SYSTEMIC LUPUS ERYTEMATOSUS ASSOCIATED WITH RHEUMATOID ARTHRITIS AND THE IMPORTANCE OF GENETIC FACTORS - CASE REPORT

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Abstract: *Systemic lupus erytematosus (SLE) is an autoimmune disease belonging to the collagenosis group. Besides the immune imbalance, there are a series of other factors contributing to its development, like genetic factors, environmental factors, hormonal factors. We are presenting the case of a 48-year old female patient, with a family history of collagenosis, initially diagnosed with rheumatoid arthritis, Raynaud's syndrome and mixed connective tissue disease, under immunosuppressive therapy with Methotrexate and Prednison. The patient reports after 14 years, the evolving of erythemato-papular lesions, suggestive for lupus, located on photoexposed areas associated with livedo reticularis racermosa, vasospastic crises Raynaud's type, arthralgia, joint swelling. After clinical and laboratory investigations and biopsy, the SLE diagnosis was confirmed, with the presence of 4 out of 11 ARA diagnosis criteria and mixed connective tissue disease was denied. Anti ds-DNA antibodies positive, anti-Ro antibodies -positive, anti –La - antibodies positive, antiphospholipid antibodies - positive and anti –RNP antibodies were negative. The particularity of the case lies in the presence within the family, of two sisters suffering from major collagenosis (SLE, RA stage IV seropositive and systemic scleroderma with severe pulmonary involvement and Raynaud's syndrome), fact which advocates for the genetic component of immune imbalance, and for the possible evolution over years of undifferentiated connective tissue disease mixed to SLE, despite immunosuppressive therapy.*

Cuvinte cheie:
colagenoze majore, lupus eritematos sistemic, poliartrită reumatoidă, factori genetici

Rezumat: *Lupusul eritematos sistemic (LES) este o boală autoimună din grupul colagenozelor cu afectare sistemică, în producerea căreia contribuie pe lângă dezechilibrul imun, o serie de factori genetici, alături de factori de mediu şi hormonali. Prezentăm cazul unei paciente de 48 ani, cu antecedente de colagenoză în familie, diagnosticată iniţial cu poliartrită reumatoidă, sindrom Raynaud şi boală mixtă de ţesut conjunctiv, aflată în tratament imunosupresiv cu Metotrexat şi Prednison. Pacienta relatează apariţia în evoluţie, după 14 ani, a unor leziuni eritemato-papulo-scuamoase, sugestive pentru lupus, localizate pe zonele fotoexpuse, dar şi la nivelul membrelor inferioare asociate cu livedo reticularis racermosa, crize vasospastice tip Raynaud, artralgii, tumefacţii articulare. În urma investigaţiilor clinico-paraclinice şi a EHP s-a stabilit diagnosticul de LES, cu prezenţa a 4 din cele 11 criterii ARA de diagnostic şi s-a infirmat boala mixtă de ţesut conjunctiv. Anticorpii anti ADN dc-pozitivi, Ac anti Ro-pozitivi, Ac anti La-pozitivi, Ac antifosfolipidici- pozitivi, iar anti RNP au fost negativi. Particularitatea cazului constă din prezenţa în familie, la două surori, de colagenoze majore (LES şi PR seropozitivă stadiul IV şi sclerodermie sistemică cu afectare pulmonară severă şi sindrom Raynaud) fapt ce pledează pentru componenta genetică a dezechilibrului imun, precum şi posibila evoluţie, în ani, din boala mixtă de ţesut conjuctiv nediferenţiată spre LES, în pofida tratamentului imunosupresiv.*

INTRODUCTION

SLE is an autoimmune disease with multiple organ involvement, of unknown etiology in which genetic and environmental factors play a role.(1) Autoimmune diseases are defined by immune response to certain auto antigens underlying tissue damage that occurs in these situations. SLE is more common in women (80-90%), suggesting an involvement of estrogens in the pathogenesis of disease, evolution being characterized by periods of exacerbation and remission.(1,2)

