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Hematological Abnormalities in Ukrainian Patients with Rheumatoid Arthritis

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Abstract

Objective: This study aims to investigate hematological abnormalities in Ukrainian patients with rheumatoid arthritis (RA) and analyze their causes.

Patients and methods: Eighty nine patients who met the American College of Rheumatology (ACR) criteria for RA were included in this study. Individuals with no history of joint pains were enrolled as healthy controls, and matched for age and ethnicity with patients of RA. All patients received methotrexate (10.5 ± 5.5 mg/week) in combination with folic acid. Steroid hormones were prescribed to 92% (19.3 ± 3.8 mg/day) of patients; nonsteroidal anti-inflammatory drugs were taken on demand. The blood count was measured to determine the white blood cell (WBC), red blood cell (RBC), hemoglobin and thrombocyte levels. TNFα, CRP and IL-1β were also investigated.

Results: Anemia was observed in 57 (64% (95% CI 53.7-73.8%)) of the patients. Most of them (70.2% (95% CI 57.5-81.5%)) had mild degree of anemia, the rest (29.8% (95% CI 18.5-42.5%)) - moderate degree of anemia. In 13 (14.6% (95% CI 8.0-22.8%)) patients was found low WBC level (3.05 ± 0.84 G/L), mainly caused by low lymphocytes level (0.74 ± 0.21 G/L). Twenty one (23.6% (95% CI 15.3-33.1%)) patients had thrombocytosis (482.0 ± 29.1 G/L). Increased sedimentation rate (37.91 ± 15.65 mm/h) was recorded in all patients. The healthy controls had normal complete blood count. The correlation analysis revealed a negative correlation between the hemoglobin level and ESR, CRP, TNFα, IL-1β concentrations. There were statistically significant positive correlations between platelets level and ESR, CRP, TNFα, IL-1β concentrations.

Conclusion: Our findings suggest that patients with RA have serious hematological abnormalities violations that can be caused by the activity of the disease.

Keywords: Anemia; Thrombocytosis; Lymphopenia; Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder characterised by inflammation in the synovium, malaise, morning stiffness and fatigue. It is associated with progressive joint destruction and, depending on the severity, may be accompanied by systemic manifestations including lung disease, rheumatoid nodules, effects on the cardiovascular system and blood [1]. The prevalence of RA, at 0.5–1%, is relatively constant in many populations but factors such as gender, race and smoking status can cause a variation in this prevalence rate [2]. Patients with RA tend to undergo exacerbations and periods of remission. If left untreated, over the course of 10–20 years RA may lead to significant disabilities and a severe reduction in the patient's quality of life [3]. Despite some success in the study of the RA pathogenesis, the stabilization of its clinical features is difficult to obtain. In this case, various RA extra-articular manifestations, including the blood system, aggravate its course and significantly complicate the therapy efficiency and opportunities.

Thus, the aim of our study was to investigate hematological abnormalities in Ukrainian patients with rheumatoid arthritis and analyze their causes

Material and Methods

This is a retrospective, single-center, non-blinded trial conducted in a Donetsk National Medical University named after M. Gorki, based on Department of Rehabilitation of State Institution «Institute of Emergency and Reconstructive Surgery named after V. K. Gusak», enrolling participants between August 2008 and September 2013 of which its design has been approved by the ethics committee of Donetsk National Medical University named after M. Gorki.

Inclusion criteria included individuals clinically diagnosed as having RA by expert physicians according to the revised criteria of American College of Rheumatology (ACR, 1987). Individuals with no history of joint pains were enrolled as healthy controls, and matched for age and ethnicity with patients of RA. Pregnant or breastfeeding patients, patients with a history of other inflammatory or non-inflammatory arthritis, the patients with anemia caused by other reasons, malignancies, chronic infectious and inflammatory diseases and other diseases in the stage of decompensation were excluded from the study.

