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# The Pattern of Anemia in Lupus

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## Abstract

Anemia is a frequent incident for patients with systemic lupus erythematosus (SLE), its incidence being reported as 18–80%. Anemia of chronic disease (ACD) is the most common hematological syndrome in the evolutionary context of SLE. In anemia of the chronic disease, cytokines stimulate the production of hepcidin, an acute phase protein, which destroys ferroportin produced by hepatocytes. As a result, Fe (iron) is not able to come out from the erythrocytes and macrophages and is trapped within them. Anemias from chronic disease are usually hypoproliferative processes. This chapter reviews the correlation between systemic lupus erythematosus and anemia of chronic disease in general (but iron-deficiency anemia in particular). This text reviews different important methods of examination used to diagnose the pathological process of lupus as an immune disease and of the hematopoietic system some of these methods include (general blood analysis, Coombs test, serum iron, hematocrit etc.). Furthermore, it will discuss the physiopathological mechanism of anemic syndrome in systemic lupus erythematosus and the changes of the immune system. In conclusion, the relevance of anemia (independent of its cause) is estimated as being both a short-term activity of the disease and long-term prognostic factor for the evolution of SLE.

**Keywords:** anemia, systemic lupus erythematosus, hematological implications

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## 1. Introduction

In general population, anemia is associated with high morbidity in different clinical conditions. For example, high prenatal risk, developmental anomalies in children, changes in immunological status, high risk of infections and pattern of hormonal and metabolic development are usually associated with anemia. Anemia is an independent risk factor for the development of cardiovascular complications in general population [1–3].

Anemia is present in approximately half of the people with active lupus. Common forms of anemia in these patients are anemia of chronic disease (ACD), followed by iron-deficiency anemia,

autoimmune hemolytic anemia, anemia of chronic kidney disease and drug induced. Other types of anemia, such as pure red cell aplasia (PRCA), myelofibrosis, B12-deficiency anemia, sideroblastic anemia, hemophagocytic syndrome and thrombotic microangiopathy, are rare forms described in lupus. Anemias from chronic disease are usually hypoproliferative processes [4, 5]. Recent studies have revealed that resistance to erythropoietin (EPO) in systemic lupus erythematosus (SLE) can be attributed to antibodies against erythropoietin (anti-erythropoietin). Reduced production and resistance to erythropoietin in patients with SLE is hypothetically associated with anemia of chronic disease (ACD) [6, 7]. Normally, red cells live only 120 days (approximately 4 months) and they constantly have to be produced by the bone marrow. The most common explanation of anemia is the production of fewer red blood cells than usual. This can be caused by an inflammation, kidney problems (when kidneys produce insufficient hormone, erythropoietin stimulates the bone marrow to produce more red blood cells), iron deficiency (without iron, hemoglobin cannot be produced—iron deficiency can be caused by excessive menstrual hemorrhage or intestinal hemorrhage caused by non-steroidal anti-inflammatory drugs, such as ibuprofen and aspirin) or diminished bone marrow caused by drugs like azathioprine and cyclophosphamide. Intestinal hemorrhage can be evident if the stool is dark and tarry, but sometimes the hemorrhage is very little and additional analysis are needed for the detection of the hemorrhage [3, 4, 8]. Anemia can be caused by the premature destruction of red blood cells, named hemolytic anemia, or by simple hemolysis. Sometimes patients with hemolysis have paler skin and in these situations the yellowish color of the skin and eyes is not a sign of liver problems. Hemolysis is often caused by specific antibodies of the disease that attach to erythrocytes. When it is accompanied by thrombocytopenia, it causes thrombotic thrombocytopenic purpura. Thrombocytopenia is found in 30–50% patients, and it is caused by antiplatelet antibodies or antiphospholipid antibodies. Both can cause severe thrombocytopenia (<50,000). Platelet transfusion is generally contraindicated in SLE because of the possibility that the patient is exposed to new antigens [5, 9].

Being essential for organ function, a large amount of iron is stored in any organism. Excretion of iron from the body is a very slow process, which occurs through epithelial desquamation and intestinal secretion.

Anemia of chronic disease is the most common hematological syndrome seen in the evolutionary context of SLE. In anemia of chronic disease, cytokines stimulate the production of hepcidin – a protein of the acute phase response, which destroys ferroportin produced by hepatocytes. As a result, iron is unable to be transported out of the erythrocytes and macrophages. Under the influence of hepcidin, iron is trapped [7, 10]. In this condition, in spite of sufficient amount of iron in the body, bone marrow suffers from insufficiency of iron.

Formation of erythrocytes is affected and their duration of life decreases. Erythrocytes are produced in the bone marrow under the influence of erythropoietin, but in anemia of chronic disease the cytokines inhibit the production of erythropoietin.

Anemia in patients with SLE is a common manifestation which can result from many causes such as changes in the immune system, followed by the activation of cytokines, digestive tract bleeding because of chronic consumption of glucocorticoids, various drugs (for example aspirin and ibuprofen), presence of enzyme deficiency that predisposes the fragility of RBCs, poor diet

and malabsorption syndrome. Sometimes SLE patients might have multiple etiological factors for their anemia. For that reason, it is important to establish a complete and correct diagnosis, taking into account different therapeutic means [5, 11].

Anemia of chronic disease is determined by a functional deficit of iron, which can be characterized by:

- hyposideremia, despite the adequate/increased amount of iron (increased ferritin in serum);
- direct suppression of erythropoiesis;
- determining the capture of the iron in macrophages;
- limiting the amount of transferrin iron necessary for erythropoiesis makes anemia mild and asymptomatic, making it morphologically normocytic/microcytic and saturation of transferrin low, suggesting the deficit of iron.

Hemoglobin is the protein present in the red blood cells that transports oxygen from lungs to other tissues of the body. Fatigue is a common symptom of lupus and also the first and most common symptom in anemia [12, 13]. Anemia can be measured and followed up in various ways, including calculation of the red blood cells, which emphasizes a reduced number of RBC, a low level of hemoglobin and hematocrit [12, 14].

The diagnosis of a real deficit of iron in a patient with chronic disease can be very difficult to determine because chronic diseases can give false-positive results for hyposideremia despite the presence of stored iron and can also give false-positive results for higher ferritin level in serum, even in the absence of stored iron—the most useful diagnostic test is the soluble transferrin receptor (STfR)/ferritin level. Soluble transferrin level (STfR) and ferritin change in opposite directions during iron deficiency; this value is extremely sensible for the metabolism of iron and can differentiate anemia from chronic disease with the real iron deficit, even if this is accompanied by a chronic disease. This value is not useful in the presence of renal dysfunction or hemodialysis, when the saturation of transferrin is <20% and ferritin <100 µg/l shows the necessity of treatment with iron [2, 14, 15].

## **2. Physiopathological mechanisms of anemic syndrome in systemic lupus erythematosus**

Anemia of chronic disease, the most frequent comorbidity in patients with SLE is normochromic normocytic, mild ( $Hb < 9.5$  g/dl) or moderate form ( $Hb < 8$  g/dl) of hyporegenerative anemia. In its physiopathology, cytokines and SLE cells change the homeostasis of iron; abnormal erythropoietin (EPO) production, inadequate response to the secretion of erythropoietin causes erythroid progenitor abnormalities in the cells and diminished life span of erythrocytes; these are caused by direct toxic effect on progenitors by formation of free radicals like nitric oxide (NO) and superoxide anion ( $O_2^-$ ) [16–18].