The role of genetic factors in causing LE is suggested by the familial aggregation of SLE cases, and the involvement of major histocompatibility complex genes. LES association with other connective tissue diseases in the same patient, explains the particular vulnerability of connective tissue. The close association between collagenosis and HLA major histocompatibility system and immune response mediated by B and T lymphocytes are reasons to suspect the involvement of auto antigens modified and / or antigens of infectious origin.(1)

CASE REPORT

We present the case of a 48-year old female patient, who was hospitalized in the Clinical Dermatology Department Sibiu, after the recent appearance of some erythemato-papulo-squamous plaques with white scales located at the face, earlobes, upper and lower limb, without scratching.

The lower limbs present superficial branching vascular pattern, purplish, irregular with the appearance of livedo reticularis racemosa. At the proximal interphalangeal joints of the fingers II and III from the left hand, she presented polyarthralgias with swelling of the affected joints, and

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vasospastic crises Raynaud's type, after exposure to cold. The patient was diagnosed with RA 14 years ago, Raynaud's syndrome and mixed connective tissue disease.

The disease started with polyarthralgias in the small joints of the hands accompanied by edema and prolonged morning pain in the small joints of the feet, also affecting elbow joints, lumbar spine, sacrum-iliac joints, while she have also vasospastic phenomenon Raynaud's type.

Disease progression was bad, the patient being hospitalized repeatedly at the Medical Clinic with feverish, polyarthralgias, myalgia and weight loss.

From family history, it can be noted:

- An older sister, diagnosed 6 years ago with SLE and RA IV stage seropositive, treated with Azathioprine 100mg/day, Prednisone 10mg/day, Hydroxychloroquine 200mg/day with moderate control of the disease. The laboratory showed: marked biological inflammatory syndrome, ANA positive, anti ds-DNA antibodies positive, complement deficiency, RF (rheumatoid factor) positive, RNP-antibodies negative.
- A younger sister was diagnosed 5 years ago with systemic scleroderma with diffuse cutaneous damage and impaired pulmonary fibrosis alveolitis and Raynaud's phenomenon. She presented anti SCL 70 antibodies- positive, anti-centromere antibodies-negative, anti-RNP antibodies positive, ANA-negative, anti-ds DNA antibodies-negative, anti-Ro and anti-La antibodies negative, anti-Sm antibodies negative, anti Jo1antibodies-negative, antimitochondrial antibodies-negative, p-ANCA-negative, c-ANCA-negative, anti-CCP antibodies negative. She received treatment with Cyclophosphamide, with corticoids, but the disease was unfavourable with: progressive skin damage, a deterioration in lung function (with effort dyspnea, moderate obstructive ventilatory dysfunction, with FEV reduced to 48%, severe hyperinflation and mild hypoxemia), decreased weight.

In our case, given the clinical manifestations, the presence of typical lesions of lupus, past medical history and family history, we established the diagnosis of SLE.

Laboratory analysis showed: ANA-positive, anti ds-DNA antibodies-positive, anti-Ro antibodies-positive, anti-La antibodies-positive, antiphospholipid antibodies-positive, RF-present, CIC present, IgG and IgM elevated, the complement-low, absent lupus cells, Coombs test-negative, cryoglobulins, cryofibrinogen-negative, anti-RNP antibodies-negative, anti Scl AC 70antibodies-negative, VDRL-negative, important biological inflammatory syndrome (ESR-erythrocyte sedimentation rate- 65mm / h), leukocytopenia-3500 / mm3, ELFO: 26% gamma globulin, liver and kidney samples-normal, HBsAg-negative, HCV antibodies-negative)

Histopathology of a skin lesion revealed ortokeratotic hyperkeratosis, with keratin plugs, vacuolises in the spinosus layer, basal layer present vacuolises and appearance of liquefaction, rete ridges are flattened, dermis contains chronic inflammatory infiltrate with lymphocytes and plasmocytes.

