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Large variability of the activity and chronicity indexes within and between histological classes of lupus nephritis

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Abstract

Systemic lupus erythematosus (SLE) is characterized by a multifaceted pathogenesis and a heterogeneous clinical expression. The kidney involvement is almost unavoidable in all forms of SLE with chronic evolution, 75% of patients developing renal lesions defined as lupus nephritis (LN) – a glomerulonephritis with an extremely diverse lesion spectrum. The present study aimed to reevaluate a series of cases diagnosed as LN, focusing on the histological features in correlation with the level of activity and chronicity. The study group comprised 46 patients. The specimens obtained through percutaneous needle biopsies were processed for light microscopy and immunofluorescence exams. The reevaluation process focused on the major morphological parameters ensuring: (*i*) a detailed description of the lesions, (*ii*) the class diagnosis in accordance with the *International Society of Nephrology/Renal Pathology Society* (ISN/RPS) classification, (*iii*) the activity and chronicity indexes. In 39 out of the total of 46 (84.78%) cases, the class of LN established at the time of the renal biopsy was confirmed in the reevaluation process. The differences in diagnosis were present in seven cases, initially considered as pure membranous glomerulonephritis – class V. The values of indexes indicated a great variability of LN within the same class. The interobserver agreement for the scoring of activity and chronicity indexes was 0.8 and 0.95, respectively. Our study emphasizes the complex lesion character, which requires an individual and accurate identification, followed by integration in the classification algorithm used to define the classes and subclasses of LN diagnosis. The degree of activity and chronicity in SLE must be refined through a much more precise correspondence between the score value and the limitation or extension of corpuscular and interstitial lesions.

Keywords: systemic lupus erythematosus, lupus nephritis, percutaneous needle biopsy, activity and chronicity indexes.

Introduction

Systemic lupus erythematosus (SLE) represents a distinct pathogenic entity among the complex framework of autoimmune diseases, ranking the second place in frequency. Taking into account epidemiological data with geographic specificity, it is unanimously accepted that the incidence and prevalence of SLE are rising, with a high regional variability. Unfortunately, data on the worldwide incidence and prevalence is even more limited. A recently published review [1], based on studies done in the last 20 years, indicates an incidence of 1 to 25 per 100 000 [2–4] and a prevalence of 20 to 150 cases per 100 000 [4, 5].

SLE is characterized by a multifaceted pathogenesis and a heterogeneous clinical expression – associated, in 90% of cases, with the presence of antinuclear auto-antibodies. The pathogenic mechanism is dominated by the specific sequences of autoimmune processes, without neglecting the influence of genetic, epigenetic, environmental, and hormonal factors [6–8]. For clinical approach the 17 criteria (11 clinical and six immunological) proposed by *Systemic Lupus International Collaborating Clinics* (SLICC) are mandatory [9].

The polymorphism is a main feature of SLE, particularly noted in the systemic form. Each location presents a large clinical variability. Therefore, the diagnosis is truly a challenge for the medical team consisting of a nephrologist, pathologist, dermatologist, rheumatologist, neurologist and occasionally pulmonologist. The kidney involvement is almost unavoidable in all forms of SLE with chronic evolution, 75% of patients developing renal lesions [10, 11] defined as lupus nephritis (LN) – a glomerulonephritis with an extremely diverse lesion spectrum [12]. The high percentage of patients with renal damage demands a solid clinical and laboratory evaluation, with the purpose of identifying the injury at an early stage. The diagnosis needs criteria in accordance with the *International Society of Nephrology* (ISN) and *Renal Pathology Society* (RPS) classification [13] established more than 10 years ago. Nowadays, heated debates on the necessity to revise this classification are taking place, due to several uncertainties and inconsistencies in the definitions of histological parameters [14], which lead to considerable interobserver variation in the assessment of lesions and diagnosis class, respectively.

The present paper reflects over 20 years of experience in the diagnosis and monitoring of renal pathology, including LN. Within this context, the purpose of our study consisted in the re-evaluation of all LN cases on record, focusing on the analysis of individual particularities of histological diagnosis in correlation with the level of activity and chronicity of each case.

