2.3% were in remission. Patients had mean hemoglobin level of 11.67 (SD±1.8 g/dl). In females, the mean hemoglobin was 11.4 (SD±1.58 g/dl), and 12.86(SD ±2.38 g/dl) in males. The prevalence of anemia was 56% (49 patients). Anemia among female patients were more frequent than in male patients (61% vs. 33%, p=0.04). The mean hemoglobin concentration in anemic patient was 10.27. Severe anemia which was defined as hemoglobin level less than 8 was seen only in two patients. Out of 49 patients with anemia full anemia work up to diagnose the cause of anemia was done. The frequency of different types of anemia is shown in Table II. Other hematological changes regarding WBC and Platelets that were found in our patients were illustrated in Table III. Comparative results between anemic and non-anemic patients are shown in Table IV. There were no significant differences in mean age of patients, ACPA positivity, types of medications used, WBC, Ferritin and Platelet level between the two groups. Characteristics of anemic patients were: being female, having longer history of the disease, higher number of DMARDs use, Lower B12 level and higher DAS score. The mean ESR, CRP, Creatinine levels were significantly increased in the anemic when compared with non-anemic group.

Table I: patients' characteristics, serological values and medications.

	NO	**%**
Female	72	82.75%
Mean age (range), years	45(18 to 80)	
Male	47.7	
Female	44	
Disease Duration (y)mean	11	
RF positive	63	72.4%
ACPA positive	56	64%
Seropositive disease*	64	74%
CRP mg/dl mean	41	
ESR mean	64	
medications		
DMARDs	87	100%
MTX	48	55.2%
HCQ	22	25.3%
SAZ	1	1.1%
Lefulomide	1	1.1%
MTX,HCQ	4	4.6%
MTX,SAZ	4	4.6%
MTX,SAZ,HCQ	7	8.1%
Oral prednisolon	23	27%
NSAIDs	66	75%

Table II: Frequency and proportion of different types of anemia

	NO	%
ACD	27	55%
IDA	13	26%
Megaloblastic /Macrocytic		8%
B12 deficiency	2	
Hypothyroidism	1	
Chronic Liver disease	1	
Auto immune hemolysis	2	5%
MDS	1	2%
PRCA/Aplastic	1	2%
Acute leukaemia	1	2%
Total	49	100%

Table III: Other hematological changes than anemia documented in patients

	Number
Leucopenia WBC < 3	2
Leucocytosis WBC > 11	12
Thrombocytopenia PLT < 140	9
Thrombocytosis PLT >400	11

Table IV: Comparative results between anemic and non-anemic patients

	Anemic patients	Non-anemic	p.value
Femal ; male	44/5	28/10	p<0.001
Mean age (year) SD	46 (17)	48(11.66)	N/S
Duration of disease in years mean	11.5	10.1	p=0.002
Medications;		25	N/S
MTX	38		N/S
HCQ	18	15	
SAZ	7	5	N/S
Number of DMARDs Mean	1.3	1.21	p<0.05
1	38	35	N/S
2	5	3	N/S
3	6	1	p<0.05
Prednisolone	15	8	N/S
NSAIDs	40	26	N/S
CRP mg/dl mean ±SD	48±12	25±9	p<0.05
ESR mean ±SD	49.5 ±24.2	43,3 ±20,5	p=0.04
RF positivity n (%)	38 (77.6)	25 (65,8)	p<0.05
ACPA positivity n (%)	30 (61%)	26 (68)	N/S
Seropositive disease * n(%)	39(80)	25(65.8)	p<0.05
DAS 28 score mean ± SD	4.46 ± 0.88	3.76 ± 0.51	p<0.05
Hematological features		13,5± 1.8	p<0.01
Hgb g/dl mean ± SD	10.27± 1,9		p<0.01
PCV mean ± SD	32.9 ± 4,3	36.1 ± 4,2	
MCV mean ± SD	80.6 ± 6.6	85,8 ± 4,9	N/S
WBC mean ± SD	7.4 ± 2,3	7.35 ± 1,6	N/S
PLT ± SD	178 ± 45	156 ± 65	N/S
Creatinine mean ± SD	1.3 ± 1,3	1,0 ± 1,0	p<0.03
B 12 ± SD	184 ± 43	246 ± 43	p<0.01
Ferritin	156±56	182±51	N/S