Chest X-ray, abdominal ultrasound, EKG were normal. Rx hands have shown moderate demineralization in line at metacarpian and interphalangeal articulations. High intensity radio opaque image in the distal metacarpus III left hand and smooth contour figure well drawn linear radiolucent around.

By corroborating the clinical and laboratory data she was diagnosed with SLE, fulfilling 4 of the 11 ARA diagnostic criteria (photosensitivity, hematological, leukocytopenia, immunological changes, anti ds-DNA antibodies-positive, ANA positive). The presence of anti-Ro antibodies, anti-La antibodies, CIC, IgG and IgM, hipocomplementemia represents other arguments that advocate for SLE; in addition, biopsy reveals changes characteristic of lupus. So, the diagnosis of mixed connective tissue disease was denied, much more as anti-RNP antibodies were negative. Secondary diagnoses are: RA seropositive and Raynaud's phenomenon. In our case, we must differentiate between joint damage in RA and the joint damage from lupus. The disease modification (biological inflammatory syndrome, RF present) and radiological appearance are suggestive of the diagnosis of RA. Currently, the patient is treated with Prednisone 10mg/day, Hydroxychloroquine 400mg/day, Methotrexate 7.5 mg / week and Pentoxifilin 800mg/day.

The role of genetic factors in triggering SLE is suggested by familial aggregation of cases of SLE, the concordance rate in monozygotic twins being between 24-59%, and in dizygotic twins between 2-4%.(1) More than 29 genes associated with lupus have been identified including: FCGR2A, PTPN22 (protein tyrosine phosphatase nonreceptor type 22), IRF 5 (interferon regulatory factor 5), STAT4 (signal transducer and activator of transcription 4), TNFSF4 (TNF ligand superfamily 4), BLK (B-lymphoid tyrosine kinase), ITGAM (integrin α M ITGAM), BANK (B-cell scaffold protein with ankyrin repeats 1), TNIP1 (interacting protein 1), RASGRP3 (RAS guanyl-releasing protein 3), IKZF1(Ikaros family zinc finger 1), LRRC18 (leucine-rich repeat-containing 18), WDFY4 (WD repeat and FYVE domain-containing family member 4), JAZF1 (juxtaposed with another zinc finger gene 1), UHRF1BP1(ubiquitin-like containing PHD and RING finger domains-binding protein 1), IRAK1(IL1 receptor-associated kinase 1), MECP2 (methyl CpG-binding protein 2 MECP2).(1,3)

It is also known the involvement of genes of the CMH class II in the occurrence of SLE, such as HLA DR2, which correlates with the presence of Ac anti Sm and HLA DR3, which is associated with Ac anti-Ro. Other genes identified with a role in triggering the SLE are HLA B8, HLA DRw52, HLA-DQw1 and HLA DQW2.(3)

SLE is associated with a genetic deficiency of complement C1q, C2, C4. There have been reported 41 cases of C1q deficiency factor and it is associated in 90% of cases with SLE. Factor C2 deficiency is more common in the European population and 33% of the patients develop SLE and is usually associated with this Ac anti Ro.(3,4)

SLE and RA show many manifestations clinical, serological and phenotypic characteristics. Various studies have shown familial aggregation of cases of SLE associated with RA.(5,6) In a study published by Icen M in 2009, which included 603 patients with RA, with the average age 58 years, 73% being women, the occurence of SLE in a period of 25 years from the diagnosis of RA was observed at 15.5 %.(7)