Patients, Materials and Methods

The study group comprised 46 patients (40 women and

six men, mean age of onset 34.16 years) diagnosed with LN at the Department of Pathology, "Dr. C. I. Parhon" University Hospital, Iaşi, Romania, between 2003 and 2016.

The specimens were obtained through percutaneous needle biopsies on native kidneys at the Clinic of Nephrology of the same Hospital. The biopsies were performed under ultrasound guidance, using a Tru-Cut 14G type needle and a Bard Instruments biopsy gun. By the informed consent, patients approved the usage of their biological material leftover after diagnostic testing for scientific purposes.

The kidney fragments were processed by using specific protocols. For the light microscopy exam, the specimens resulted from paraffin-embedded blocks were stained by using Hematoxylin–Eosin (HE) and special stainings (trichrome with Green Light and Aniline Blue, Periodic Acid–Schiff, Methenamine Silver, Congo Red). Immunofluorescence was performed on frozen sections, using anti-IgG fluorescein isothiocyanate (FITC) (F0202, Dako, Denmark), -IgA FITC (F0204, Dako, Denmark), -IgM FITC (F0203, Dako, Denmark), -C3 FITC (F0201, Dako, Denmark), -C1q FITC (F0254, Dako, Denmark) antibodies (1:20 dilution). Positive and negative controls were run simultaneously, according to the antibodies specifications.

To achieve the proposed aim of the present study, each case was reevaluated through microscopic examination by three independent pathologists. The reevaluation process focused on the major morphological parameters ensuring: (*i*) a detailed description of the lesions (Table 1), (*ii*) the class diagnosis in accordance with the ISN/RPS classification [13], (*iii*) the activity and chronicity indexes in accordance with the algorithm formulated by the *National Institute of Health* (NIH) [15] (Table 2).

Table 1 – ***Key points in the assessment of the renal biopsy***

Glomerular lesions	▪ number of damaged renal corpuscle (focal or diffuse lesion); ▪ mesangial proliferation: hypercellularity, increased number of mesangial cells, matrix deposits; ▪ endocapillary proliferation: exudative component, due to an increased number of endothelial cells and infiltrating monocytes (intracapillary leukocytes); ▪ basement membrane changes: thickness, wire loops aspect; ▪ hyaline thrombi; ▪ segmental sclerosis; ▪ crescents: cellular, fibrocellular, fibrous glomerulosclerosis.
Interstitial lesions	▪ inflammatory infiltrate; ▪ interstitial fibrosis; ▪ tubular atrophy.

Table 2 – ***Activity and chronicity indexes [15]***

Activity index (maximum value = 24)	Chronicity index (maximum value = 12)
Glomerular lesions	
▪ endocapillary proliferation; ▪ fibrinoid necrosis, karyorrhexis; ▪ cellular crescents*; ▪ hyaline thrombi, wire loops deposits*; ▪ leukocyte infiltration.	▪ glomerulosclerosis; ▪ fibrous crescents.
Tubulo-interstitial lesions	
▪ inflammatory infiltrate	▪ interstitial fibrosis; ▪ tubular atrophy.

Scored from 0 to 3; *Double scored.

Results

In 39 out of the total of 46 (84.78%) cases, the class of LN established at the time of the renal biopsy was confirmed in the reevaluation process.

Class II LN was characterized by lesions confined to mesangial areas: mesangial hypercellularity, based on the existence of three or more mesangial cells per each mesangial area, and mesangial matrix expansion.

Cases diagnosed as class III LN presented both active and chronic proliferative lesions comprising less than 50% of the renal corpuscles (RCs). These lesions, having a segmental pattern, consisted in endocapillary hypercellularity with consequently luminal decrease and obliteration, fibrinoid necrosis of the capillary walls, mesangial proliferation, crescents, and sclerosis.