Changes in the immune system determine the activation of T lymphocytes ( $CD^{3+}$ ) and monocytes, followed by the production of cytokines such as interleukin-1 (IL-1), interleukin-6

(IL-6), interleukin-10 (IL-10), tumor necrosis factor alpha (TNF $\alpha$ ) and interferon-gamma (IFN-gamma), which stimulate the storage of iron in macrophages and synthesis of ferritin (FT), which causes decreased availability of iron for erythropoiesis. IFN-gamma, TNF $\alpha$  and IL-1 have inhibitory effect on the proliferation and differentiation of erythroid progenitors. TNF $\alpha$  and IFN-gamma inhibit the production of erythropoietin in kidney. IL-6 and IL-1 (responsible especially for systemic manifestations in SLE, including anemia) were the first cytokines discovered, implicated in stimulating the secretion of hepatic hepcidin. These cytokines, being the essential elements in the anemia pathogeny of patients with multiple myeloma, acting either independently or through producing hepcidin [10, 17]. Hepcidin represents the link between these two essential mechanisms (immunologic and homeostatic dysfunction) involved in the pathogenicity of ACD.

In conclusion, not all the causes of anemia in the chronic disease SLE are well known. The most characteristic types of anemia are iron-deficiency anemia, autoimmune hemolytic anemia, anemia from chronic kidney failure, vitamin B12-deficiency anemia and other forms. The disease is most frequent in women, does not have a well-known cause and has a special association with some genes of the immune response. Some affected systems are represented by central and peripheral nervous system, lungs, heart, kidneys, serous and other elements of the blood. Other systems of the body may also be affected, infrequently. Some other forms of anemia found in lupus disease are as follows.

### **2.1. Autoimmune hemolytic anemia (AHA)**

- AHA is a rare phenomenon in patients with lupus. Hemolytic anemia may be classified into two major groups: with antibodies at cold and hot temperatures. AHA with hot antibodies is mediated by IgG antibodies that can interact with antigens only at 37°C, and the reaction with cold antibodies can be as low as 4°C. Coomb test is directly positive and involves one of the following elements that interact with the surface of the erythrocytes such as IgG.
- Other hematological disorders such as neutropenia is a common abnormality that amplifies the risk of secondary infections in patients with SLE, but can also be an index of the disease state. In addition to neutropenia, lymphopenia is also reported to be a frequently seen hematological disorder in patients with lupus [4, 9].

### **2.2. Leucopenia**

It is a hematological disturbance that occurs in half of the patients with SLE, circulating granulocytes being decreased because of granulocytopenia by destruction in the peripheral circulation (antigranulocyte antibodies, hypersplenism), bone marrow dysfunction, drug-induced cytopenia (azathioprine), lymphocytopenia through non-immunological mechanisms (drug induced), immunological mechanisms (antilymphocyte-dependent antibodies IgM) and nonspecific antibodies, which interact with lymphocytes. Leucopenia appears in over 50% of patients with SLE and is associated with granulocytopenia or lymphopenia. Most of the times leucopenia can be reversible with adequate immunosuppressive therapy [7, 17, 19].



Often, leucopenia can be a good gravity index regarding the disease activity, and it can also appear as a response to the cytotoxic therapy. Leucopenia and neutropenia are the findings often present in active lupus, but rarely reach such a low level to cause the infections.

The number of cells can be decreased by azathioprine, cyclophosphamide and other drugs. Thus, the number of white cells should always be monitored during the treatment of SLE. If the number of white cells decreases too much, lowering the doses of the drugs or discontinuation of the treatment should be done. Dysfunction of the immune system, which causes widespread infection in SLE, is not reflected in the usual blood tests [11, 12, 19, 20].

### 2.3. Thrombocytopenia

Mild thrombocytopenia (number of thrombocytes 100,000–150,000/ $\mu$ L) is present in 25–50% of patients with SLE and those with less than 50,000/ $\mu$ L appears to be only 10%. The most common cause of thrombocytopenia in SLE is the autodestruction of thrombocytes.

Impaired production of thrombocytes is drug induced (as a result of bone marrow suppression). The main underlying mechanism of this event is the binding between immunoglobulin and thrombocyte after the destruction in spleen, almost similar to idiopathic thrombocytopenic purpura. Antibodies against thrombocytopenic purpura were detected in the serum of patients with SLE and correlated with thrombocytopenia [10, 13, 21].

Idiopathic thrombocytopenic purpura can be the first sign in SLE, followed by other symptoms that can appear later. In these cases, the presence of high antinuclear factor (ANAs) titer of nuclear antigen increases the possibility of having SLE. A detailed clinical and laboratory examination in many of these cases may reveal the supplementary index of SLE. Patients with lupus suffer frequently from osteoporosis, because they sum up the risk of predominant feminine population and long-term corticosteroid therapy [3, 14].

Specific antibodies for coagulation factors are seen in SLE, which is frequently associated with bleeding. These antibodies are usually present against II, VIII, IX, XI or XII factors. This abnormality is accompanied by hypercoagulation and not by major bleedings. The blood of a SLE patient can be hypercoagulable for various reasons other than procoagulant antibodies; these include inherited deficiency of C, S factors or IIIrd antithrombin. Urinary loss of antithrombin III in patients with nephrotic syndrome also leads to a hypercoagulability state.

## 3. Methods of investigation

**The laboratory examination** has particular importance in the diagnosis of the pathological processes of lupus as an immune disease and of the hematopoietic system. Ideally, a peripheral blood analysis is done that includes all the disease manifestation by the quantity and quality index, for example morphological characteristic of erythrocytes, leukocyte, morphological modifications of leukocytes and the presence of the pathological cells. These

values provide significant data for establishing the diagnosis for hematological maladies. Investigations of the number of reticulocytes and thrombocytes also have an important role in the diagnosis [1].

**General blood analysis.** Its purpose is to calculate the number of erythrocytes and leukocyte. Evaluation of the hemoglobin level, erythrocytes and hematocrit index is done for confirmation of anemia. A complete hemogram is performed to evaluate the global hematopoietic system and the presence of inflammation. A particular importance is given to the morphological study of erythrocytes from the blood smear, diameter and the form of erythrocytes (by anisocytosis and poikilocytosis mark) [2, 22].

**Hemoglobin** is a tetrameric molecule and contains iron with porphyrin structure. Iron is capable of reversible link with oxygen only in ferric phase. Iron oxidation in its ferric phase determines the methemoglobin formation, which alters the absorption and determines the brownish blood coloration. Normal limits of hemoglobin is 120–140 g/l for women.

The majority of authors distinguish three grades of anemia: grade I—the content of hemoglobin varies from 91 to 110 g/l, grade II—hemoglobin values vary from 71 to 90 g/l and grade III—the level of hemoglobin fluctuates from 51 to 70 g/l [1, 17].

**Erythrocytes.** The number of erythrocytes represents the main test for evaluation of erythropoiesis. Erythrocytes are investigated by measuring the concentration of hemoglobin and hematocrit; based on the values of erythrocyte index: medium erythrocyte volume (MEV), mean corpuscular hemoglobin concentration (MCHC) and mean quantity of hemoglobin in erythrocyte (MCH) are calculated by the analyzer. All these values characterized erythrocytic population qualitatively.

