SYSTEMIC LUPUS IN MALES – CLINICAL-LABORATORY, IMMUNOLOGICAL AND HISTOLOGICAL CHARACTERISTICS

At. Kundurdjiev¹, M. Nikolova¹, A. Kostadinova¹, D. Genov¹, M. Hristova¹, N. Koleva¹, R. Gancheva², Zl. Kolarov², D. Kiurkchiev³, E. Todorova³, D. Monov⁴, K. Chupetlovska⁴, T. Todorov⁵, V. Minkova⁶, J. Ananiev⁶
¹Clinic of Nephrology, University Hospital Sv. Ivan Rilski, Medical University – Sofia, Bulgaria
²Clinic of Rheumatology, University Hospital Sv. Ivan Rilski, Medical University – Sofia, Bulgaria
³Department of Clinical Immunology, University Hospital Sv. Ivan Rilski, Medical University – Sofia, Bulgaria
⁴Intensive Care Unit, University Hospital Sv. Ivan Rilski, Medical University – Sofia, Bulgaria
⁵Department of Clinical Pathology, Medical University – Sofia, Bulgaria
⁶Department of General and Clinical Pathology, Medical Faculty, Trakia University – Stara Zagora, Bulgaria

Abstract: Systemic lupus erythematosus is a chronic, systemic, non-organ-specific autoimmune disease that affects all organs and systems of the human body and is characterized by the production of autoantibodies against nuclear antigens. Its prevalence in Europe reaches 1:2500. It affects mostly women (female : male ratio = 9:1) in fertile age group (15-45 years). The clinical course of lupus in males is characterized by more aggressive clinical course and the development of serious complications, such as vasculitis, central nervous system involvement, antiphospholipid syndrome, etc. For the period of 7 years (2012-2019) we observed overall 18 male patients with systemic lupus, 11 with biopsy-proven renal involvement and 7 without clinically significant renal disease (proteinuria < 0.5 g/24 h, no erythrocyturia/cylindruria, normal renal function), mean age at the diagnosis 39.6 ± 12.3 years. All patients received pathogenetic treatment (corticosteroids + cytotoxic agents). Three had secondary antiphospholipid syndrome, 1 – inflammatory bowel disease, 1 – seronegative spondyloarthropathy. Three had type 2 diabetes. The authors discuss the clinical, immunological and histological characteristics and the therapeutic approach in males with systemic lupus.

Key words: systemic lupus, lupus nephritis, antiphospholipid syndrome, male, clinical characteristics, autoantibodies, treatment

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, systemic, non-organ-specific autoimmune disease that affects all organs and systems of the human body and is characterized by the production of autoantibodies against nuclear antigens [1]. Its prevalence in Europe reaches 1:2500. It affects mostly women (female : male ratio = 9:1) in fertile age group (15-45 years) [2].

The clinical course of lupus in males is characterized by more aggressive clinical course and the development of serious complications, such as discoid lesions, vasculitis, serositis, thrombosis, central nervous system involvement, lupus nephritis, antiphospholipid syndrome, etc. [3, 4].

The aim of our study was to evaluate the clinical-laboratory, immunological and histological characteristics in male patients with SLE and the significance of these markers for the therapeutic approach.

MATERIALS AND METHODS

For the period of 4 years (2016-2019) we observed overall 18 male Caucasian patients with systemic lupus, 11 with biopsy-proven renal involvement and 7 without clinically significant renal disease (proteinuria < 0.5 g/24 h, no erythrocyturia/cylindruria, normal renal function), mean age at the diagnosis 39.6 ± 12.3 years. All patients received pathogenetic treatment (corticosteroids + cytotoxic agents). Three had secondary antiphospholipid syndrome, 1 – inflammatory bowel disease, 1 – seronegative spondyloarthropathy. One patient with class III lupus nephritis had chronic hepatitis B – on treatment with Lamivudine.

The diagnosis SLE was based on the presence of 4 classification criteria [5]. The history of thrombo-embolic incidents with or without thrombocytopeny and positive antiphospholipid antibodies and/or lupus anticoagulant defined the presence of secondary antiphospholipid syndrome (SAPS).

All patients were taken complete medical history and physical examination, underwent abdominal ultrasound, echocardiographic investigation and ultrasound examination of the neck.