Class IV LN was defined by the damage of 50% or more of RCs, the lesions affecting minimum half of the glomerular tuft (segmental lesions – class IV-S) in three cases, and more than half of the glomerular tuft (global lesions – class IV-G) in the other 15 cases. Class IV-S was characterized by segmental endocapillary proliferation influencing capillary walls, with or without associated capillary necrosis, whereas in class IV-G we identified a diffuse endocapillary, mesangial and/or extracapillary proliferation. The large spectrum of active (wire loops, hyaline thrombi, endocapillary cellular proliferation, inflammatory cell infiltration, fibrinoid necrosis, cellular crescents) and/or chronic (glomerulosclerosis, fibrocellular/fibrous crescents) lesions permitted the subsequent classification for the cases diagnosed as class IV-S and class IV-G, respectively.

In class V LN, almost all RCs presented a global, diffuse thickness of the capillary basement membrane. The special stains allowed the identification of the subepithelial deposits, as spikes (Methenamine Silver) or fuchsinophilic granules (trichrome stains) located on the extern part of basement membrane or an evident double contour aspect (Periodic Acid–Schiff, trichrome stainings), indicating the presence of intramembranous deposits or new synthesis of basement membrane components.

The diagnosis of class V LN was based on the existence of more than 90% of globally sclerotic RCs.

The differences in diagnosis were present in seven cases, initially considered as pure membranous glomerulonephritis – class V. In these cases, the histopathological reassessment added a secondary diagnosis, as follows: class IV-S (A/C) – diffuse segmental proliferative and sclerosing LN (active and chronic lesions) – two cases, class IV-G (A/C) – diffuse global proliferative and sclerosing LN (active and chronic lesions) – five cases.

Table 3 summarizes the present distribution of nephritis class by ISN/RPS classification criteria.

Figures 1–6 illustrate the specific glomerular lesions in different classes of LN.

The results of the reevaluated activity and chronicity indexes are given in Table 4. The values of indexes indicated a great variability of LN within the same class. The interobserver agreement for the scoring of activity and chronicity indexes was 0.8 and 0.95, respectively.

Table 3 – ***Classification of LN cases***

Diagnosis	No. of cases
Class II Mesangial proliferative LN	2
Class III Focal LN	
▪ Class III (A/C) Focal proliferative and sclerosing lupus nephritis (active and chronic lesions)	2
Class IV Diffuse LN	18
▪ Class IV-S (A) Diffuse segmental proliferative lupus nephritis (active lesions)	1
▪ Class IV-S (A/C) Diffuse segmental proliferative and sclerosing lupus nephritis (active and chronic lesions)	2
▪ Class IV-G (A) Diffuse global proliferative and sclerosing lupus nephritis (active lesions)	1
▪ Class IV-G (A/C) Diffuse global proliferative and sclerosing lupus nephritis (active and chronic lesions)	13
▪ Class IV-G (C) Diffuse global sclerosing lupus nephritis (chronic inactive lesions with scars)	1
Class V Membranous LN	18
▪ Class V Membranous LN	11
▪ Class V Membranous LN associated with Class IV-S (A/C) Diffuse segmental proliferative and sclerosing LN (active and chronic lesions)	2
▪ Class V Membranous LN associated with Class IV-G (A/C) Diffuse global proliferative and sclerosing LN (active and chronic lesions)	5
Class VI Advanced sclerosis LN	6

LN: Lupus nephritis.

Table 4 – ***Distribution of the activity and chronicity indexes values within and between classes of LN***

Class of LN	Activity and chronicity indexes								
II	0/3	3/3							
III	6/9**								
IV-S (A)	9/3								
IV-S (A/C)	12/9	15/12							
IV-G (A)	9/0								
IV-G (A/C)	6/12	9/3	12/3	12/9**	15/3	15/6***	15/9**	18/6	24/6
IV-G (C)	6/9								
V	0/0	3/0**	6/3	9/0	12/12	18/6	18/12	21/6	24/12**
V, IV-S (A/C)	12/9	18/3							
V, IV-G (A/C)	24/6	24/9 × 2	24/12**						
VI	3/9***	3/12	12/12						

LN: Lupus nephritis. *One case; **Two cases; ***Three cases.