Number of erythrocytes as a single parameter has insignificant diagnostic value, so that the correct evaluation of erythrocyte mass is done through the correlation with hematocrit.

**Hematocrit** is the volume percentage (vol%) of red blood cells in blood. It is normally 45% for men and 40% for women. It is considered an integral part of a person's complete blood count results, along with hemoglobin concentration, white blood cell count and platelet count. The hematocrit with erythrocytic index is used in the diagnosis of diverse types of anemia [3, 4].

**Serum iron** is determined using colorimetric method and helps in the diagnosis of iron deficiency. Serum iron is a medical laboratory test that measures the amount of circulating iron that is bound to transferrin. Clinicians carry out this laboratory test when they are concerned about iron deficiency, which can cause anemia and other problems. About 65% of the iron in the body is bound up in hemoglobin molecules in red blood cells. About 4% is bound up in myoglobin molecules. Around 30% of the iron in the body is stored as ferritin or hemosiderin in the spleen, the bone marrow and the liver. Small amounts of iron can be found in other molecules in cells throughout the body. None of this iron is directly measurable from serum level.

However, some iron circulate in the serum. Transferrin is a molecule produced by the liver that binds one or two iron ions, i.e. ferric iron,  $\text{Fe}^{3+}$ ; transferrin is essential if stored iron is to be moved and used. Most of the time, about 30% of the available sites on the transferrin molecule are occupied. The test for serum iron measures the iron molecules that are bound to transferrin

and circulating in the blood. The extent at which transferrin molecules are occupied by iron ions can be another helpful clinical indicator, known as percent transferrin saturation. These tests are generally done at the same time. Considering the laboratory results together is an important part of the diagnostic process for conditions such as anemia, iron-deficiency anemia, anemia of chronic disease and hemochromatosis.

It is extremely important to collect the blood correctly for determining the serum iron. It was noted that the tubes washed with distilled water contained traces of iron. Another important matter to be considered is that the patient should not get any iron medication at least 5 days before analysis [8, 23].

**Ferritin content in serum** facilitates the diagnosis of iron deficiency in pre-latent period. Ferritin is the diagnostic marker in iron deficiency, and the latex-test method is validated for the evaluation of iron storage. Ferritin is measured in the serum using polyclonal antibodies for ferritin absorbed by the latex particles. The established norm is 10.00–160.00 g/l. Values under 10.00 g/l are considered low.

**Erythropoietin (EPO)**, a glycoprotein hormone secreted by the kidney in the adult and by the liver in the fetus, which acts on stem cells of the bone marrow to stimulate red blood cell production (erythropoiesis). The Biometrica EPO ELISA test is a immunofermentative in vivo diagnostic test, which determines the quantity of serum erythropoietin. The glycoprotein hormone erythropoietin (EPO) is an essential growth and survival factor for erythroid progenitor cells, and the rate of red blood cell production is normally determined by the serum EPO concentration. EPO production is inversely related to oxygen availability, so that an effective feedback loop is established, which controls erythropoiesis. Since recombinant EPO became available as an effective therapeutic agent, significant progress has also been made in understanding the basis of this feedback control. The main determinant of EPO synthesis is the transcriptional activity of its gene in liver and kidneys, which is related to local oxygen tensions. This control is achieved by hypoxia-inducible transcription factors (HIF), consisting of a constitutive beta-subunit and one of two alternative oxygen-regulated HIF alpha subunits (HIF-1alpha and HIF-2alpha). In the presence of oxygen (normoxia), the HIF alpha subunits are hydroxylated, which targets them for proteasomal degradation. Under hypoxia, because of the lack of oxygen molecule, HIF cannot be hydroxylated and is thereby stabilized. Although HIF-1alpha was the first transcription factor identified through its ability to bind to an enhancer sequence of the EPO gene, more recent evidence suggests that HIF-2alpha is responsible for the regulation of EPO. Although EPO is a prime example for an oxygen-regulated gene, the role of the HIF system goes far beyond the regulation of EPO, because it operates widely in almost all cells and controls a broad transcriptional response to hypoxia, including genes involved in cell metabolism, angiogenesis and vascular tone. Further evidence suggests that apart from its effect as an erythropoietic hormone, EPO acts as a paracrine, tissue-protective protein in the brain and possibly also in other organs [11].

**Coombs test.** Circulatory anti-erythrocyte antibodies are detected using indirect Coombs test. Unlike direct Coombs test that uses patient's erythrocytes, indirect test uses serum. At the second phase, this mixture is supplemented with a solution that contains human antiglobulin antibodies. If antibodies exist in the patient's serum, agglutination appears.



**Thrombocytes.** Normal thrombocytes are represented as small cytoplasmic fragments, light blue colored, with azurophilic diffuse small grains (red-purple), with a diameter of 2–4  $\mu\text{m}$  and oval in shape. The number of thrombocytes can be estimated in the analyzer or in the smear. The normal value of thrombocytes is  $180.0\text{--}320.0 \cdot 10^9/\text{l}$ , and the values under 180 thousand are considered as decreased—thrombocytopenia.

**Leukocytes**—the white cells from the plasma. Depending on the function and their role, leukocytes are divided in five categories: basophil, eosinophils, lymphocytes, monocytes and neutrophils. Normal values of leukocytes are  $4.0\text{--}9.0 \cdot 10^9/\text{l}$ .

**ESR (Westergren)**—Erythrocyte sedimentation rate is the rate at which the red blood cells make sediment during 1, 2 hours or 15 minutes.

ESR is regulated by the equilibrium between pro-sedimentary factors, main being fibrinogen, and the negative charge of erythrocytes. The Westergren method is the most frequent method used to determine the erythrocyte sedimentation rate.

The ESR is a simple nonspecific screening test that indirectly measures the presence of inflammation in the body. It reflects the tendency of red blood cells to settle more rapidly in the face of some disease states, usually because of increases in plasma fibrinogen, immunoglobulins and other acute-phase reaction proteins. Changes in red cell shape or numbers may also affect the ESR.

There are two main methods used to measure the ESR: the Westergren method and the Wintrobe Method. Each method produces slightly different results. Most laboratories use the Westergren method.

## 4. Methods and results

Through analyzing the instruments used for evaluating the SLE activity, we chose the Systemic Lupus Activity Measure (SLAM) index that reflects the clinical and laboratory parameters of SLE. The score of this instrument varies between 0 and 20 points, being considered preferable as compared to Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), for the appreciation of anemia in context with SLE [24]. SLAM is a quantity index that includes 37 parameters, compared to 10 domains that reflect the state of 8 organs and systems (constitutional, reticuloendothelial, pulmonary, cardiovascular, neuromotor, hematological, ocular and articulations) shown by laboratory data. Each domain is marked from 3 to 11 parameters.

We obtained the next distribution: low activity is mentioned till 10 points, medium—10–20 points and high grade—over 20 points [3].

In accordance with the purpose, a group of 110 patients with systemic lupus erythematosus have been selected. About 87 of the investigated patients complied with SLE diagnosis criteria issued by the American College of Rheumatology, which constituted the baseline study group. We had only one male patient, so we excluded him from our research to avoid gender misrepresentation.

