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Hematologic manifestations of rheumatic diseases

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Abstract

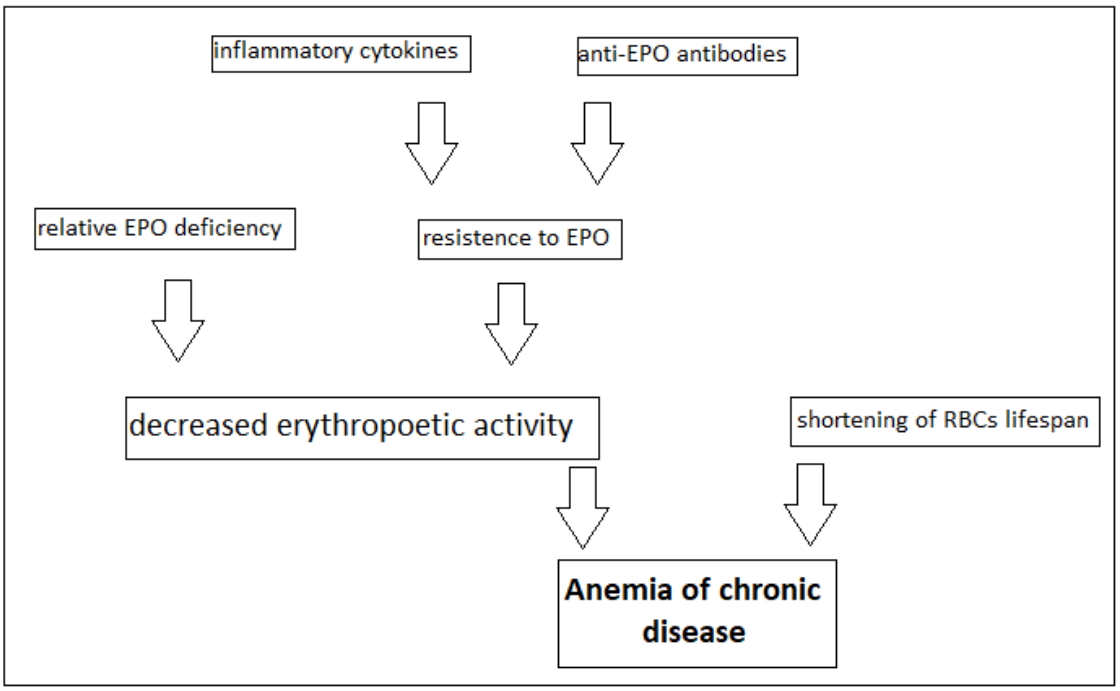
Rheumatic diseases are, by their very nature, multisystemic entities with vast array of possible hematologic manifestations. The mechanisms of different hematologic manifestations tend to be complex and vary from patient to patient. The presence of a given hematologic abnormality can, in some instances, be a prognostic factor with varying utility in different disorders. Recent research in basic sciences has contributed to the understanding of hematologic complications of autoimmune diseases. The aim of this work is to give a brief overview of the latest research on the pathophysiology of hematologic manifestations in rheumatic diseases, with epidemiologic considerations included when available. Special attention has been paid to the pathophysiology of anemia and the challenges of its diagnosis.

