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The Incidence of Anemia in Patients with Rheumatoid Arthritis

Aida Eshmurzaeva[1], Marif Karimov[1], Iskandar Mavlyanov[1], Marina Sibirkina[1], Nigora Tukhtaeva[1] and Bekhzod Abdullaev[2*]

[1]Department of Rheumatology, Tashkent Medical Academy, Tashkent, Uzbekistan.
[2]GP Faculty, Tashkent Medical Academy, Tashkent, Uzbekistan.

Authors' contributions

This work was carried out in collaboration between all authors. Author AE designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors MK and BA managed the literature searches and manuscript editing. Authors IM, NT and MS did the manuscript review. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Background: Rheumatoid arthritis (RA) is an autoimmune, systemic disease that affects the joints. In RA, the body's immune system destroy body's tissue for a foreign invader. This leads immune system to attack the protective cushion of tissue and fluid between the joints. The result is swelling, stiffness, and pain in the joint.
The body's misfiring immune system also may go after the body's soft tissues, like cartilage, and organs such as the heart, eyes, and veins. Ultimately, RA can cause permanent damage, disability, and anemia. Evaluation of progress in RA and anemia control at the population level is increasingly important. It is not only a medical but also an economic issue, since the onset of the disease in most common cases is observed in people of working age [1,2].
Methods: Retrospective analysis representing in this article was performed through 1250 case histories of patients with RA who was received inpatient treatment in the Department of

**Corresponding author: E-mail: abdullayev-behzod@mail.ru;*

Rheumatology 3-clinic Tashkent Medical Academy (TMA) in period from January 2010 to January 2015. Authors analyzed spreading spectrum of anemia in RA patients via verified laboratory data. Authors studied the age and gender characteristics of patients with anemia that occurred after RA and the degree and severity of anemia.

Results: The results of the study showed that 1250 patients were treated with a diagnosis of RA, men were 116 (9.28%), women – 1134 (90.72%). Most patients were at the working age. According to the disease activity, patients separated into 3 degree. 140 (11.2%) of them were in I degree, and 834 (66.72%) in II degree and 276 (22.08%) in III degree. In most cases, the disease duration ranged from 1 to 5 years 418 (33.44%).

The results showed that 874 patients of the 1250 patients have a verified diagnosis of anemia as a comorbidity, which amounted to 69.92%. Almost two-thirds of patients with rheumatic pathology was found anemia varying degrees. Among them, women accounted for 71.7%, men were 28.3%.

Conclusion: Among patients with RA, the prevalence of anemia manifestations is relatively high. Leading cause of anemia in patients with rheumatoid arthritis is iron deficiency anemia. The incidence of anemia is directly depends on the age of patients and duration of disease.

Keywords: Rheumatoid arthritis; anemia; erythrocytes; iron deficiency; hemoglobin.

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disease that primarily affects to joints. RA affects all ethnic groups throughout the world, women are affected 2.5 times more than men [1]. The onset of the disease can occur at any age, but its peak incidence is between 40 and 50 years of age [2]. RA characterized by symmetrical erosive arthritis (synovitis) and a wide range of extra-articular manifestations. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), which commonly are elevated during inflammatory processes. These have been found to correlate with the degree of the disease activity [3,4].

Anemia frequently is a concomitant feature in chronic disease. It is often related to the underlying disease like chronic renal failure, which anemia develops by means of a decreased erythropoietin production. And other example is gastrointestinal bleeding caused by a malignant, infectious or inflammatory process, hemolysis in inflammatory disorders and malignant bone marrow infiltration, malignancy and numerous causes of (chronic) disease associated with hematuria, menorrhagia and hemolysis. Anemia can also be an indirect complication of the underlying disease, e.g. by means of poor nutrition or toxic side effects of drug therapy [5]. Nowadays, approximately 9315,7 people per 100,000 population have been developed different degree and types of anemia in Uzbekistan [6]. Anemia develops slowly and nonprogressively within the first month of the underlying disease and its severity is to some extent correlated with disease activity [7]. After one month's duration of the underlying disorder the hemoglobin (Hb) level is constant and independent of disease duration. The Hb rarely reaches a level below 70% of normal in uncomplicated cases. Generally the cellular indices remain normal, but mean corpuscular hemoglobin (MCH) and mean corpuscular volume (MCV) can be low, even without iron deficiency [8]. The reticulocyte count is low for the degree of anemia.

At the present, approximately 0.5% of adults suffers from RA in the world. The functional disability is the result of progressive joint destruction, significant morbidity and premature mortality [1-3,9]. Moreover, synovial membrane of joints is damaged; it is continued hyperplasia and edema in synovial tissue, accompanied by progressive destruction of cartilage and bone tissue. As a result, disability of locomotor apparatus is developing and risk of premature death is increasing [10].