In our study, we obtained the data about the onset disease age that ranged from 21 to 62 years (mean age— $32.8 \pm 1.32$ ), but more often the disease was established at a young age—between 21 and 39 years. The mean age of the patients at the time of examination was  $41.37 \pm 1.4$  (21–65 years), with the onset of the disease at 8.6 years of age. At the moment of examination, patients were mostly between 21 and 39 years and only eight were over 50 years old. We were also interested in analyzing the duration of the disease—from 1 to 365 months (30 years).

In this study, each patient was evaluated individually. We analyzed the obtained results from SLAM compartments—general, clinical and laboratory. In each compartment, we included five possible answer variants: 1—absent or normal; 2—easy; 3—moderate and 4—severe. It is noted that in SLAM the “not examined patient” heading is included.

Fever has been characterized by the levels scored in the SLAM, and the indices like oral and nasal ulcers, alopecia, vasculitis, Raynaud syndrome and anti-DNA antibody-dc had two answers **Yes** or **No**, which signifies **the presence** or **the absence** of them. Other components of SLAM score, which refers to the component status, were represented by a hematological evaluation of some variables such as leukopenia, thrombocytopenia and lymphopenia; stratification of hemoglobin levels and ESR represents the severity of pathological process.

Skin damage was manifested by the nose or mouth sores, rashes, malar erythema and photosensitivity. The detection of at least one of these conditions adds a clinical score SLAM and it is expended to disease activity. Cutaneous manifestations such as maculopapular erythema or deep lupus has denoted with 3 points of damage to more than 50% of the body surface (ASC), with 2 points to extinction of 20–50% and with only 1 point in case of involvement of less than 20% of the area of the manipulation. Similarly, the presence of vasculitis has been noted with the respective score summary area involved. Eye manifestations are presented by corpuscles, bleeding (retinal or colloid) or episcleritis, papillitis or pseudomotor cerebri, and depending on the absence or presence and severity of these events, it produces a score from 0 to 3 points for each clinical index. The central nervous system is affected frequently in lupus patients. The most frequently symptoms were migraine, epilepsy and chorea.

Chronic ulcers, avascular necrosis and hemolytic anemia were observed in our patients with a frequency of 17.4, 8.7 and 8.7%, respectively. Our data on the incidence of avascular necrosis and chronic ulcers are similar to those shown in the literature, and only for hemolytic anemia, the data were lower than the presented percentage of Giannouli [25]. We diagnosed a small number of valvulopathy (8.7%). Referring to confirm secondary APS by laboratory variables, we found that more often anticardiolipin (ACL) IgG antibodies were found than IgM—60.9 vs. 30.4%, which shows that ACL IgG antibodies have sensitivity and high specificity and can be indicated in the research plan of patients with SLE in order to forecast possible thrombosis. Analyzing the results described, we concluded that APS was associated with SLE in 26.7% of cases, which corresponds to the data reported by Duarte [23]—28% of cases, but it differs from some older records invoked by Nossent et al. [7], they detected APS in 54% of patients with SLE. Typical signs of antiphospholipid syndrome—thrombosis—have been developed frequently in 60.9% of patients, including 21.7% of these were recurrent. Antiphospholipid syndrome with concomitant thrombosis in the system of more veins and/or arteries called APS cascading or Asherson’s syndrome, which endangers the patient’s

life or seriously alters the quality of life through complications that may arise. Obstetric pathology was associated frequently in 52.2% of cases examined and negatively affected the prognosis of the disease. This compromises the possibility of a normal pregnancy; therefore, patients with APS associated with SLE can conceive only by an adequate treatment and should be under rigorous surveillance.

We came across a patient with the medical history of systemic lupus erythematosus, iron-deficient anemia and symptoms of antiphospholipid syndrome. From this case, relevance of hematological damage in SLE and APS patients has emerged. So, we continued research analyzing hematologic risk factors that increase individual susceptibility in SLE patients in terms of morbidity and mortality through hematologic damage, including autoimmune hemolytic anemia. Preventive hematology succeeded to prove undoubtedly that by addressing hematologic risk factors significant reduction of the incidence, prevalence, complications and mortality from diseases of the hematopoietic system could be reduced.

Less has been disclosed on the overlapped quantitative influence of hematologic risk factors in patients with autoimmune inflammatory chronic diseases such as idiopathic inflammatory myopathies, Sjogren's syndrome and SLE, as it admits that the risk factors interact between themselves, multiplying the hematological risk, which may impact the patient's condition during the morbid evolution of the disease. For these reasons, we analyzed the morbid hematologic risk factors in two distinct groups by quantifying them, choosing for individuals with SLE and healthy people.

At the next stage, we tried to analyze disease activity and organic damage index depending on the grade of anemia and the presence of anti-DNA antibodies.

According to our results, high SLAM scores (18.78) were associated with severe anemia with Hb level of 51–70 g/l, and they were having organic damage index values of 1.15. In our study, the lowest values of the examined indices were demonstrated in the absence of anemia (SLAM – 7.17, damage index – 0.56) with a background of negative anti-DNA. In the medium and moderate forms of anemia, SLAM score and damage index were moderately elevated.

Analyzing the anticardiolipin antibodies, IgG and IgM, in all these groups, we found that the average IgG antibodies was higher in the group of patients with ACD—12 (35%) cases versus patients in groups with iron-deficient anemia and AHA, where the indices were 5 (25%) and 1 (20%) ( $p > 0.05$ ).

The same frequency was also observed in the level of anticardiolipin IgM antibodies. Patients (20 (33.9%)) with iron-deficient anemia and AHA + ARF (anemia of renal failure) had identical levels of IgM anticardiolipin antibodies in 20% of cases, whereas the ACD patients had a higher rate of 26.5%. We noted that the C3 complement level was reduced to over 80% of cases of anemia in all groups, a situation that indicates high disease activity.

Analyzing the frequency of high titers of anti-DC DNA, we observed that in groups of patients with chronic anemia and iron-deficiency anemia this index was positive in 70% of cases and reported in 44 patients as compared to Group III, where DNA anti-DC was positively observed only in 2 (40%) patients.

In the third group of patients, lupus nephritis was detected more frequently in 60% of cases, whereas in groups of patients with anemia of chronic disease and iron-deficiency anemia, lupus nephritis was detected in 40% of cases. The differences were statistically significant ( $p < 0.01$ ).

For confirming anemia and the quantification of its intensity, we appealed to the index of the disease activity in hematological lupus—Systemic Lupus Activity Measure (SLAM), which is a test that measures the activity of the disease in patients with SLE through the condition of 23 clinical and 7 laboratory parameters commensurate with points. The total possible score of this instrument varies between 0 and 20 points. Unlike SLEDAI, the SLAM index includes not only objective signs and laboratory parameters but also the evaluation of the hemoglobin level and the hematocrit. Analyzing the obtained data, we discovered that of the 59 patients with anemia, 34 (57.6%) were diagnosed with anemia of chronic disease and accumulated an average of  $22.6 \pm 1.94$  according to the SLAM score, a result that is equal to a high activity of the disease; 20 patients (33.9%) with iron-deficiency anemia received  $18.9 \pm 1.14$  score having a moderate-high activity of the disease and 5 (8.5%) of the interviewed patients with other types of anemia obtained  $24.9 \pm 1.03$ , a score qualified as a high activity of the disease.

## 5. Statistical evaluation of the used methods

Data obtained as a result of investigations were processed by computerized analysis (SPSS), correlation and discriminating variation. The degree of correlative relations between the evaluated parameters was assessed using the correlation coefficient  $R$ .