Key words: anemia, rheumatic disease, autoimmune disorder

Introduction

Anemia

Anemia of chronic disease (ACD) is thought to be caused by a decreased erythropoietic activity with slight shortening of red blood cell (RBCs) lifespan as an additional factor. Relative erythropoietin (EPO) deficiency and resistance to EPO, either cytokine- [1] or antibody-mediated [2] has been proposed as an important factor and its supplementation may have therapeutic importance [3]. Much attention has been paid to the alleged role of inflammatory cytokines in the pathogenesis of ACD, with researchers highlighting a dual, EPO- dependent and EPO-independent mechanism through which they contribute to the development of ACD [4]. Tumor necrosis factor (TNF) alpha has been determined to be significantly increased in various studies on patients with ACD. A study found an overall higher level of TNF alpha in rheumatoid arthritis (RA) subjects who had laboratory values consistent with ACD, with hemoglobin levels that were in inverse relationship to TNF alpha concentrations [5]. The same study showed that, in vitro, TNF alpha inhibits erythroid colonies in both RA patients with ACD and in the control group consisting of RA patients without ACD. This anti-erythropoietic property of TNF alpha was stronger in the ACD group than in the control group. The inhibitory effect was effectively counterbalanced by adding TNF alpha inhibitors to the cultures.. The same property of anti-TNF alpha antibody was established in another study on RA patients with ACD [6] and a study that followed ankylosing spondylitis patients receiving an anti-TNF therapy [7]. Previous studies described the development of anemia in rats injected with TNF alpha [8] and showed that recombinant TNF negatively influences iron uptake by macrophages, thus contributing to the hypoferremia state that characterizes ACD [9].



Coombs test positive patients may not necessarily have autoimmune hemolytic anemia (AIHA) and relying on this testing alone to identify the patients with this type of anemia leads to an overestimation [10]. Relying on reticulocyte count, around 10% of systemic lupus erythematosus (SLE) patients were found to develop hemolytic anemia either prior to or after their diagnosis. Most of these patients had laboratory values consistent with AIHA at the time of their diagnosis which means it is typically an early manifestation of SLE. Patients with severe AIHA showed higher systemic disease index SDI scores and had more autoimmune complications, including thrombocytopenia. The occurrence of AIHA didn't affect mortality rates in an independent manner. Due to a shortage of data, the study didn't establish any associations between antibody titers and the occurrence of AIHA [11] Compared to SLE patients with other types of anemia, those with AIHA have lower haemoglobin values. The degree of anemia didn't correlate with disease activity. Patients with AIHA frequently tested positive for both IgG and IgM aCL antibodies. Other associations included low complement levels and presence of anti-dsDNA antibodies. The median time in which the correction of anemia was achieved was 3 month for individuals with AHA, which was significantly shorter than for other types of anemia. [2]. Another study found a positive, independent correlation between AHA occurrence and IgG aCL antibody titers, thrombocytopenia, renal involvement and prospective risk of thrombosis. [12] AIHA in SLE patients seems to be more common in pediatric population. Its severity is also greater in children than in adults with SLE [13] AIHA is much less common in primary Sjogren syndrome. One Chinese study found that AIHA accounted for 8% of total cases of anemia

in Sjogren syndrome, with less than 1% of patients affected. Another, larger study, also from China, found a greater prevalence of AIHA in primary Sjorgen Syndrome, determined to be at 2,8%. Patients with AIHA differed markedly from the rest of the cohort in their clinical presentation, with significantly fever symptoms of xerostomia and arthralgia, and more pronounced edema, fever and liver dysfunction. They were also more likely to have other cytopenia, but their ANA, SS-A and SS-B antibody titers didn't differ significantly from non-AIHA group [14]

IDA can be difficult to differentiate from other causes of anemia in patients with chronic inflammatory states, as inflammation influences classical markers of iron deficiency [15]. Functional iron deficiency, which characterizes ACD is caused by a deranged mobilization of iron, and not by iron stores depletion. Bone marrow iron stores can be used to differentiate between the two, but the test is cumbersome and expensive. Soluble transferrin receptor (sTfR) and transferrin receptor- ferritin index (TfR-F index) are other valuable tools that can be useful in establishing a correct diagnosis [16,17]. Relying on sTfR alone may be of limited diagnostic utility, as evidenced by a study on a population of anemic RA patients [18] ACD and IDA are not mutually exclusive and high transferrin receptor levels in patients with other laboratory values suggestive of ACD can point to such co-occurrence [19]A study found that RA patients with IDA had lower disease activity compared to ACD group, but their anemia was worse than in ACD-RA patients [20],which is in contrast to a study on SLE population in which IDA was characterized by the mildest severity among anemia aetiologies [2]

Platelet abnormalities

Platelet abnormalities are commonly found among patients with rheumatic diagnoses. They include both thrombocytopenia, that feature most prominently in systemic lupus erythematosus, primary Sjogren syndrome, antiphospholipid syndrome, dermatomyositis and systemic scleroderma [21], and increased platelet count, most commonly seen in rheumatoid arthritis, but also in patients with inflammatory bowel disease [22].