In the presented cases, there is a need to identify the risk factors associated with the occurrence of RA (the most common HLA DR1 and HLA DR4) and those involved in the occurence of SLE (HLA DR2, HLA DR3, HLA B8, HLA DRw52, HLA DQw1, HLA DQw2) to assess the risk of the disease. It is also important to identify the risk factors in the patient's daughter. Common genes have been identified as associated with the occurence of the SLE and RA: BLK PTPN22, STAT4, FCGR2A, PRDM1, and genes of TNFAIP3 MCA.(3,6) RA is more commonly associated with the subtype HLA DR1 and HLA DR4, 10% of patients with RA have at least one degree relative affected by the disease.(8)

In a study by R. Priori in 2003, in which he evaluated the risk of SLE in the relatives of patients with autoimmune diseases and vice versa, was found that 22, 7% of patients with SLE who had a relative with autoimmune diseases, the risk

increasing with the number of relatives affected. The probability of autoimmune disease in relatives of patients with SLE, was higher than in the normal population, and the risk is two times greater if they are women.(9)

In our case, it is important to point out the possible evolution of an undifferentiated collagenosis to SLE, shaping an immunological profile evolution during the years (14 years).

In terms of the transmission of susceptibility to develop SLE, studies show that if the mother has LES, the daughter's risk of developing the disease is of 1: 40 and the sun's of 1: 250 cases.(4)

Because lymphocytes play a role in altered reply immune in SLE, various subpopulation of lymphocyte are useful to monitor disease activity. CD27 is a useful marker for subsets of B lymphocyte differentiation, which fall into three categories: naive B lymphocytes (CD 19+/ CD 27-), lymphocytes B in memory (CD 19+/CD 27+ or CD 19+/CD 27dim) and plasmocytes (CD 19+/CD 27++or CD 19+/CD 27 high). In SLE percentage of plasmocytes (CD 19 +/CD27 ++) is increased related directly with disease activity index and the titer of anti dsDNA antibodies. However, elevated CD 27 high cells were observed in patients with negative Ac ADN dc but positive for other antibodies (anti SM, Anti Ro, Ac anti La, Ac antihistones). The percentage of naive B cell and B cell memory is low in LES. As a result of immunosuppressive therapy, the naive B cells CD 27- and plasmocytes CD27++ are reduced instead the B cells with memory CD 27 + are not affected. This suggests that the relapses may have links with the memory cell retention CD 27+. Studies show that the subsets of B lymphocytes circulating are influenced by the duration of the disease. In the evolution of the disease, it was noticed the increase of CD 27 high number B cells and decrease of CD 27- cells.(2,5,9)

In SLE, the T lymphocytes play an important role in the alteration of self tolerance by increasing the production of auto antibodies by auto reactive B lymphocytes. Normally, the suppressive action of regulatory T cells contributes to the maintenance of tolerance to self. Studies have shown that in patients with SLE, in the active period, there was a decline in the number of regulatory T lymphocytes (CD4 +/CD 25 +) in the periphery.(3)

CONCLUSIONS

The severity of the patient's disease results from the combination of two collagenosis with severe evolution, expressed by the intensity of the immunological disturbances in this case. In addition, the presence of antiphospholipid antibody is associated to an increased risk of thrombosis, endocarditis and myocardial dysfunction. Also the presence of anti –ds DNA antibodies is usually associated with renal impairment.

The particularity of the case presented consists in the presence in 3 out 5 sisters of collagenosis with severe evolution, namely, an older sister with RA and SLE, endocarditis a younger sister with systemic scleroderma with sever pulmonary form, and in the case presented initially diagnosed, the disease mixed connective tissue and subsequently, the firm shaping of RA and SLE diagnosis.

This fact underlines the importance of genetic factors involved in the occurrence of these severe collagenos cases which should be identified. Also, there is a possibility for the involvement of estrogens in the pathogenesis of the disease.

Finding relatives prone to developing lupus disease - in this case the patient's daughter, by determining the genotype HLA DR2, HLA-DR3, HLA B8, HLA DRw52, HLA DQw1, HLA DQW2 would allow taking measures to prevent its installation. In addition, the perspective gene therapy could make great progress in controlling these diseases.

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