Conclusive differences between the mean values of the parameters studied in different batches were estimated using the Student's  $t$  test.

Comparing the results of the disease estimated by two questionnaires, it has been inferred that the SLAM, which was drawn up after multiple multidimensional studies, is based on the experience in the field of the assessment of disease activity to patients with lupus, which can be validated as a sensitive instrument in measuring lupus activity and for detection of possible hematological changes in this pathology. The SLAM index is variable, with the instruments and patients included in the study group, and it seems that it has outrun the SLEDAI of being informative in measuring lupus activity, the signs and symptoms activation of pre-existing hematological changes. It should be noted that SLAM evaluates, like the SLEDAI does, light organic manifestations, as well as the serious ones, which define the prognosis of the disease and the amount of organic damage index.

We were interested to estimate general state of health through SLAM, which is not stipulated in the SLEDAI. And that is because a person without neurolupus, but with a poor general condition estimated by the SLEDAI may display a low score, and the same patient assessed after SLAM can display with proper activity according to the index that is constitutionally expended score from hematological changes. We recorded the importance of the accuracy of the applied tool according to the hypothesis, the first-ever SLAM is designed to record only the symptoms reported by the patient due to SLE, but sometimes it becomes difficult to distinguish claims of secondary manifestations of light lupus exacerbations.



In the tests for the evaluation of disease activity in accordance with the questionnaire, in addition to SLAM, clinical examination has taken into account and some laboratory **variables** such as **the number of leucocytes, lymphocytes, platelets, hemoglobin** and **ESR**. Hemoglobin values ranged between 68 and 148 ( $107.6 \pm 2.1$ ) g/l, they being an indication of anemia. Leukocyte index in the batch of examined patients noted in average 1900–8800 ( $4.38 \pm 0.3$ ). The average values of lymphocytes were  $9942 \pm 0.4$  (variations between 565 and 1900 or from 12 to 36%), and the level of platelets has been downsized considerably— $246,900 \pm 9.2$  (numerical variations between 111,200 and 450,000).

We analyzed the ESR as important hematological index, which increased the number of patients to 64% (74.4% advertising and reflecting the high activity of the disease).

We were interested to analyze the titers fractions C3 and C4 of the complement, along with the complement titer, which ranged between 1:4 and 1:128. It is worth noting that complement C3 fraction joined in the range of 6.8 to 130 mg/dl ( $23.4 \pm 3.4$ ), predominantly being low. C4 fraction was found for low and medium ( $8.22 \pm 1.48$ ) with variations between 4.0 and 22.4 mg/dl, the most common being dropped in the majority of patients with systemic lupus erythematosus.

We were interested in comparing the results of two cohorts in the SLAM. Patients included in the study were divided, as we agreed in two batches: with anemia—59 cases (68.6%) and without anemia—27 cases (31.4%).

To analyze anemic syndrome, two groups, which consisted of 59 patients with anemia and 27 patients without anemia, were numerically different to compare, so later we resorted to instrumental indexes included in the scale of assessment of the SLAM disease activity.

Comparing groups through the constitutional component, it was estimated that the patients who had various types of anemia, constitutional abnormalities, included in this section, were detected more frequently than those without anemia ( $p < 0.05$ ). We also found that the skin of the patients in the first group, with anemia were more frequently affected, compared with the group of patients without anemia and fatigability (43.2%) were present in bigger intensity was expressed in the batch of patients with anemia. It could define the basic disease, but precipitated by the presence of anemia.

Collaboration obtained outlined in the following: oral ulcers, periangle erythema and photosensitivity were found in a greater number of patients with anemia—46 (77.9%) in comparison with batch without anemia, where they were detected in 18 (66.7%) patients. In addition to erythema alopecia and discoid lesions being extended to patients with anemia.

After the estimation of lupus activity on cardiovascular impairment, the results revealed higher values in the batch of patients with anemia to 61.0% (versus 29.9% cases), and in the group without anemia, we can summarize that the activity has an impact on disease anemia or maintain this pathology. Speaking about the effect of SLE on central nervous system, it was observed especially in patients with anemia, accounting for 57.6% of cases having an impact on lupus activity. Our data transpose with literature data show that the damage to the nervous system reflects the activity of the disease in patients with anemia [3].



Comparing the values of lymphocytes in both groups of patients, we have revealed that lymphocytopenia was more specific in the group of patients with anemia—49.1% of cases had decreased lymphocyte levels as low as 565 cells. Thrombocytopenia was also more common in patients with the beginning of anemia in lupus. As a matter of fact, the ESR, primarily, is a common index, and it was investigated in terms of different rates of acceleration, depending on the activity of the disease. Defining line was inspired by the study of LIGHT XXIX (Villa, 2005), which divided the ESR values into four categories: <12—normal, 12 to 30—average acceleration, 30 to 50—moderate hike and over 50 mm/hour—marked acceleration, the results being calculated after an hour and the possibility of making a finding after 2 hours (to 6–24 mm).

We were interested in analyzing the disease activity and damage rate index of various categories of ESR. ESR has been determined to be of average elevation—12 to 30, moderate elevation—30 to 50 and marked as acceleration—over 50 mm/hour.

We analyzed whether the activity, SLAM index and IL are reflected in ESR. According to the data, ESR was independently associated with high scores of SLAM. It was found that accelerated ESR associated with both disease activity, as measured by the SLAM, and with high scores of the SF-36, which had been in decline. The relation between index variables and effect on the quality of life as measured by the SF-36 was foreshadowed.

It should be noted that the increase in ESR was not dependent on the organic damage index. We can conclude that the erythrocyte sedimentation speed is a relevant test and can be considered a sensitive index. ESR has been correlated with disease activity, assessed by SLAM and has impact on the quality of life, based on estimates by the SF-36.

## **6. Risk factors for the development of hematologic manifestations in SLE**

We took the risk factors as a research vector in order to highlight and analyze their impact later on the installation of hematological lupus and their interference with the subsequent development of the disease. Data displayed in the recent related literatures highlight both general and specific risk factors for hematological lupus. General risk factors are hypertension, diabetes, obesity, dyslipidemia, smoking (more than 10 cigarettes per day), valvular heart disease and/or atrial fibrillation, cumulative doses of glucocorticosteroids >10 g, oral contraceptives, pathology of thyroid (history of hypo- or hyperthyroidism, antithyroid therapy or HRT) and family history of psychiatric illness [18]. Specific risk factors involve increased levels of antiphospholipid antibodies, the presence of lupus anticoagulant and antiphospholipid syndrome and the presence of Raynaud's phenomenon, livedo reticularis and cutaneous vasculitis [10, 14].

An imperative of assessing anemia is presented by identifying and stratification of the importance of each clinical and serological parameter suggested as a risk factor for hematopoietic system involvement in lupus [13].

From the study, we observed that the most commonly found index in patients with lupus was the antiphospholipid syndrome, which was present both in patients without hematological damage—8 (9.3%) cases and in those with severe hematological damage—15 (17.4%) cases. Our survey data coincide with those stipulated in researches throughout the world, where the association of antiphospholipid syndrome is most often reported anemia pattern in lupus.