> Both pathogenesis and clinical picture of thrombocytopenia secondary to an autoimmune disease differ between various rheumatic diseases [23].
>
> ITP is found in around a third of SLE patients [21,23] and can correlate with disease activity and constitute a relevant prognostic factor for, among others, lupus nephritis [24] and earlier death [25].

ITP is found more often in patients positive for dsDNA antibodies. The pathogenesis of ITP in SLE is complex and multifactorial. Various autoimmune factors have been suggested to play a role, among which figure anti-platelet, anti-phospholipid, anti-thrombopoietin and

anti-CD40L antibodies [26]. SLE patients with ITP have been shown to more often present with decreased levels of complement components, particularly C4, which may suggest a possible implication of C4 deficiency in the pathogenesis of ITP [21]. Thrombocytopenia in SLE patients is usually mild and doesn't require additional treatment. In rare cases that run a more severe course with excessive purpura formation or platelet count below $<50 \times 10^3$, the treatment of choice include glucocorticoids and, occasionally, azathioprine as a steroid-sparing agent [26]. The research on the subject of ITP complicating the course of pSS has thus far consisted of rare case studies, hence the unknown incidence of ITP in pSS. Xerostomia and increased SAA levels are probably more commonly found in pSS patients with IPS [21]. A few clinical studies have described a possible positive therapeutic effect of intravenous immunoglobins infusions [29] and low-dose rituximab [30] in pSS patients with IPS. Some, albeit small-scale studies show that up to one fourth of patients with antiphospholipid syndrome (APS) have thrombocytopenia [31.32]. The pathogenesis of thrombocytopenia in APS patients is largely unknown [33]. The treatment of thrombocytopenia in APS patients is standard[23]. Thrombocytopenia is observed only sporadically in patients suffering from systemic scleroderma and is thought to be causally associated with microangiopathy [33]

Leukocytes abnormalities

Abnormalities in the number of white blood cells are common in rheumatic diseases. Both increase and decrease in the total amount of leukocytes or of particular fractions can be observed. One study found WBC levels to be lowered in 66% of patients suffering from systemic lupus erythematosus (SLE) [34], while another one found leukocytopenia to be present in 38% individuals with Sjogren syndrome [46]. Lymphopenia is the most common abnormality in SLE, with both lympho- and neutropenia being related to high risk of infection in the patients [36]. It has been proven that leukopenia in SLE is usually caused by immunological factors affecting either bone marrow or peripheral blood [35]. Leukocytic antibodies, which were found in 60-79% of all patients in one study, play an important role in the pathogenesis of leukopenia in individuals diagnosed with SLE [37,38]. The antibodies combine with leukocytes leading to their eventual destruction in the mechanism of ADCC and complement related cytotoxicity. This is significant especially in patients with lymphopenia. The antibodies were identified in a much higher percentage of the patients with leukopenia (55.6%) as compared to the group with SLE without this abnormality [43]. The other important factor in the pathogenesis of decreased WBC count is lowered expression of peripheral CD55 and CD59 regulating proteins. Such protein deficiency might