In all patients were performed routine clinical-laboratory investigations (whole blood count, biochemical tests, liver enzymes, lipid profile, electrolytes, coagu-
lation studies), urine tests (dip-stick investigation, urinary sediment, proteinuria) using standard methods; immunological studies (antinuclear, ANA, anti-DNA, antineutrophil cytoplasmic, ANCA, anticycliccitoantibody, ACL, lupus anticoagulant, LA, C3 and C4 complement fractions), using standard methods. All patients were investigated for viral hepatitis B (HBs antigen) and C (anti-HCV antibodies), and viral replication was investigated if needed. Renal biopsy was performed if indicated – proteinuria > 0.5 g/24 h, erythrocyturia, casts in urinary sediment, impaired renal function.

**RESULTS**

Of all 18 male SLE patients, 4 criteria for the diagnosis of SLE had 11 individuals (7 with and 4 without clinically significant renal involvement), 5 criteria had 5 (3 with and 2 without renal involvement, 6 criteria had 1 patient with and 1 without renal involvement (Table 1). Overall 11/18 patients underwent renal biopsy and the following classes of lupus nephritis (LN) were detected: class I had 2/11 (in one patient with significant mesangial IgA deposition and in one in combination with diabetic nephropathy), 1/11 had class II LN, 3 had class III (in one with marked mesangial deposition of IgA), 4 had class IV and one class V LN. One patient underwent re-biopsy and transition from class IV to class V LN was observed.

Table 1. Number of SLE diagnostic criteria in male SLE patients with and without clinically significant renal involvement

| Number of criteria | With renal involvement | Without renal involvement | p    |
|--------------------|------------------------|---------------------------|------|
| 4                  | 7                      | 4                         |      |
| 5                  | 3                      | 2                         |      |
| 6                  | 1                      | 1                         |      |

The distribution of SLE criteria among the studied patients is presented in Table 2.

All patients with biopsy-prove LN had proteinuria > 0.5 g/24 h, 6 had > 1 g/24 h, 3 had > 2 g/24 h, and 3 had > 3 g/24 h. Two had clinical-laboratory data for severe nephritic syndrome – one had class 4 and one – class V LN. Overall 7 patients had erythrocyturia, renal failure had 6, in 3 of them renal function was restored after 6 months of pathogenic treatment, and 3 remained with low grade renal failure (serum creatinine < 150 mmol/l). In all patients the pathogenic treatment lead to decrease in proteinuria, erythrocyturia subsided in 2 and renal function restored within normal limits in 3 with those with renal dysfunction at baseline.

Table 2. Classification criteria for the diagnosis of SLE in male patients with and without renal involvement (p not significant for the comparative analysis LN vs. no LN)

| Criteria / number of SLE patients | With renal involvement | Without renal involvement |
|-----------------------------------|------------------------|--------------------------|
| Renal involvement                 | 11                     | 1                        |
| Hematological involvement         | 1                      | 1                        |
| Skin involvement (malar or discoid rash) | 9                   | 7                        |
| Photosensitivity                  | 3                      | 7                        |
| Oral ulcerations                  | 1                      | 1                        |
| Joint involvement                 | 9                      | 4                        |
| Serositis                         | 1                      | 1                        |
| Positive ANA                      | 9                      | 7                        |
| Positive DNA                      | 8                      | 5                        |
| Central nervous system involvement| 1                      | 1                        |

ANA were positive in 9/11 LN patients vs. 7/7 without LN. DNA antibodies were positive in 8/11 and 5/7, respectively. Overall 3 patients had positive anticycliccitoantibodies 2/11 with and 1/7 without LN, in all three in combination with thrombotic incidents (ischemic strokes defining SAPS). During the follow-up, two patients with LN died of pulmonary embolism – one with and one without secondary antiphospholipid syndrome.

All patients received pathogenic treatment:

– monotherapy with corticosteroids – 7/11 LN patients,
– combined treatment corticosteroids + antimalarial – 1/11 with + 5/7 without LN;
– corticosteroids + intravenous immunoglobulins (IVIG) – 1/11 with LN;
– corticosteroids + cytotoxic agent + antimalarial or IVIG – 2/11 with + 1/7 without LN.

All patients received anticoagulant and/or antiaggregant medication. Three had diabetes mellitus and were on antidiabetic medications.

The comparative analysis of male SLE patients with and without renal involvement showed that these with LN are slightly older (42.6 ± 13.7 compared to 34.9 ± 4.9 years, p < 0.05), and have higher serum creatinine (189 ± 94.2 vs. 78.2 ± 12.3, p < 0.05, due to the presence of lupus nephritis) and more often have articular involvement and positive DNA antibodies (p not significant for the last two comparisons). None of the LN patients had photosensitivity. No other significant differences were noted between the two subgroups.