According to the following data, the presence of livedo reticularis in patients without anemia was detected in 14 (16.3%) cases and in patients with anemia in 17 (19.7%) cases. Thus, we presume that the presence of livedo reticularis in the study conducted by us is associated with hematologic manifestations and can be considered as a risk factor of a hematopoietic system involvement in patients with lupus. The newest scientific reports present the Raynaud syndrome as a specific risk factor for developing anemia, mainly for ACD (anemia of chronic disease) and iron-deficient anemia [7, 13]. According to our data, Raynaud syndrome was present less—only in 3 (3.5%) patients without anemia and in 6 (6.9%) patients who developed anemia.

Clinical examination of patients noted that cutaneous vasculitis has been associated closely with various events in the development of anemia and was present in 12 (13.9%) patients, since patients without anemia only in 5 (5.8%) cases.

In addition to specific risk factors, we were concerned about examining generic risk factors that were less connected with anemia before. We found a close association between hypertension and hematological manifestations—11 (18.6%) patients. It is important to mention that in 2 (2.3%) cases where diabetes was detected, hematological syndromes were observed simultaneously. Following the examination, we reported that factors such as obesity, dyslipidemia, smoking excessively and cumulative dose of glucocorticosteroids >10 g were identified mainly in patients who developed various hematologic manifestations.

A special role is given to valvulopathy, which was detected in 5 (5.8%) patients without anemia and 6 (6.9%) patients with anemia. The studies in the domain show a high frequency of anemia in patients with valvulopathy of left heart in systemic lupus erythematosus [20]. Other research highlights the frequent association of renal and hematological manifestations in lupus [11, 26]. According to data reported, kidney damage was detected in 4 (4.6%) patients without anemia and in 24 (27.9%) patients with anemia. The risk profile is complemented by another factor, such as compromised neuropsychiatric history detected in 5 (5.8%) patients in the group with hematological antidamage (clarify).

Summarizing the exposed view of the risks of the patients with SLE, we can register that antiphospholipid syndrome, livedo reticularis, skin vasculitis, smoking, cumulative dose of glucocorticosteroids >10 g and kidney damage are more commonly found in the context of a hematological lupus than in those without impaired heme.

## 7. Synthesis of the obtained results

At the current stage, the study of the hematological manifestations in systemic lupus erythematosus (SLE), which is a severe, multisystem autoimmune disease of unknown etiology

with varied clinical and paraclinical expressions associated with a hyper production of auto-antibodies and with a potentially major fatality rate, represents a domain of scientific interest and an important medicosocial issue [19].

In the past 5 years, thanks to immunological and morphopathological achievements and the usage of techniques of fundamental organic research, important progress was obtained in regard to the diagnosis, monitoring and the treatment of autoimmune diseases.

Nevertheless, the diagnosis of this disease [11] and the bearing of the expenses of the social support persist because SLE has a major potential of disablement and thereby affects the quality of life severely. The prevention of relapses transforms into an extension of the remissions leading to a mostly regular social inclusion and reduced social costs through limiting the hospitalization time [24]. Still, the impact of the pathology of the hematopoietic system on the quality of life remains uncertain.

In the presented paper, we intended to analyze the modern research regarding the clinical and paraclinical diagnosis of systemic lupus erythematosus. We have examined a group of patients with lupus by thoroughly researching the hematopoietic system—a clinical criteria discussed in the specialty literature. In the past 10 years, these discussions [12, 13] are related not only to the classically iterated clinical manifestations but also to their quantification through instruments and also using hematological, immunological and paraclinical methods.

In our study, the female/male ratio was 86 (100%), respectively, 0. Analyzing the average age of onset, we have established that the onset of the disease was at various ages—from 21 to 62 years old (average  $32.8 \pm 1.32$ ) but essentially young people are affected. At the moment of examination, the patients observed were averagely  $41.37 \pm 1.40$  with variation intervals 21–65 years. The analysis of the disease duration detected significant divergences: from 1 month up to 365 months (48 years). In the study, we have examined patients with an average evolution span of the lupus process of 98.28 months ( $8.6 \pm 0.47$  years), most frequently between 1 month and 5 years. A study of prospective analysis was accomplished by Harly (1989) [11] but with an average evolution span of the lupus process of 5.4 months and because of the shorter stage, a disparity of results is presumed when it comes to a comparison to our own data regarding the cumulative doses of corticosteroids and the index of organ lesion.

Throughout our study, we were interested in distinguishing the etiological aspect of the moment of onset of SLE, an aim for which we have intended to reflect the specter of triggers through the overlap of anamnestic data that were accurately collected from the patients included in the study and divided into two groups: those with anemia and those without anemia. Our results revealed the presence of stress in 11.1% of those who did not develop anemia and in 10.2% of those who developed hematological syndromes during the disease. This determined us to consider that the psychoemotional stress was significantly involved in both groups included in the study. Exposure to low temperatures was identified both in the evolutionary context of the patients without anemia—18.5% and in that of those with anemia—20.3%. Another trigger, antecedents of exposure to sun, was detected in 33.3% of lupus patients without subsequent hematological manifestations and in 27.1% of those who developed anemia. It seemed that the exposure to sun generated the systemic lupus

erythematosus but it somehow was a more protective measure for the following lesion of the hematopoietic system while the vaccination was less actively implicated in the onset of lupus—in 3.7% but those cases presented with a significant potential of hematopoietic system implication in the course of the disease—in 1.7% of cases. Simultaneously, we established that 29.6% of the patients without anemia and 32.2% of those with anemia could not outline any causes that led to SLE, this leaving room for more elaborate studies on this topic in the future.

Thus, the comparative assessment of the conditions which preceded the disease in the study groups revealed that the insolation and the exposure to low temperatures take up the biggest share as triggers for the development of hematological syndromes in systemic lupus erythematosus, while the psycho-emotional stress and the vaccination are not directly responsible for the onset of lupus but their impact on the development of anemia is not excluded.

For the estimation of the activity of lupus, we chose a validated instrument—the SLAM index. The results of the investigation confirmed that the use of this index is also practicable in the dynamic assessment of the activity of the process and the implication of the hematopoietic system rendered through anemia, leukopenia, lymphopenia, thrombocytopenia and accelerated erythrocyte sedimentation rate. Referring to the average score of the SLAM index, it was higher in the patients included in the study than in the prospective study presented by Bertoli (2007) [24], constituting  $22.6 \pm 1.94$  versus  $19.4 \pm 5.5$ . It should be noted that on the position of significant discrepancy is the fact that all the patients from our group of study were receiving corticosteroids, whereas in the reference study only 69.2% of the patients were receiving corticosteroids at the moment of the examination.

The clinical picture of lupus presented very diversely by involving different organs and systems. We wanted to compare the frequency of the diagnostic criteria ACR 1997 for SLE met by the patients in our group of study and those from the reference study reported by Giannouli (2006) [23], where the prevalence of anemia between the lupus patients was 50%. Similar data were published by Bertoli (2007) [20]. Considering that we detected a rate of 68.8% of hematopoietic system implication in our study, we continued to compare our results with other studies. In this connection, we discovered that the results obtained by Voulgares (2000) and Alastair [1] proved the hematopoietic system affliction at a rate of 14 and 80%, respectively. It is noteworthy that in the longitudinal study LUMINA LI (2007) [24] carried out on a cohort of 613 patients in the hematological modifications were present in 62.3% of cases. Therefore, our results are similar to the data of some studies, whereas they differ substantially from others. It is difficult to explain the big difference for the hematopoietic system impairment, but we can suppose that the cause has been the recently instituted lupus—only 5 months in the reference group, while the hematopoietic system implication is a rare manifestation.