cause sensitization of leukocytes and other cells to complement related lysis [39,40]. Multiple observations also reveal a strong correlation between leukopenia and elevated IFNα levels [41]. Oke and Brauner in their study published in June 2017 elucidated the role of IFN-λ1, IFN-α and IP-10 in the pathogenesis of lupus leukopenia. The study involved 261 patients and 261 individuals forming the control group. In the experimental group the level of these cytokines was higher in patients with stronger manifestation of the disease and lower WBC values. Higher IFNα level was noticed mainly in patients with leukopenia, whereas IFN-λ1 in those with lymphopenia. However, in individuals with both lympho- and leukopenia both IFN-λ1 and IFN-α levels were elevated. Higher IP-10 also correlates with leukopenia and lymphopenia. All these suggest that differing cytokine profiles have varying effect on haematological disorders in SLE [42]. For neutropenia in SLE, certain factors were also identified as possible causes of its prevalence. The presence of G-CSF autoantibodies was suspected to be one of them. However, although in the study conducted by Hellmich and Csernok the antibodies were found in the majority of patients with neutropenia in SLE, their exact role in the pathogenesis of neutropenia was proven in single cases only. In all other cases, no biological function of the autoantibodies was found. Nonetheless, the research revealed a correlation between neutropenia and higher levels of both anti-G-CSF and G-CSF. This may suggest insensitivity of other patients' bone marrow cells to the action of G-CSF irrespective of its elevated levels [44]. The suppression of both proliferation and maturation of progenitor marrow cells can result from the presence of specific antibodies in the serum. Liu, Ozaki and others revealed the presence of such antibodies and their suppressive action on marrow cells [45]. Apart from the destruction in the peripheral blood, these seem to be the major pathways leading to neutropenia.

As for Sjogren syndrome, hematological disorders were found in 56% of patients. In the experimental group studied by Castor and others, 38% had leukopenia (in that, 38% lymphopenia and 10.5% neutropenia) [46]. The reason for neutropenia remains unknown. Greater amount of neutrophil precursors may suggest its peripheral destruction related to the presence of antibodies. The inhibiting effect of cellular and humoral factors on the production of neutrophils in the bone marrow or on destruction of the precursor cells is also suspected [47].

Leukocytosis can be a laboratory manifestation of rheumatic diseases such as adult Still's disease (ASD) [48], systemic lupus erythematosus (SLE) [49], and rheumatoid arthritis (RA) [10]. Leukopenia, which is in correlation with disease activity in SLE [50], is not the only laboratory results seen in this disease: leukocytosis in SLE patients may be caused either by infection or high doses of glucocorticoid treatment [49]. In Canadian Cohort Study a

leukocyte count of 15,000/mm3 or greater was present in 50 (81%) out of 62 patients with ASD, whose median age of disease onset was 24 years. Leukocytosis among patients with Still's disease was followed by normocytic and normochromic anemia in 68% of studies cases [48]. Usually immature form of granulocytes predominate which is suggestive sepsis [51]. A study examining bone marrow from 12 adult patients with Still's Disease showed marked hypoplasticity with low histiocytosis and plasmocytosis which was reflective of myeloid hyperplasia, a possible cause of leukocytosis in patients with ASD [52]. As for the rheumatoid arthritis, one of the studies revealed leukocytosis greater than 10.000/mm3 in 27% of individuals from the experimental group. The prevalence was significantly higher (40%) in patients receiving steroid therapy at that moment than in those without such treatment (7.5%). A positive correlation between leukocytosis and the activity of arthritis has been proven, as patients with elevated WBC levels showed more severe manifestation of the disease within the joints.

Eosinophilia's is not common in rheumatic diseases. It may occur in dermatomyositis, progressive systemic sclerosis, vasculitis, Sjögren's syndrome and rheumatoid arthritis (RA). Study involving 1000 patients with eosinophilia and rheumatic diseases found a negative correlation between symptoms such as vitiligo, dryness of the mouth, fatigue and eosinophilia. There was a statistically significant relationship between eosinophilia and nonsteroidal anti- inflammatory drugs (NSAID) usage. Moreover, a strong positive correlation between eosinophilia-related syndromes, such as hypereosinophilic syndrome (HES) or eosinophilic gastroenteritis and the prevalence of rheumatic diseases, has been found [59]. In general, treatment of eosinophilic arthritis with corticosteroids has been proven to be more effective than the administration of NSAIDs [58]. When eosinophilia occurs among patients with rheumatoid arthritis, a differential diagnosis is usually required [53]. A cohort study of French Society for Rheumatology revealed that 26 patients (3.2%) out of 804 with RA of recent onset had baseline eosinophilia (eosinophil >500/mm3), which was mild in a majority of cases. Study suggested that the response to the treatment might be worse in patients with recognized eosinophilia. This group also had a higher morning stiffness and disease activity [54]. On contrary, the Argentinian study found that eosinophilia (eosinophil count > 300/mm3) occurred among 7.33% of the patients with RA. According to this study eosinophilia was not related to the disease severity, it was due to secondary causes, such as parasites [55].Another study claim that eosinophilia may be potentially related to a Methotrexate therapy [53,56].