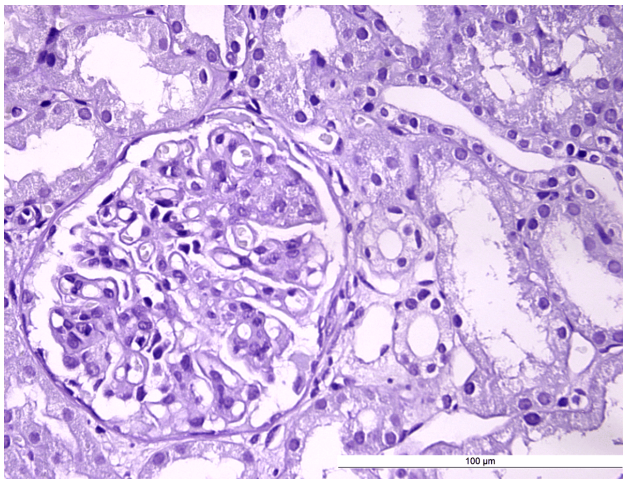

Figure 1 – ***Moderate hypercellularity in mesangial areas – lupus nephritis (LN) class II. HE staining, ×400.***

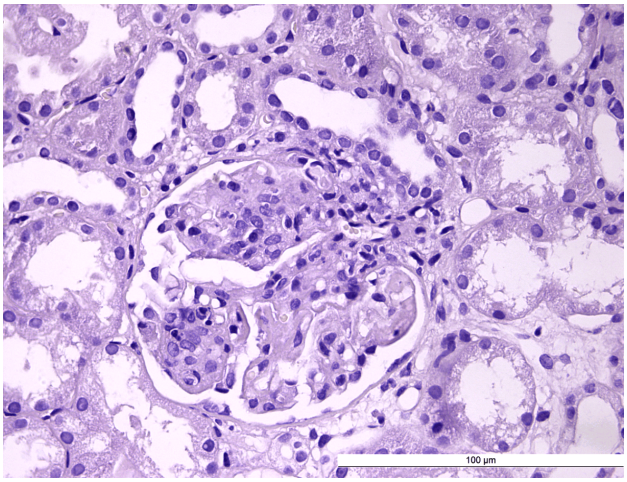

Figure 2 – ***Endocapillary proliferation, early stage of segmental sclerosis – LN class III (A/C). HE staining, ×400.***

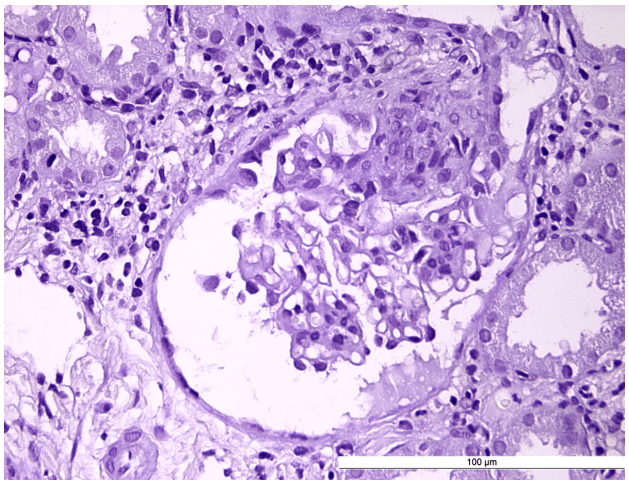

Figure 3 – ***Endocapillary proliferation limited to a glomerular lobule – LN class IV-S (A). HE staining, ×400.***

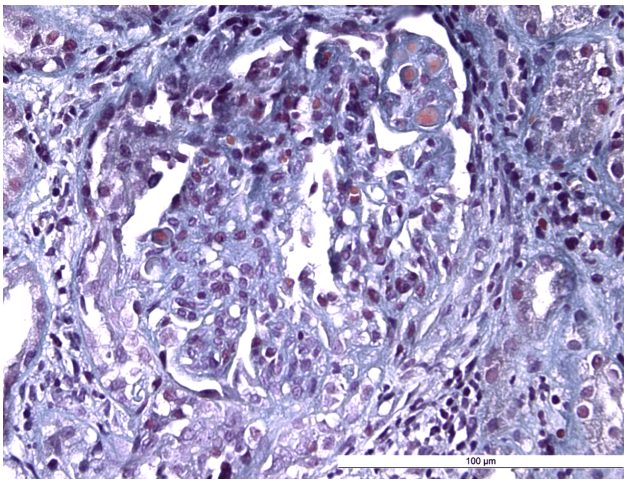

Figure 4 – ***Extended endocapillary proliferation, hyaline thrombi, fibrocellular crescent – LN class IV-G (A/C). Trichrome staining, ×400.***