For obvious reasons, we referred our results to the data from other studies which reported to the presence of lupus diagnostic criteria: oral ulcerations, arthritis and arthralgia, serositis and renal lesions and we deduced that these attest in similar proportions to those appreciated by the prospective study of Harley (1989) [18]. Our data noted that the presence of photosensitivity in 65.1% of the patients and that of the malar erythema in 89.5 versus 36–41.5%, respectively, which were discovered in the study of reference Harley (1989). The data referring to



hematological and immunological modifications and the antinuclear antibodies are similar to those appreciated throughout our study—64.3% cases. In all the patients with systemic lupus erythematosus, we remarked the presence of antinuclear autoantibodies (ANA) and anti-double-stranded DNA (anti-dsDNA), at least one of these indexes was found positive in the patients included in the study. According to the criteria defined by the American College of Rheumatology (ACR), the diagnosis of systemic lupus erythematosus was established on the basis of 4 or more criteria from the 11 criteria stated by the ACR, characteristics that were found simultaneously or successively in the patients investigated by our studies.

The study carried out analyzed the lupus patients with a hematological pathology, confirmed by a hematologist and the patients who did not manifest a pathology of the hematopoietic system. Through clinical and paraclinical examination of the hematopoietic system of the patients with SLE from the selected group, we deduced that the disease can affect the hematopoietic system at any level, but has a predilection for these types of ailments: anemia, leukopenia, lymphopenia and thrombocytopenia.

In our study, the number of hematological syndromes has correlated positively with the high score of the SLAM index and the SLICC/ACR score, which suggested that more hematological manifestations could be associated with the high activity of the disease and can predispose to a further organ lesion. Nevertheless, some hematological events in SLE may only be the clinical presentation, persistent even at a low activity of the disease, without specific serological markers.

According to the investigational objectives, we analyzed the possible relations between the clinical manifestation, the activity of the process and the organ lesion. The results of the research under this aspect have estimated that the evolution of the hematological manifestations depends on the activity of the lupus process. The impact of these on the organ lesion index and the quality of life was recorded. The index of organ lesion becomes higher with the display of hematological events: anemia, leukopenia, lymphopenia and thrombocytopenia, which lower the patient's quality of life significantly. Despite the frequent hematological manifestations in SLE, there are no specific clinical or paraclinical tests for the diagnosis of the implication of the hematopoietic system in SLE, and there are also no specific clinical or paraclinical tests for the diagnosis of the implication of the hematopoietic system in the disease evolution, all these imposing the necessity of further research and the imperative demand for finding specific biomarkers for anemia.

With the purpose of establishing the importance of the reduction of erythropoietin level as a hypothetical biomarker that is associated with hematological disorders in lupus, particularly of the anemia of the chronic disease, we stratified the values depending on the obtained results. We examined the level of erythropoietin in 57 patients from the study group, in 3 of whom other types of anemia were found, 20 presenting iron-deficiency anemia of different degrees and 34 patients had the anemia of the chronic disease. Continuing the analysis of the presented data, we discovered that in 43 patients the level of the researched index was subnormal—between 1.12 and 3.22  $\mu\text{IU/ml}$ . In 20 patients, the level of erythropoietin was estimated as normal and the diagnosis emitted—iron-deficiency anemia. We overlapped our records with the results in recent literature and we affiliated towards the principle that the level of erythropoietin may be useful in detecting the anemia in lupus. According to the data of Schett (2010) [3], the low titer of erythropoietin correlates with the anemia of the chronic disease in lupus, and the data only



confirmed this statement. All of the findings support the opinion that these patients require a dynamic evaluation and monitoring.

Calculations for the total doses of corticosteroids, also named cumulative dose, preoccupied us into relating it to the involvement of the hematopoietic system in the lupus process. The cumulative dose of corticosteroids was calculated according to the prednisolone dose administered orally throughout the disease, also including the pulse therapy. The cumulative dose, as is known, not only increases during the disease but also includes the pulse therapies which imply the administration of high doses of corticosteroids—1500 to 3000 mg (1.5–3.0 g) in a single cure or the programmed pulse therapy with a dose of 500 mg monthly. We divided the patients according to the quantity of corticosteroids administered and we considered the quantity below 5 g as a low dose, between 5 and 10 g as a medium dose and higher than 10 g as a high dose [11]. After the summary dose of corticosteroids, our patients accumulated mostly medium and high doses of corticosteroids—above 5 g. We did not detect a correlation of the doses of corticosteroids with the disorders of the hematopoietic system in the group of study.

According to the outlined objectives, we were motivated to analyze the damage to the hematopoietic system in accordance with the criteria for SLE elaborated by ACR (1999). The analysis of the results obtained shows a large and diverse specter of hematopoietic system implications in SLE. Of 86 patients examined in the study, the hematopoietic system implication and more precisely anemia were present in 59 (68.6%) patients. At the same time, the same patient may develop one or more hematological syndromes. Our data correspond to the data of the recent scientific methods dedicated to the assessment of the anemia in the context of lupus, including those reported by the cohort study carried out on 345 patients under the supervision of Voulgares and Kokori (2000) [23], which reported the clinical incidence of hematological manifestations in 38.4% of the patients.

From this study of reference, we ascertained that the most frequent hematological syndromes were the anemia of chronic disease—37.1% cases (39.5% in the patients examined by us), iron-deficiency anemia—35.6% (versus 23.2% in our study), followed by autoimmune hemolytic anemia—14.4% and other types of anemia—12.9% cases. According to these results we observe similarities between the frequency of the hematological syndromes detected in the patients from the study of reference and those enrolled in our study.

Therefore, the diversity of hematopoietic system damage reveals the indubitable value of applying the criteria developed by ACR (1999) for evaluating the patients with SLE.

Continuing the research on this subject, we insisted on the thorough approach of anemia as a form of hematopoietic system affliction in SLE. Anemia and other hematological disorders, such as leukopenia, lymphopenia and thrombocytopenia, are still a challenge for the diagnosticians for reasons which include the fact that they could be either a direct manifestation of SLE or a secondary response to a chronic disease that affects the quality of life.

We tried to assess the indexes important for SLE in the patients without anemia tied to lupus and in those with the anemia of chronic disease. From the data reported before, it can be derived that the average age of onset in the patients without anemia was 34.73 years, whereas in the patients with anemia of chronic disease was 37.2 years. The patients with anemia of the

chronic disease also had been sick for a longer period of time—123.4 months compared to those without anemia—80.6 months. It has been determined that the accentuation of anemia happens during the disease. According to the activity of the disease appreciated through the SLAM index, it was established that the patients with anemia of chronic disease had the highest activity of the disease—22.6 points, whereas those without hematological manifestations showed a moderate activity—15.8 points. The index of organ lesion: SLICC was highest in patients with anemia of chronic disease showing values of 1.6 points qualified as an index of moderate organ lesion compared to the first group where the SLICC index was 0.5 points. Our data correspond to those affirmed in a study of reference, Vila (2009) [23] which reveals that anemia and other hematological syndromes occur on the background of active SLE and are associated with a longer age of the disease as well as the organ lesions are more emphasized.