Referenes:

[1] 5 Means RT Jr, Krantz SB. Inhibition of human erythroid colony-forming units by gamma interferon can be corrected by recombinant human erythropoietin. Blood 1991; 78:2564–7.

[2]Michalis Voulgarelis, Styliani I G Kokori, John P A Ioannidis, Athanasios G Tzioufas,Despina Kyriaki, Haralampos M Moutsopoulos Anaemia in systemic lupus erythematosus: aetiological profile and the role of erythropoietin Ann Rheum Dis 2000;59:217–222

[3] Peeters HR, Jongen-Lavrencic M, Bakker CH, Vreugdenhil G, Breedveld FC, Swaak Recombinant human erythropoietin improves health-related quality of life in patients with rheumatoid arthritis and anaemia of chronic disease; utility measures correlate strongly with disease activity measures AJ. Rheumatol Int. 1999;18(5-6):201-6.

[4] Faquin WC, Schneider TJ, Goldberg MA. Effect of inflammatoty cytokines onhypoxia-induced erythropoietin production. Blood 1992;79:1987–94.

[5] Vreugdenhil G, Löwenberg B, Van Eijk HG, Swaak AJ Tumor necrosis factor alpha is associated with disease activity and the degree of anemia in patients with rheumatoid arthritis.Eur J Clin Invest. 1992 Jul;22(7):488-93.

[6]Davis D, Charles PJ, Potter A, Feldmann M, Maini RN, Elliott MJ, Anaemia of chronic disease in rheumatoid arthritis: in vivo effects of tumour necrosis factor alpha blockade..
Br J Rheumatol. 1997 Sep;36(9):950-6.

[7]Niccoli L, Nannini C, Cassarà E, Kaloudi O, Cantini F.Frequency of anemia of inflammation in patients with ankylosing spondylitis requiring anti-TNFα drugs and therapy-induced changes.Int J Rheum Dis. 2012 Feb;15(1):56-61

[8] Tracey KJ, Wei HE, Manogue KR, Fong Y, Hesse DG, Nguyen HT, Kuo GC, Beutler B, Cotran RS, Cerami A, Lowry SF. Cachectin/tumor necrosis factor induces cachexia, anemia and inflammation. J Exp Med 1988;167:1211-27.

[9] Alvarez-Hernandez X, Liceaga J, McKay IC, Brock JH. Induction of hypoferremia and modulation of macrophage iron metabolism by tumor necrosis factor. Lab Invest. 1989;61:319-322.

[10]S Giannouli, M Voulgarelis, P D Ziakas, A G Tzioufas Anaemia in systemic lupus erythematosus: from pathophysiology to clinical assessment Ann Rheum Dis 2006;65:144–148

[11]Durán S, Apte M, Alarcón GS, Marion MC, Edberg JC, Kimberly RP, Zhang J, Langefeld CD, Vilá LM, Reveille JD Features associated with, and the impact of, hemolytic anemia in patients with systemic lupus erythematosus: LX, results from a multiethnic cohort; Lumina Study Group. Arthritis Rheum. 2008 Sep 15;59(9):1332-40.

[12] Kokori SI1, Ioannidis JP, Voulgarelis M, Tzioufas AG, Moutsopoulos HM Autoimmune hemolytic anemia in patients with systemic lupus erythematosus.. Am J Med. 2000 Feb 15;108(3):198-204.