The prevalence of patients with RA reaches 1% and the economic loss of society is comparable with those who suffers from coronary heart disease [11]. If effective therapy absent, life expectancy decrease 3 years for women and 7 years for men [12,13]. During the natural process of RA, and even while making the standard therapy, 60-90% of patients lose their ability to work and 1/3 become disabled after 20 years of disease commencement [14].

2. MATERIALS AND RESEARCH METHODS

The diagnosis of RA was established on the basis of criteria of American Rheumatism Association. Additionally, authors employed classification and nomenclature that was

proposed by the Research Institute of Rheumatology of the Russian Federation Medical Sciences Academy (MSA) (1991). Retrospective analysis was applied to 1250 case histories of patients with RA who received inpatient treatment in the Department of Rheumatology III clinic TMA for the period from 2010 to 2015, with attention to the role that sex, age, and renal function play on the development of anemia. We analyzed the frequency of occurrence anemia as verified on the basis of laboratory data.

To confirm the diagnosis and determine the severity of anemia together with the routine tests such as: Counting the number of red blood cells ($2.7x10^{12}$/l to $3.8x10^{12}$/l) hemoglobin level ($\leq$110), counting of reticulocytes; were conducted special research methods: A detailed general analysis of blood morphology and red blood cells, ferrokinetics, identification of glycosaminoglycan in portions of gastric juice.

To evaluate the morphology of erythrocytes was determined index of deformability of red blood cells by the modified method C. Janner (1984). Serum iron was determined with using the reagents of firm “La Hema Bio-La-Test Iron” (Czech Republic). Was held enzyme-linked immunosorbent assay of serum ferritin. For this purpose, we used polystyrene plates with sensitized antiferritin antibody, dissolved in 0.05 M bicarbonate, buffer pH 9.6.

Also analyzed serum transferrin with immunochemical method, in a variant radial immunodiffusion.

3. RESULTS

The results of the study showed that 1250 patients were treated with a diagnosis of RA, men were 116 (9.28%), women – 1134 (90.72%). The mean age of the patients was 49±3 years, with gender distribution of 9.28% (n=116) males and 90.72% (n=1134) females.

RA is known that chronic diseases, often accompanied by the development of anemia of chronic diseases. In addition, due to the autoimmune nature of RA to provoke the occurrence of anemia of autoimmune origin and may be due to the effects of medication used to treat the underlying disease – RA.

All patients were treated in the Rheumatology Department of the TMA and 874 patients had a verified diagnosis of anemia as a comorbidity, which counted 69.92%. Therefore, almost 2/3 patient with rheumatic pathology was found anemia varying degrees. Among them, women accounted for 71.74% of men is 28.26%.

All patients (100%) were diagnosed radiologically and confirmed by the articular form of RA. 100% noted a slowly progressive course of RA and 30 (24.9%) of them revealed minimal activity in the process. Clinical indices of articular syndrome in patients with RA were investigated in 26 joints. This is stimulated by soreness of 26 joints. Soreness of joints talocalcaneal, wrist, elbow, shoulder and tarsal joints were determined by means of passive movements in them, carried out by a doctor and pain other joints moderate through pressure on them. According to the degree of disease activity was classified and I degree included 140 (11.2%) patients, II degree included 834 (66.72%), and III degree – 276 (22.08%) were examined. In most cases, the disease duration ranged from 1 to 5 years in 418 (33.44%) patients. In retrospective study, patients with seropositive RA were taken in 73.6%, a seronegative patients with RA compared with 26.4% of the total number of patients.

The study of etiologic causes of anemia in the patients showed that 68.5% cases were characterised to iron deficiency anemia, 24.6% cases were anemia of chronic diseases and only 6.9% cases – autoimmune in nature. Consequently, the vast majority of patients with RA anemia are iron deficiency in nature. In the present study, the investigated frequency of occurrence of anemia depending on individual age groups of patients with RA and results of these studies were presented in Table 1.

Table 1 shows that the highest share of patients with anemia in the categories of 41-50 years and 51-60 years, which accounted 61.327% of patients with RA.

Among the examined patients with RA, anemia was diagnosed based on laboratory data, the highest prevalence of anemia was also observed exactly these age groups (Table 1). However, their higher occurrence, if verified among patients with anemia was noted in the age of 51-60 years (33.8%), among patients with anemia based on laboratory data reported in the age group 41-50 years. Apparently, patients were diagnosed anemia according to generated laboratory parameters (hemoglobin, count of red blood cells, etc.), and then clinical symptoms of the disease are developed.