According to the outlined objectives, we evaluated the parameters regarding the patient's quality of life using the SF-36 score. The SF-36 accumulated values were 61 points in the patients without anemia and 41 points in the patients with moderate and severe depression; this being interpreted as a sign of a significantly reduced quality of life. An important study of reference carried out by Stoll (2009) [13] was dedicated to evaluating the quality of life of the patients with SLE and anemia. This study reveals a suggestive detail such as the fact that the routine assessment of the quality of life of the patients with SLE may facilitate the early detection of anemia.

Of course, we were also tempted to analyze the predictors of a reserved prognosis for the patients with SLE who during the disease develop a large variety of hematological syndromes that have an impact on the quality of life. After the analysis of our own data, we cataloged as such the manifestations of renal lesion, thrombocytopenia and a high level of anticardiolipin (aCL) antibodies presented in the patients with SLE and their role in inducing or associating hematological syndromes.

The analysis of diverse clinical manifestations in the hematological lupus was necessary because the persisting clinical indexes may pass on into the class of risk factors. Despite the fact that the paraclinical signs are included in the diagnosis criteria, we analyzed the cases included in the study group by stages. The study carried out by us detected high titers of anti-dsDNA in both groups but only in 6 (23.0%) of the patients without anemia and 56 (94.9%) in those with anemia. Given the fact that aCL (anticardiolipin antibodies) is an index associated with disorders of the hematopoietic system, the analysis of the level of aCL antibodies, Ig and IgM, in the two groups of patients with lupus was a priority. It is to be remarked that in both groups the patients had high levels of anticardiolipin (aCL) IgG antibodies, but in the group without hematological lesions, their frequency was 22.2%, whereas in the patients with hematological lupus it was 28.8% ( $p > 0.05$ ). Continuing the examinations under this aspect, we detected anticardiolipin (aCL) IgM antibodies in 1 (3.7%) patient who did not develop anemia and in 4 (6.8%) patients who manifested anemia; the data obtained in our study being similar to those in a retrospective longitudinal study carried out by Pasero (2009) [14].

The antiphospholipid syndrome was present both in the patients without hematological disorders—8 (29.6%) cases and in those with hematological disorders—in 15 (25.4%) cases. Besides, the data obtained in our study coincide with those stipulated in the research carried out globally, according to which the association of the antiphospholipid syndrome is most

frequently reported in relation to the pattern of hematological events. According to the data that analyze the presence of livedo reticularis in the patients without anemia, we discovered 4 (25.9%) of such cases, and in those with anemia this characteristic of the disease was signaled in 21 (35.6%) of the cases. Thereby, we conclude that the presence of livedo reticularis in the study carried out by us was associated to hematological manifestations and may be considered a factor that implies the risk of hematopoietic system affliction in the patients with lupus. Recent investigations report the presence of Raynaud syndrome as a specific risk factor for the development of anemia [18], but according to our data, the Raynaud syndrome was a rarely assessed phenomenon—in 1 (3.7%) patient without anemia and in 4 (6.8%) of those who did not develop anemia.

We intended to use valid instruments for the assessment of the quality of life in the patients with SLE. For this purpose, we applied the SF-36 questionnaire in its short version (short form-36). SF-36 is a brief way of testing but in the special literature there are also other sets of indexes used for reflecting the quality of life such as SF-20. According to the literature data, the SF-36 questionnaire possesses the capacity to evaluate the patients with lupus exhaustively—a quality for which we preferred it in evaluating the impact of the hematopoietic system affliction on the quality of life of the lupus patients. The low quality of life of these people both by the mental health and the physical health, predominantly the physical one conditioned by the hematopoietic system afflictions in 35.6% of the cases. We compared our results with the data presented by Harley and Urowitz (2010) [22, 27], which indicate both the implication of the mental component and the physical one in determining the quality of life of the patients with hematopoietic dysfunctions on the background of lupus.

The data obtained by us after carrying out the study detected similar results with those reported by Harley (1989) [22], especially the ones referring to the vitality domain, physical function, general health and pain, but there were differences regarding affectivity and social function.

We analyzed comparatively the patients with anemia by means of the disease activity index, the organ lesion index and the impact of these on the quality of life. Our results were similar to those obtained in the study done in parallel with ours and recently emitted by other teams of researchers in the world [23], who confirmed that the quality of life index is inversely proportional to the activity of the disease and the organ lesion index for the patients with anemia.

Another study of reference carried out by Nossent and Locatelli (2004) [7] was dedicated to the interrelations of different dimensions and subscales of the generic questionnaire SF-36. Both our data and those from the study of reference denote the prevalence of low scores (<50 points) among the patients with SLE. In contrast to our data, the patients enrolled in the study by Moitinho (2011) [11] accumulated even higher scores—between 81-0 and even 91-100, which were not observed among our patients. Thus, the data provided by the SF-36 questionnaire attest the impact of the hematopoietic system dysfunctions in SLE on the quality of life, most of all through the development of major hematologic syndromes, by affecting all the criteria which characterize it. The low scores among the patients without hematological afflictions invoke that the chronic disease itself implies an important role in the patient's life, the patient being often forced to review some aspects of their daily life, including some in regard to social relations and professional preoccupations.

Even if it is insistently approached in several scientific centers, recognizing the hematological manifestations in the early stages of lupus still remains a challenge for the clinicians. Correctly attributing the hematological syndromes to those caused by the primary disease or to those that present as a reaction to suffering from a chronic and incurable disease or to the adverse reactions to medication or to some metabolic dysfunctions still remains a diagnostic dilemma [5, 13]. Because the physiopathology of these clinical manifestations is not fully elucidated, they cannot be attributed unequivocally to anemia.

An important moment and a problem with a difficult evolution are the subclinical manifestations of the hematopoietic system implication in SLE, which require an early identification and a gradual therapeutic intervention in order to improve upon the further disabilities of the patients. In this connection, the lack of a consensus in regard to the application of different hematological tests with a different potential of sensibility makes its mark. In the absence of a diagnostic standard and potential specific biomarkers for the hematologic affliction, various serological explorations and laboratory investigations are used to support the clinical diagnosis. The results of our study confirm this situation.

Our data correspond to those reported by Bertoli et al. LUMINA LI (2007) [20] and reveal that anemia is strictly associated with the activity of the disease and the organ lesion index both at the disease onset and during its evolution; this association being even closer than that with the anti-dsDNA antibodies. Moreover, anemia is associated with several clinical manifestations including, but not only, those that reflect a more severe disease such as the neuropsychiatric or renal implication. Ideally, the biomarkers have to be standardized and vastly applied especially when the hematocrit assessment is an easy and accessible test and can be considered a cheap indicator of the disease evolution, which allows the clinicians to anticipate the intermediary and long-term consequences of the lupus infection [22].

In our study, the relevance of anemia (independently of its cause) was estimated as being both a short-term prognostic factor (the activity of the disease) and a long-term (lesion index) prognostic factor for the evolution of the disease. The estimated data in the lupus patients with anemia corresponded to those reported in the special literature and invoked the necessity of the improvement of early exploration, including through raising the awareness of the rheumatologists and the cooperation with the general practitioner, the hematologists, etc., who could advisedly get involved in the early detection of hematological dysfunctions, because through their improvement with specific methods, it is possible to maintain a long-term good quality of life.

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