[13] Gormezano NW, Kern D, Pereira OL, Esteves GC, Sallum AM, Aikawa NE, Pereira RM, Silva CA, Bonfá E Autoimmune hemolytic anemia in systemic lupus erythematosus at diagnosis: differences between pediatric and adult patients.. Lupus. 2017 Apr;26(4):426-430

[14]Wen W,Liu Y,Zhao C,Sun X, Zhang C, Li Z. Clinical and serologic features of primary Sjögren's syndrome concomitant with autoimmune hemolytic anemia: a large-scale cross-sectional study. Clin Rheumatol 2015 Nov;34(11):1877-84

[15]Lipschitz DA,Cook JD,Finch CA A clinical evaluation of serum ferritin as an index of iron stores. N Engl J Med. 1974 May 30;290(22):1213-6.Clin Lab Haematol.

[16] Suominen P,Möttönen T,Rajamäki A,Irjala K. Single values of serum transferrin receptor and transferrin receptor ferritin index can be used to detect true and functional iron deficiency in rheumatoid arthritis patients with anemia, Arthritis Rheum.2000 May;43(5):1016-20.

[17] Margetic S, Topic E, Ruzic DF, Kvaternik M, Soluble transferrin receptor and transferrin receptor-ferritin index in iron deficiency anemia and anemia in rheumatoid arthritis, Clin Chem Lab Med. 2005;43(3):326-31.

[18]Siebert S,Williams BD,Henley R,Ellis R,Cavill I,Worwood M, Single value of serum transferrin receptor is not diagnostic for the absence of iron stores in anaemic patients with rheumatoid arthritis, 2003 Jun;25(3):155-60

[19] Das Gupta A, Abbi A, High serum transferrin receptor level in anemia of chronic disorders indicates coexistent iron deficiency, Am J Hematol. 2003 Mar;72(3):158-61.

[20] Ravindran V,Jain S, Mathur DS, The differentiation of anaemia in rheumatoid arthritis:parameters of iron-deWciency in an Indian rheumatoid arthritis population, Rheumatol Int. 2008 Apr;28(6):507-11

[21] Liu Y, Chen S, Sun Y, et al. Clinical characteristics of immune thrombocytopenia associated with autoimmune disease: A retrospective study. Wang. Y, ed. Medicine. 2016;95(50):e5565.

[22] Griesshammer M, Bangerter M, Sauer T, Wennauer R, Bergmann L, Heimpel H.
Aetiology and clinical significance of thrombocytosis: analysis of 732 patients
with an elevated platelet count. J Intern Med. 1999 Mar;245(3):295-300

[23] Cines DB, Bussel JB, Liebman HA, Luning Prak ET. The ITP syndrome: pathogenic and clinical diversity. Blood. 2009;113(26):6511-6521.