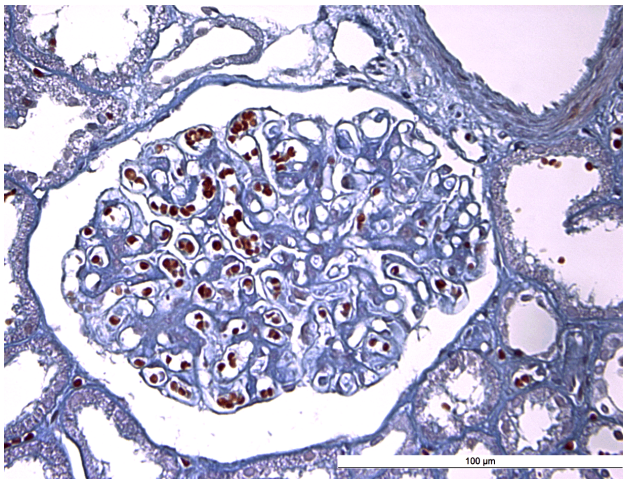

Figure 5 – ***General thickening of the capillary wall – LN class V. Trichrome staining, ×400.***

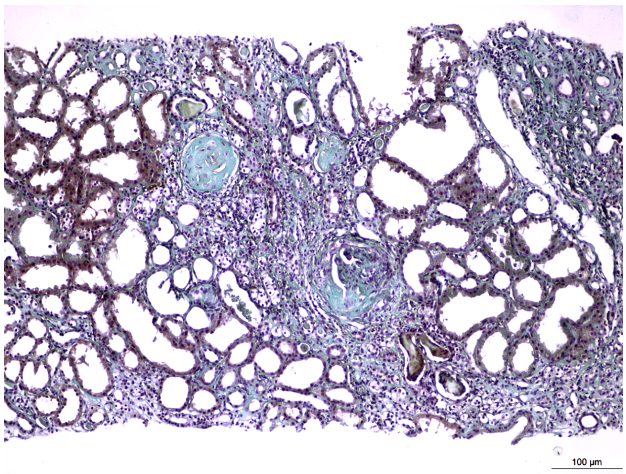

Figure 6 – ***Progressive and complete glomerulosclerosis, tubulointerstitial nephritis – LN class VI. Trichrome staining, ×100.***

Discussion

SLE is a disease with complex clinical manifestations and chronic evolution, frequently complicated with multiple organ involvement. The most frequently damaged site, in the long-term evolution, is the kidney. This particular type of lesion – namely LN – worsens the long-term prognosis.

The autoimmune component responsible for the pathogenic mechanisms involves the abnormal activity of the autoreactive B-lymphocytes and formation of abnormally activated T-lymphocytes, resulting in auto-antibody, immune complexes and cytokines production, which promote an inflammatory response [8, 16, 17]. This is how the chronic behavior of lupus is maintained. Unavoidably, a great number of patients with LN will develop chronic kidney disease.

Unfortunately, the exact pathogenic mechanism of SLE is yet to be discovered and does not facilitate the initiation of a targeted treatment that could ensure the healing. The existing therapeutic options, although extremely diverse, are capable of controlling the clinical features and slowing disease progression [18–20]. Therefore, establishing a complete diagnosis, which would allow choosing and initiating proper treatment is critical [21]. In the evaluation of renal lesions, the gold standard is the renal biopsy [22].

The renal biopsy was introduced in 1950 and the evaluation of tissue samples by using light microscopy was afterwards improved by the introduction of electron microscopy and immunofluorescence techniques [23]. A high quality biopsy sample has to allow a good lesion analysis and a clear classification according to diagnosis class, based on the ISN/RPS system [13, 18].