Investigator's evaluated clinical signs and symptoms, studied data's from the ambulatory patient card (when patients start receive RA therapy, dose of medications, blood analysis before history of disease etc.) and were responsible for the whole process of treatment including adjusting of the medicine's doses.

All patients received standard RA therapy no less than 6 months that included methotrexate (10.5 ± 5.5 mg/week) in combination with folic acid. Steroid hormones were prescribed to 92% (9.3 ± 3.8 mg/day) of patients; nonsteroidal anti-inflammatory drugs were taken on demand.

After obtaining their informed consent in writing, venous blood was drawn with sterile syringe, and immediately transferred into a pre-labelled blood collection vial containing anticoagulant K2EDTA (for complete blood count), vacuum blood-collecting tubes containing EDTA-2Na (for TNFα and IL-1β) and plain glass vacutainers (for serum CRP determination). The blood count was measured electronically by the ABX Micros ES 60 hematology analyzer (Horiba ABX SAS, Montpelier, France), erythrocyte sedimentation rate (ESR) - according to the modified method of Westergren. The plasma samples were obtained by centrifugation at 3300×g for 15 min and immediately frozen at -80 until used for determination of protein levels. TNFα and IL-1β were measured by *immunoassay* using «Multiscan» (LabSystem, Finland) with test-system «Bender MedSystems» (Bioscience, Austria). Serum CRP was measured by high-sensitivity immunoturbometric assay (Tina-quant CRP (Latex); Roche Diagnostics, Mannheim, Germany).

The World Health Organization (WHO) criteria for anemia uses a hemoglobin threshold of <120 g/l for women and <130 g/l for men [4]. Definition of mild, moderate and severe anemia also was indicated by the WHO, 2001 [4].

Processing of the results was performed on a personal computer using statistical analysis package "MedStat" version 4.0 for Windows software program (The MEDSTAT Group, Inc., Ann Arbor, MI).. Comparison between groups was performed using parametric or non-parametric tests, as appropriate. For normality test the χ^2 and W Shapiro-Wilk criteria were used. Data fitted normal distribution were presented as "mean ± standard deviation", if the distribution was not normal - as the median (Me (25 -, 75-percentile)). For comparison of means of two normally distributed samples, Student's t-test was used. For non-normal distributions, quantitative comparison of the two groups was performed using the Mann-Whitney test. Comparison of the relative values was performed using the χ^2 criterion. Significant association was defined by a p value<0.05.

Results

The pre-specified duration of the enrolment period was five years and during that time we interviewed 145 patients with RA and 24 healthy controls. 35 did not meet inclusion criteria, 22 declined to participate. A total of 89 patients were enrolled.

Anemia was observed in 57 (64% (95% CI 53.7-73.8%)) of the patients (mean hemoglobin concentration – 107.0 ± 8.3 g/L), when all in control group had normal hemoglobin level (126.3 ± 5.8 g/L). Most of patients (70.2% (95% CI 57.5-81.5%)) had mild degree of anemia, the rest (29.8% (95% CI 18.5-42.5%)) - moderate degree. In 13 (14.6% (95% CI 8.0-22.8%)) patients low WBC level (3.05 ± 0.84 G/L) was found, mainly caused by low lymphocytes level (0.74 ± 0.21 G/L), when all in control group had normal WBC count (7.21 ± 1.98 G/L) Twenty one (23.6% (95% CI 15.3-33.1%)) patients had thrombocytosis (482.0 ± 29.1 G/L) and all in control group had normal platelets count (257.3 ± 30.5 G/L). Increased sedimentation rate (37.91 ± 15.65 mm/h) was recorded in all patients and was normal in all healthy control (7.21 ± 2.53 mm/h).

The mean ESR, CRP, TNFα, IL-1β levels were significantly increased in the patients group when compared with the controls (Table 1).