[24] Ktona E, Barbullushi M, Backa T, Idrizi A, Shpata V, Roshi E. Evaluation of Thrombocytopenia in Systemic Lupus Erythematosus and Correlation with Different Organs Damages. Materia Socio-Medica. 2014;26(2):122-124.
[25] Jung J-H, Soh M-S, Ahn Y-H, et al. Thrombocytopenia in Systemic Lupus Erythematosus: Clinical Manifestations, Treatment, and Prognosis in 230 Patients. Louthrenoo. W, ed. Medicine. 2016;95(6):e2818.
[26] Hepburn AL, Narat S, Mason JC. The management of peripheral blood cytopenias in systemic lupus erythematosus. Rheumatology (Oxford). 2010 Dec;49(12):2243-54.
[27] Klepfish A, Friedman J, Schechter Y, Schattner A. Autoimmune neutropenia, thrombocytopenia and Coombs positivity in a patient with primary Sjögren's syndrome. Rheumatology (Oxford). 2001 Aug;40(8):948-9.
[28] Tachibana J, Sugai S, Yoshioka R, Sawada M, Shimizu S, Hirose Y, Takiguchi T, Konda S. [Four patients with thrombocytopenia associated with Sjögren's syndrome]. Nihon Naika Gakkai Zasshi. 1988 Nov;77(11):1697-703. Japanese.
[29] Choung BS, Yoo WH. Successful treatment with intravenous immunoglobulin of severe thrombocytopenia complicated in primary Sjögren's syndrome. Rheumatol Int. 2012 May;32(5):1353-5.
[30] Zhou L, Xin XF, Wu HX. [The efficacy and safety of low-dose rituximab in treatment of primary Sjögren's syndrome with thrombocytopenia]. Zhonghua Nei Ke Za Zhi. 2012 Jan;51(1):37-41. Chinese.
[31] Cuadrado MJ, Mujic F, Munoz E, Khamashta M, Hughes G. Thrombocytopenia in the antiphospholipid syndrome. Annals of the Rheumatic Diseases. 1997;56(3):194-196.
[32] Thrombosis and thrombocytopenia in antiphospholipid syndrome (idiopathic and secondary to SLE): first report from the Italian Registry. Italian Registry of Antiphospholipid Antibodies (IR-APA). Haematologica. 1993 Sep-Oct;78(5):313-8.
[33] Sébastien Lepreux, Anne Solanilla, Julien Villeneuve, Joël Constans, Alexis Desmoulière and Jean Ripoche (2012). Blood Platelets and Systemic Sclerosis, Systemic Sclerosis - An Update on the Aberrant Immune System and Clinical Features, Dr Timothy Radstake (Ed.), ISBN: 978-953-307-869-4, InTech
[34] Estes, D. et al . 1971. The natural history of systemic lupus erythematosus by prospective analysis. Medicine1971: 85–95
[35]Alastair L. HepburnSantosh NaratJustin C. Mason, The management of peripheral blood cytopenias in systemic lupus erythematosus, Rheumatology (Oxford) 2010 Dec;49(12):2243-54
[36]Carli L, Tani C, Vagnani S, Signorini V, Mosca M Leukopenia, lymphopenia, and neutropenia in systemic lupus erythematosus: Prevalence and clinical impact--A systematic literature revie, Semin Arthritis Rheum.2015 Oct;45(2):190-4
[37]Butler WT, Sharp JT, Rossen RD, Lidsky MD, Mittal KK, Gard DA. Relationship of the clinical course of systemic lupus erythematosus to the presence of circulating lymphocytotoxic antibodies. Arthritis Rheum. 1972 May-Jun;15(3):251-8.
[38]P. Stastny and M. Ziff Antibodies against cell membrane constituents in systemic lupus erythematosus and related diseases. I. Cytoxic effect of serum from patients with systemic lupus erythematosus (SLE) for allogenic and for autologous lymphocytes. ClinExpImmunol. 1971 Apr; 8(4): 543–550.
[39] García-Valladares I1,Atisha-Fregoso Y,Richaud-Patin Y,Jakez-Ocampo J,Soto-Vega E,Elías-López D,Carrillo-Maravilla E,Cabiedes J,Ruiz-Argüelles A,Llorente L. Diminished expression of complement regulatory proteins (CD55 and CD59) in lymphocytes from systemic lupus erythematosus patients with lymphopenia. Lupus.2006;15(9):600-5.
[40] Ruiz-Argüelles A1, Llorente L. The role of complement regulatory proteins (CD55 and CD59) in the pathogenesis of autoimmune hemocytopenias. Autoimmun Rev. 2007 Jan;6(3):155-61.
[41] Lars Rönnblom. Potential role of IFNα in adult lupus.Arthritis Research & Therapy201012 (Suppl 1)S3
[42] Oke V,Brauner S,Larsson A,Gustafsson J,Zickert A,Gunnarsson I,Svenungsson E. IFN-λ1 with Th17 axis cytokines and IFN-α define different subsets in systemic lupus erythematosus (SLE). Arthritis Res Ther. 2017 Jun 15;19(1):139.
[43] Li C1,Mu R1,Lu XY2,He J1,Jia RL1,Li ZG1 Antilymphocyte antibodies in systemic lupus erythematosus: association with disease activity and lymphopenia. J Immunol Res. 2014;2014:672126
[44]Bernhard Hellmich,Elena Csernok,Helmut Schatz,Wolfgang L. Gross, and Armin Schnabel Autoantibodies against granulocyte colony-stimulating factor in Felty's syndrome and neutropenic systemic lupus erythematosus.Arthritis Rheum.2002 Sep;46(9):2384-91.
[45] H Liu, K Ozaki,Y Matsuzaki,M Abe,M Kosaka, andS Saito. Suppression of haematopoiesis by IgG autoantibodies from patients with systemic lupus erythematosus (SLE).Clin Exp Immunol. 1995 Jun; 100(3): 480–485.
[46]Castro MF,Andreu J,Sanchez-Piedra C, et al AB0519 Laboratory abnormalities in patients with primary sjogren's syndrome Annals of the Rheumatic Diseases 2017;76:1232.
[47]J Friedman, A Klepfish, Ami Schattner, Edward Miller Agranulocytosis in Sjögren's syndrome: Two case reports and analysis of 11 additional reported cases Semin Arthritis Rheum.2002 Apr;31(5):338-45.
[48]Pouchot J, Sampalis JS, Beaudet F, Carette S, Décary F, Salusinsky-Sternbach M, Hill RO, Gutkowski A, Harth M, Myhal D, et al. Adult Still's disease: manifestations, disease course, and outcome in 62 patients. Medicine (Baltimore).1991 Mar;70(2):118-36.
[49] Boumpas DT, Chrousos GP, Wilder RL, Cupps TR, Balow JE. Glucocorticoid therapyfor immune-mediated diseases: basic and clinical correlates. Ann Intern Med. 1993 Dec 15;119(12):1198-208