* Any positivity of RF or ACPA

Discussion

Anemia is frequently associated with RA and significant gaps remain in comprehension of the true prevalence or consequences of anemia in patients with RA. [12] A recent review article suggested that anemia is likely going to have serious clinical consequences, regardless of the cause of anemia. [13] In our study, we assessed the prevalence of anemia and its relation with comprehensive set of parameters covering clinical, laboratory and serological values among rheumatoid arthritis patients. The prevalence of anemia among our rheumatoid patients was 56%. It was more frequent in female than in male patients 61% vs. 33% respectively. This prevalence was really varied between studies in the literature [14]. This variability may be

explained by some differences in the definition of anemia in these studies. In a metanalysis done by Wilson A et al, he estimated that the prevalence of anemia ranged between 33% and 60%.[15] Han et al. conducted a study using definition of anemia as a hemoglobin concentration in males of <130.0 g/L and in females of<120.0 g/L. and found a prevalence of anemia in women (39%) and men (32%).[16] In contrast, Ricerca et al. defined mild anemia as a hemoglobin level <120.0 g/L with no provision made for differences between men and women and estimated the prevalence were virtually identical for the 74 male and 60 female patients with RA: 27.0% and 26.7%, respectively.[17] The majority of cases of anemia in Rheumatoid Arthritis can be related to chronic disease or iron deficiency. Distinguishing ACD from iron-deficiency state in the setting of chronic inflammatory process is complex because Serum ferritin which is used for diagnosis of IDA is more difficult to interpret because it is an acute phase reactant and conditions such as chronic inflammatory disorders (including RA) may increase the serum ferritin concentration.[18] Serum level of ferretin less than 30 g/l is considered as an absolute value to define IDA, but In our study we have taken a value of ferretin less than 100 g/l and microcytosis (MCV <80 fl to consider iron deficiency anemia and diagnosis of ACD by exclusion of other causes of anemia validating guidance by Reinisch et al on how to address IDA in patients with Inflamatory bowel disease. [19] According to this criteria, IDA was found in 27% of our anemic patients and ACD was observed in 55%. Similar to our study Peeters et all reported that iron deficiency anemia caused 23% and anemia of chronic disease 67% of observed anemia.[20] Other rare types of anemia found in our study are: Autoimmune hemolytic anemia, Aplastic anemia, Megaloblastic anemia and Myelodysplastic syndrome. The etiology of these types of anemia could be related to chronic inflammatory process in rheumatoid arthritis or side effects of long duration of exposure to drugs especially Methotrexate and Chloroquine. [21] in these rare types of anemia, we documented severe degree of anemia and needed bone marrow biopsy. Patients from anemic group have more active disease than patients from non-anemic group that can be shown by longer duration of history of disease and higher DAS28 score in anemic group. Mean ±SD of DAS 28 in the anemic group was 4.46 ± 0.88 while in non-anemic was 3.76 ± 0.51. The two values put both groups in moderate level of disease activity and that conclude that most of our patients had their RA uncontrolled. Patients with anemia had higher percentage of seropositive disease, higher ESR and CRP level. It is well known that these markers are used in prediction and assessment of prognosis of RA. Higher levels mean more joint destruction, extra-articular diseases and poor quality of life.[22] Our results are similar with a study by Wolfe and colleagues who reported that higher ESR, CRP and RF levels were all predictors of anemia in patients with RA.[23] Almost all patients diagnosed with RA in our clinics were started on DMARDs as a first line treatment and DMARD monotherapy especially with MTX is the regimen chosen by almost all our rheumatologists to initiate treatment. Combination therapy increase the efficacy of treatment in induction of remission in uncontrolled RA. [24] The combination of DMARDs were used more frequently in the anemic group and that conclude that patients with anemia had more uncontrolled disease. Lastly in this study we found a significant association between anemia and elevated creatinine level and low B12 level. We found no significant relationship between anemia and age, other hematological changes (WBCs and platelets) and serum ferritin in our study. A drawback of the study is that it is a retrospective study and the small number of patients as it is a single centre study and done in a short period of time. Biological treatment is not available in our hospital and we did not follow up our anemic patients because our aim was to document the prevalence of anemia and its associated factors not the effect of treatment and it could be the aims of next studies.

Conclusion

This study gives useful clinical and laboratory information in respect to a cohort of RA patients with anemia. Anemia in RA

has many causes and complete evaluation is necessary for diagnosis and therapeutic management. Treatable causes were commonly identified. Our study clearly illustrates that more than half of patients with RA had anemia and ACD was the most common type, thus supporting the statement that more attention should be paid to this complication in our patients with RA. It is also concluded that patients with anemia tend to have more severe disease than patients with anemia.

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