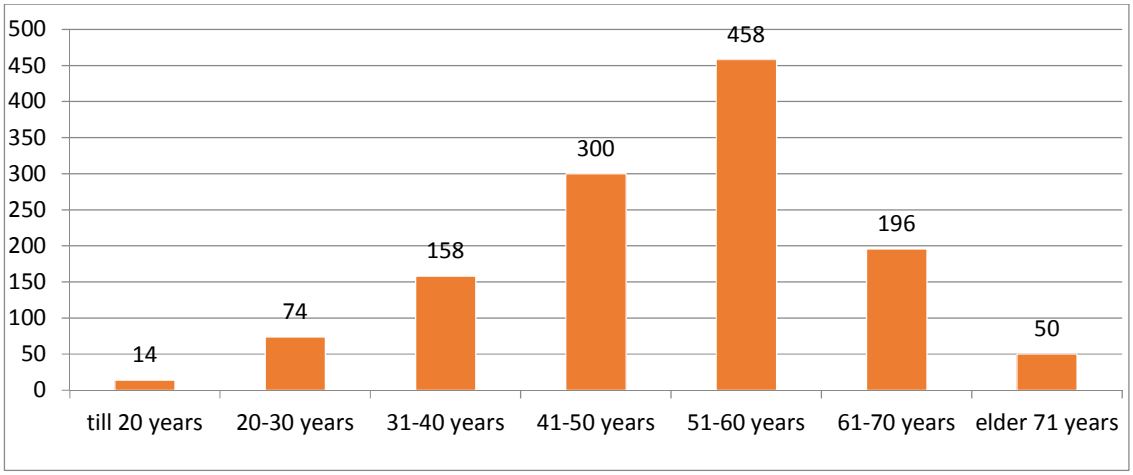

Fig. 1. Age characteristics of the examined patients

Table 1. Distribution of patients with RA depending on age groups

The age of patients	RA+anemia	RA+anemia on the basis of analyses	All patients
Till 20 years	4	8	12
21-30 years	40	22	62
31-40 years	72	46	118
41-50 years	80	140	220
51-60 years	186	130	316
61-70 years	62	50	112
Elder 70 years	20	14	34
Total amount	**464**	**410**	**874**

Hemoglobin was measured by a modified cyanmethemoglobin colorimetric analysis at 540 nm. (7.4-10.8 mmol/1). Reticulocyte count was assessed by vital staining with brilliant cresyl blue, expressed as a ratio of red cells (‰). Mean corpuscular volume was calculated from hematocrits and number of erythrocytes (Ht/ery's); (81-96 fl (femtoliter)). Mean corpuscular hemoglobin was calculated from hemoglobin and number of erythrocytes (Hb/erythrocytes). (1600-2200 amol). The inclusion criteria were the following: Patients with RA whose hemoglobin was in the range of >80 and <109 g/l, color index (CPU) of <0.85, serum iron (SG) <12 mmol/l.

Serum iron was assessed by colorimetric analysis of a ferrous iron/ferene complex at 595 nm without deproteinization and with reduction by ascorbic acid (14-30 µmol/1). Transferrin was determined with a Baker nephelometer 420. (44-80 µmol/1). Serum ferritin was measured by solid phase enzyme immunoassay (20-150 µg/1). Erythrocyte-ferritin was assessed after centrifuging erythrocytes with removing of the buffy coat and supernatant. The sedimentated erythrocytes were resuspended with 166 mM NaCl. This washing procedure was reiterated twice. The final red cell sediment was hemolyzed at 0℃ after which the supernatant was examined for ferritin.

Vitamin B12 and folic acid were eliminated using a radio assay technique. Reference values vitamin B12: >150 pmol/l and folic acid >7 nmol/l).

Erythropoietin in serum was evaluated to use a sandwich radioimmunoassay with monoclonal antibodies. In 50 healthy donors mean Epo was 14.5±4 U/1 which was considered normal. In 100 control sera mean Epo level was 22±4 U/ml).

According to disease activity erythrocyte parameters was showed.

Erythrocyte parameters	I (n=140)	II (n=874)	III (276)
Hb (mmol/l)	8.2 (7.6-8.5)	6.2 (4.3-6.8)	6.2 (5.3-7.1)
Mean corpuscular volume (fl)	91 (81-97)	78 (70-99)	84 (79-96)
Mean corpuscular hemoglobin (amol)	1883 (1620-2080)	1546 (1314-2007)	1649 (1519-1954)
Reticulocytes (‰)	10 (1-22)	21 (9-43)	32 (12-69)

Iron status:

s-iron (µmol/l)	8 (6-12)	4 (1-7)	5 (2-10)
Transferrin (µmol/l)	64 (51-77)	58 (38-80)	49 (37-65)
Ferritin (µg/l)	30 (11-189)	26 (9-98)	88 (46-223)

To assess the role of underlying pathology in the onset and progression of anemia, dependence of the frequency of occurrence of anemia on the duration of RA currents were analyzed (Fig. 2).