[50] Newman K, Owlia MB, El-Hemaidi I, Akhtari M. Management of immune cytopenias in patients with systemic lupus erythematosus - Old and new. Autoimmun Rev. 2013 May;12(7):784-91.

[51] Chung JW, Suh YJ, Song HJ, Choi JH, Park HS, Cho SR, Suh CH. Pure red cell aplasia and adult-onset Still's disease. Clin Rheumatol. 2004 Aug;23(4):368-70.

[52] Min JK, Cho CS, Kim HY, Oh EJ. Bone marrow findings in patients with adult Still's disease. Scand J Rheumatol. 2003;32(2):119-21.

[53] Kargili A, Bavbek N, Kaya A, Koşar A, Karaaslan Y. Eosinophilia in rheumatologic diseases: a prospective study of 1000 cases. Rheumatol Int. 2004 Nov;24(6):321-4.

[54] Guellec D, Milin M, Cornec D, et al. Eosinophilia predicts poor clinical outcomes in recent-onset arthritis: results from the ESPOIR cohort. *RMD Open*. 2015;1(1):e000070.

[55] Chiardola F, Schneeberger EE, Citera G, Rosemffet GM, Kuo L, Santillan G, Maldonado-Cocco JA. Prevalence and clinical significance of eosinophilia in patients with rheumatoid arthritis in Argentina. J Clin Rheumatol. 2008 Aug;14(4):211-3

[56] Bruyn GA, Velthuysen E, Joosten P, Houtman PM. Pancytopenia related eosinophilia in rheumatoid arthritis: a specific methotrexate phenomenon? J Rheumatol. 1995 Jul;22(7):1373-6.

[57] Syed KM, Pinals RS. Leukocytosis in rheumatoid arthritis. J Clin Rheumatol. 1996 Aug;2(4):197-202.

[58] Tay C. Eosinophilic arthritis. Rheumatology (Oxford). 1999 Dec;38(12):1188-94.

[59] Diny NL, Rose NR, Čiháková D. Eosinophils in Autoimmune Diseases. *Frontiers in Immunology*. 2017;8:484.