At the same time, repeated renal biopsies allow monitoring lesion progression – including the transition from one class to another [24]. Moreover, it is possible to quantify treatment response and customize or modify the medical approach accordingly, either by continuing on the same path or by adjusting treatment dosage in a relation with the regression or progression of the initial lesions, as well as long-term outcome prognostic [22, 25].

The ISN/RPS classification includes elements that differentiate between an active and a chronic disease status, based on the morphology of the renal corpuscle [13]. In parallel, the activity and chronicity indexes [15], as indicators of the reversibility or irreversibility lesion

potential, offers additional information regarding the relation between lesion background and different therapeutic outcomes [24].

Unlike the ISN/RPS classification, the semi-quantitative system that leads to determining the activity and chronicity indexes is based not only on renal corpuscle damage, but also on interstitial changes – inflammation, tubular atrophy and interstitial fibrosis [15, 23, 26]. Therefore, the class of LN diagnosis, according to the ISN/RPS classification, should be supplemented with the activity and chronicity indexes [23], the interstitial damage being a major parameter in assessing the evolution and therapeutic response [23, 27–30].

Our study revealed the progressive character of the specific LN lesions: on one hand, the transition from focal to diffuse lesions; on the other hand, from an limited mesangium injury to an extensive endocapillary and extracapillary damage, initially segmental, and later on global, ending in changes of the glomerular basement membrane and in the development of glomerulosclerosis. In this morphological picture, the complementary active and/or chronic lesions are present either independently, or in association. All these elements justify the difficulty of the LN diagnosis.

We highlight the fact that the extreme variability of the activity and chronicity indexes within the same class of diagnostic indicates the individuality of each case. The analysis of the obtained data indicates the following:

- cases included in the class II of LN have a lower value of the activity and chronicity indexes;
- the value of the activity and chronicity indexes increases with class of LN;
- the greatest variability of the activity and chronicity indexes corresponds to the cases with class IV of LN;
- there is a relative association between the type of lesions (acute, acute and chronic, exclusively chronic) and activity and chronicity indexes also in the class V of LN;
- the activity and chronicity indexes have similar values for cases included in class IV, V and VI of LN, respectively.

These observations represent a major argument in favor of differential therapeutic approaches in relation with score values. An activity index >12 or a chronicity index >4 are signs of a more reserved prognosis [31]. Active lesions may be reversible, although they have a high destructive potential, and will benefit from immunosuppressant treatment (corticotherapy associated with cytotoxic medication), a combination that does not offer favorable results in the case of chronic lesions. On the other hand, the greater the chronicity index, the lower the chance of lesion reversibility – and the progression towards chronic kidney disease are more probable. That is why the cases with a low or medium value of the chronicity index require a more aggressive therapy, in order to recover as much of the renal function as possible [32].

In our study, we obtained a good interobserver agreement for the activity index (0.8) and an excellent one for the chronicity index (0.95). Unfortunately, the interobserver reproducibility for the activity and chronicity indexes is relatively low [23, 33, 34]. In the evaluation process, the bias is the consequence of the fact that the number of active and/or chronic lesions needed for quantification is not clearly specified [23]. One point of view claims that identifying an active feature and/or a single criterion of chronicity in just one renal corpuscle, or interstitial area, respectively, are enough to grant a corresponding score value, thus defining activity and/or chronicity [18, 23, 35].

The question that rises in the current nephropathological practice is whether it is right to give the same score value to a single lesion as well as to multiple lesions. In our opinion, the degree of activity and chronicity in SLE must be refined through a much more precise correspondence between the score value and the limitation or extension of corpuscular and interstitial lesions. Therefore, the variability of the activity and chronicity indexes opens a new perspective towards clearer clinico-morphological correlations, in order to identify morphological factors with a higher degree of objectivity, which would ensure better prognosis estimation and a differential, personalized treatment.

Conclusions

Our study emphasizes the complex lesion character, which requires an individual and accurate identification, followed by integration in the classification algorithm used to define the classes and subclasses of LN diagnosis. The values of the activity and chronicity indexes specific to each case indicate the variability of LN within the same staging class, with impact in therapeutic approach and prognosis prediction.

Conflict of interests

The authors deny any conflict of interests, funding and other personal relationship with other people or organizations related to this study.

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