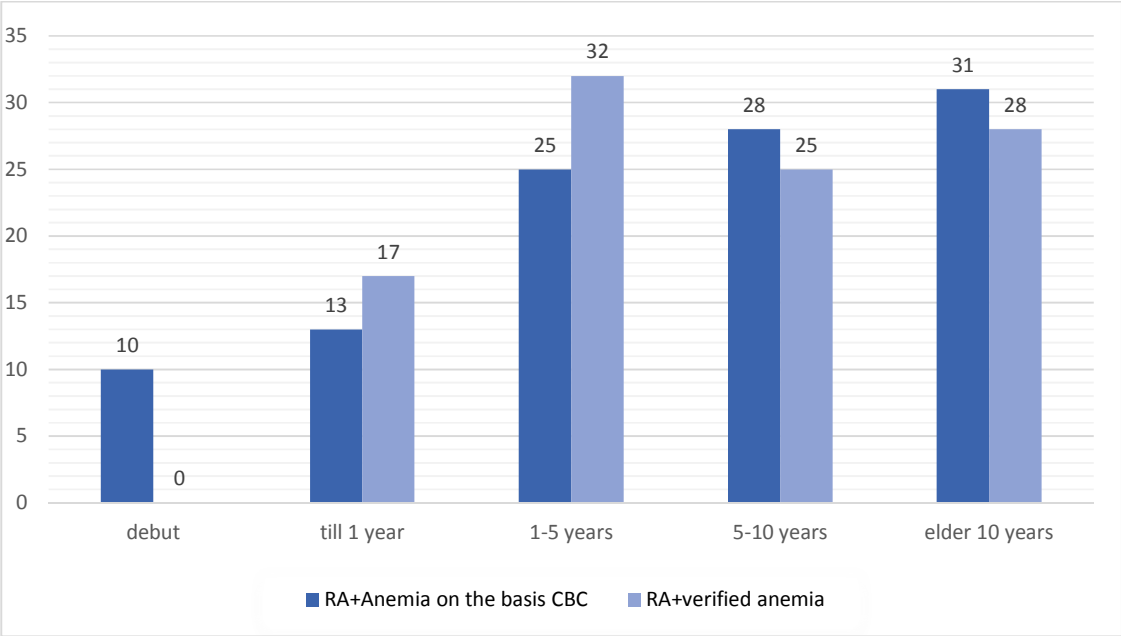

Fig. 2. The distribution of patients with rheumatoid arthritis on the duration of anemia history

As can be seen from Fig. 2, at the onset of the disease, patients with verified disease have been identified, and with the lengthening of the duration of the underlying disease, the prevalence of anemia tended to increase. A similar pattern emerges when examining this relationship among patients with anaemia identified on the basis of complete blood count (CBC). However, unlike patients with verified anemia in this group were able to identify anaemia even in patients with debut RA. Therefore, the results suggest that the long RA flows, more common anemia. Although these results do not exclude concomitant nature of anemia in patients with RA, but it is not proof. However, attests to the role of aggravating anemia.

4. DISCUSSION

Medications commonly used to manage RA, including non-steroidal anti-inflammatory drugs (NSAIDs) and steroids, may also promote the development of anemia. These drugs can cause chronic irritation, bleeding of the stomach lining, and damage to absorb of the iron. Factors may be associated with ACD are a disturbed iron metabolism, an ineffective or inhibition of erythropoiesis, hemolysis, leucocyte endogenous mediators and decreased levels or decreased responsiveness to erythropoietin. Damage of the iron metabolism may compensate through reserved iron in the body and may not be immediately apparent, but over time, it can lead to anemia [15,16].

5. CONCLUSION

The retrospective analysis showed that among patients with RA relatively high proportion of patients with manifestations of anemia. However, there is an underdiagnosis of anemia. Common causes of anemia in RA patients is of primary importance in iron-deficiency anemia. The incidence of anemia is directly dependent on the patients age and duration of RA. RA patients in the period of inpatient treatment, with little or no anti-anemic therapy. Antianemic therapy is recommended for treatment on an outpatient basis and spans a limited contingent of patients.

The main factors contribute to determine that anemia in patients with RA is quite common; 2/3 part of patient has the symptoms of anemia. Secondly, the main causes of anemia during RA were visceral, a long-term course of the disease, and the frequent use of NSAIDs and GCs.

Anemia in RA has a multifactorial cause and complete evaluation is necessary for diagnostic and therapeutic consequences.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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