**DISCUSSION**

SLE is a chronic and multisystemic autoimmune disease that affects mainly women. Yet, approximately 4–22% of SLE patients are men [2] and they
show a more severe visceral involvement and clinical course with more frequent involvement of certain tissues and organs, including discoid rash, psychosis, pericarditis, lympho- and thrombocytopeny and LN [6]. Some investigators suggest that in men SLE is diagnosed later in life [7], but others do not observe such differences [8]. In our series of men with SLE, clinically significant renal involvement was present in 11/18 patients (61.1%) and proliferative nephropathies were the most prevalent histological type (7/11, 63.6%). Of particular interest is the presence of significant mesangial IgA deposits in two of the LN patients that is in accordance with the literature data of the possibility for development if IgA nephritis in SLE [9]. Three of our patients had history of diabetes. Therefore, one should not forget that the presence of diabetes does not automatically exclude the possibility for the development of other nephropathy and in the presence of nephritic urinary sediment, positive autoantibodies, systemic involvement and discrepancies between the duration of diabetes and the presence of renal failure or high-grade proteinuria the patient is indicated renal biopsy to rule out other concomitant renal pathology [10].

In our cohort of patients we observed higher prevalence of skin and articular involvement in men and lower prevalence of hematological involvement, oral ulcerations and serositis compared to the prevalence on women in the literature [4], that require further comparative studies in Bulgarian population.

Of particular interest is the fact that in part of the patients we could not detect ANA and/or DNA antibodies at baseline that is in accordance with the hypothesis for “seronegative” SLE that requires dynamic follow-up in the future. Our case series underlines that the presence of diabetes does not automatically exclude the presence of immune nephropathy and the diabetes is not a contraindication for the pathogenic treatment of immune nephropathies. Further comparative studies between men and women with SLE and LN in Bulgarian population are needed to clarify the differences in therapeutic approach.

In conclusion, the presented series of male SLE patients demonstrates a subgroup of lupus patients with high prevalence of skin, renal and articular involvement and lower prevalence of hematological, oral ulcerations and serositis. Overall 3/18 (16.7%) had clinical and laboratory data for SAPS. A small proportion had negative ANA and/or DNA antibodies that require dynamic follow-up in the future. Our case series underlines that the presence of diabetes does not automatically exclude the presence of immune nephropathy and the diabetes is not a contraindication for the pathogenic treatment of immune nephropathies. Further comparative studies between men and women with SLE and LN in Bulgarian population are needed to clarify the differences in therapeutic approach.

Библиография / References

1. Manson JJ, Rahman A. Systemic lupus erythematosus. Orphanet J Rare Dis 2006;1:6.
2. Lu LJ, Wallace DJ, Ishimori ML et al. Male systemic lupus erythematosus: a review of sex disparities in this disease. Lupus 2010;19:119–129.
3. Tan TC, Fang H, Magder L et al. Differences between male and female systemic lupus erythematosus in a multiethnic population. J Rheumatol 2012;39:759–769.
4. Faez ST, Hossein Almodaresi M, Akbarian M, et al. Clinical and immunological pattern of systemic lupus erythematosus in men in a cohort of 2355 patients. Int J Rheum Dis 2014;17:394–399.
5. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25(11):1271–1277.
6. Soto ME, Vallejo M, Guíllén F, et al. Gender impact in systemic lupus erythematosus. Clini Exp Rheumatol 2004;22:713–721.
7. Wallace DJ, Hahn BH, eds. Dubois’ lupus erythematosus, 6th edn. Philadelphia: Lippincott Williams & Wilkins, 2002.
8. Murphy G, Isenberg D. Effect of gender on clinical presentation in systemic lupus erythematosus. Rheumatology 2013;52:2108–2115.
9. Da Silva LS, Almeida BL, De Melo Ak, et al. IgA nephropathy in systemic lupus erythematosus patients: case report and literature review. Rev Bras Reumatol Engl Ed 2016;56(3):270–273.
10. M. Nikolova, A. Iliev, G. Venkov, et al. Association of type 2 diabetes and membranous glomerulonephritis. Med Pregled 2006;42(3):100–102.
11. Bohan A. Seronegative systemic lupus erythematosus. J Rheumatol 1979;6(5):534–540.

Постъпила за печат: 29.07.2022 г.

Адрес за кореспонденция:
Д-р М. Николова
Клиника по нефрология
УМБАЛ „Св. М. Рилски”
МУ – София
e-mail: milena_i_dani@abv.bg

Submitted: 29.07.2022

Correspondence address:
Dr. M. Nikolova, MD, PhD
Clinic of Nephrology
University Hospital Ivan Rilski
MU – Sofia
e-mail: milena_i_dani@abv.bg