Parameters	Groups		p values
	Patients, n=89	Healthy controls, n=24	
ESR, mm/h	37.91 ± 15.65	7.21 ± 2.53	p=0.001
CRP, mg/dL	48.27 ± 12.18	4.38 ± 1.28	p=0.001
TNFα, pg/mL	32.54 ± 9.71	1.21 ± 0.13	p=0.001
IL-1 β, pg/mL	166.32 ± 18.54	2.39 ± 0.81	p=0.001

Table 1: Comparison of the laboratory parameters of RA of two groups

The correlation analysis revealed a negative correlation between the hemoglobin level and ESR, CRP, TNFα, IL-1β concentrations (Table 2).

Parameters	Correlation coefficient (r)	p values
ESR, mm/h	-0.62	p<0.001
CRP, mg/dL	-0.61	p<0.001
TNFα, pg/mL	-0.59	p<0.001
IL-1β, pg/mL	-0.57	p<0.001

Table 2: The results of a correlation analysis between the hemoglobin level and the laboratory parameters of RA activity

There was statistically significant positive correlation between the platelets level and ESR, CRP, TNFα, IL-1β concentrations (Table 3).

Parameters	Correlation Coefficient (r)	p values
ESR, mm/h	+0.48	p<0.001
CRP, mg/dL	+0.37	p<0.001
TNFα, pg/mL	+0.42	p<0.001
IL-1β, pg/mL	+0.59	p<0.001

Table 3: The results of a correlation analysis between the platelets level and the laboratory parameters of RA activity

Discussion

Thus, we found that 64% (CI 53.7-73.8%, p=0.05) of patients with RA has anemia of mild and moderate severity. Reasons that could cause reduction in hemoglobin level in RA include a blunted erythropoietin response by the RBC precursors, decreased survival of the RBCs, defective iron absorption and glucocorticoids influence [5]. Defective macrophage iron retention may also contribute to anemia by interrupting iron delivery to the erythroid precursor cells. Furthermore, anemia may be precipitated by impaired iron utilization in which the functional iron levels are low, but the tissue iron levels are normal or high [6]. It is also now clear that inflammatory cytokines released during anemia in RA can alter systemic iron metabolism by inducing the excess synthesis of hepcidin, the iron regulatory

hormone. Since hepcidin inhibits iron exportation from cells by blocking ferroportin activity, the root cause of the hypoferremia and iron-restricted erythropoiesis in anemia can be attributed to the excess hepcidin levels [7]. Our scientific work confirmed the inhibitory role of cytokines by the revealed negative correlation between the hemoglobin level and TNFα, IL-1β concentrations.

Thrombocytosis is a common complication of RA, and is presumably caused by an up-regulation in megakaryocytopoiesis [8]. It is believed that hematopoietic cytokines, particularly thrombopoietin may participate in the processes of inflammation [9]. At the same time, despite the increase in the platelet number, their life expectancy in patients with RA is reduced [10]. Some researchers believe that this fact reflects the presence of high disease activity [11]. Ertenli et al. [12] revealed that RA patients with thrombocytosis have increase in IL-6, IL-1β and IL-4 levels, whereas patients with normal or reduced platelet concentration have normal cytokines level. We also get the positive correlation between the platelets level and IL-1β, CRP, TNFα that could suggest the influence of high disease activity on these cells.

Lymphocytes play a central role in the pathogenesis of RA. The rheumatoid synovium contains large numbers of lymphocytes and plasma cells, many of which bear the markers of activation. We have shown that 14.6% of RA patients have lymphopenia in the absence of Felty's syndrome. The lymphopenia could appear due to a depression in circulating T-cell numbers while the number of circulating B-cells remains normal and it is not simply a feature of disease activity [13]. Some studies showed that generate functional T-cell lymphopenia result in the development of a variety of organ-specific autoimmune diseases in animal models [14]. Others suggest that it appears not to be sufficient for the development of human autoimmunity, which may require additional environmental and genetic factors to progress to clinical disease [13].

Conclusion

Thus, in patients with RA, serious hematological abnormalities violations that can be caused by the activity of the disease were revealed. Therefore, patients with RA requires regular hematological monitoring and, if necessary, timely and adequate correction of any violations.

Funding

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